DOI: 10.1111/1744-9987.13749

Therapeutic Apheresis and Dialysis

WILEY

GUIDELINES

The Japanese Society for Apheresis clinical practice guideline for therapeutic apheresis

Takaya Abe[1] | Hidenori Matsuo[1,2] | Ryuzo Abe[1] | Shinji Abe[1] | Hiroaki Asada[1] | Akira Ashida[1] | Akiyasu Baba[1] | Kei Eguchi[3] | Yutaka Eguchi[1] | Yoshihiro Endo[1] | Yoshihiro Fujimori[1] | Kengo Furuichi[1] | Yutaka Furukawa[3] | Mayumi Furuya[1] | Tomoki Furuya[1] | Norio Hanafusa[1] | Wataru Hara[1] | Mariko Harada-Shiba[1] | Midori Hasegawa[1] | Noriyuki Hattori[1] | Motoshi Hattori[1] | Sumi Hidaka[1] | Toshihiko Hidaka[1] | Chika Hirayama[3] | Shigaku Ikeda[1] | Hideaki Imamura[1] | Kazuaki Inoue[1] | Keita Ishizuka[1] | Kiyonobu Ishizuka[1] | Takafumi Ito[1] | Hitomi Iwamoto[1] | Syoko Izaki[1] | Maki Kagitani[1] | Shuzo Kaneko[1] | Naoto Kaneko[1] | Takuro Kanekura[1] | Kiyoki Kitagawa[1] | Makio Kusaoi[1] | Youwei Lin[1] | Takeshi Maeda[1] | Hisashi Makino[1] | Shigeki Makino[1] | Kenichi Matsuda[3] | Takao Matsugane[1] | Yusuke Minematsu[3] | Michio Mineshima[1] | Kenichiro Miura[1] | Katsuichi Miyamoto[1] | Takeshi Moriguchi[1] | Mayumi Murata[3] | Makoto Naganuma[1] | Hajime Nakae[1] | Shinya Narukawa[1] | Atsushi Nohara[1] | Kyoichi Nomura[1] | Hirofumi Ochi[1] | Atsushi Ohkubo[3] | Takayasu Ohtake[1] | Kazuya Okada[1] | Tomokazu Okado[1] | Yoshiki Okuyama[1] | Susumu Omokawa[1] | Satoru Oji[1] | Norihiko Sakai[1] | Yuichiro Sakamoto[1] | Shigeru Sasaki[1] | Motoyoshi Sato[1] | Mariko Seishima[1] | Hidetoshi Shiga[1] | Homare Shimohata[1] | Noriko Sugawara[1] | Kohei Sugimoto[1] | Yasushi Suzuki[1] | Masato Suzuki[1] | Takashi Tajima[1] | Yasuhiro Takikawa[1] | Satoru Tanaka[1] | Kenjiro Taniguchi[3] | Satoko Tsuchida[1] | Tatsuo Tsukamoto[1] | Kenji Tsushima[1] | Yasunori Ueda[1] | Takashi Wada[1] | Hiromichi Yamada[1] | Hiroyuki Yamada[1] | Toshihiko Yamaka[3] | Ken'ichiro Yamamoto[3] | Yoko Yokoyama[1] | Norihito Yoshida[1] | Toyokazu Yoshioka[1] | Ken Yamaji[1,4]

This article is translated from Japanese with permission from the Japanese Society for Apheresis. The original article was published as "The Japanese Society for Apheresis clinical practice guideline for Therapeutic Apheresis 2021" in the Japanese Journal of Apheresis, 40:105–397, 2021.

[1]The Japanese Society for Apheresis Guidelines Preparation Committee

[2]Former President, The Japanese Society for Apheresis

[3]The Japanese Society for Apheresis Guidelines Working Group

[4]President, The Japanese Society for Apheresis

Correspondence
Takaya Abe, Department of Urology, Iwate Medical University School of Medicine, 2-1-1, Idaidori, Yahaba-cho, Shiwa-gun, Iwate 028-3695, Japan.
Email: takayabe@iwate-med.ac.jp

Funding information
The Japanese Society for Apheresis provided funding for the development of the guideline, and no compensation was paid to the members of the guideline preparation committee or the guideline development WG. In addition, no funding was received during the guideline development from any organization that may have an interest in it, such as companies that manufacture or sell the medical devices or drugs discussed in the guideline.

Abstract

Most of the diseases for which apheresis therapy is indicated are intractable and rare, and each patient has a different background and treatment course prior to apheresis therapy initiation. Therefore, it is difficult to conduct large-scale randomized controlled trials to secure high-quality evidence. Under such circumstances, the American Society for Apheresis (ASFA) issued its guidelines in 2007, which were repeatedly revised until the latest edition in 2019. The ASFA guidelines are comprehensive. However, in the United States, a centrifugal separation method is mainly used for apheresis, whereas the mainstream procedure in Japan is the membrane separation method. The target diseases and their backgrounds are different from those in Japan. Due to these differences, the direct adoption of the ASFA guidelines in Japanese practice creates various problems. One of the features of apheresis in Japan is the development of treatment methods using hollow-fiber devices such as double filtration plasmapheresis (DFPP) and selective plasma exchange and adsorption-type devices such as polymyxin B-immobilized endotoxin adsorption columns. Specialists in emergency medicine, hematology, collagen diseases/rheumatology, respiratory medicine, cardiovascular medicine, gastroenterology, neurology, nephrology, and dermatology who are familiar with apheresis therapy gathered for this guideline, which covers 86 diseases. In addition, since apheresis therapy involves not only physicians but also clinical engineers, nurses, dieticians, and many other medical professionals, this guideline was prepared in the form of a worksheet so that it can be easily understood at the bedside. Moreover, to the clinical purposes, this guideline is designed to summarize apheresis therapy in Japan and to disseminate and further develop Japanese apheresis technology to the world. As diagnostic and therapeutic techniques are constantly advancing, the guidelines need to be revised every few years. In order to ensure the high quality of apheresis therapy in Japan, both the Japanese Society for Apheresis Registry and the guidelines will be inseparable.

KEYWORDS

apheresis, clinical practice guideline

1 | BACKGROUND AND BASIC POLICY FOR THE DEVELOPMENT OF THE GUIDELINE

Most of the diseases for which apheresis therapy is indicated are intractable and rare, and each patient has a different background and treatment course before starting apheresis therapy. Furthermore, apheresis targets a wide variety of diseases, including emergency medicine, hematology, collagen diseases/rheumatology, respiratory medicine, cardiovascular medicine, gastroenterology, neurology, nephrology, and dermatology, and a wide range of medical departments are involved. In addition, apheresis therapy is a treatment using extracorporeal circulation, which requires knowledge of clinical engineers, nursing care and nutritional management tailored to individual conditions, and application for medical subsidies such as the intractable disease medical expense subsidy system. Therefore, this guideline has been developed to improve the quality of daily medical care by providing standard techniques and appropriate indications for the various medical departments and medical staff involved in apheresis therapy.

In developing a clinical practice guideline, evidence from research papers and other sources must be collected in a systematic way using the established method of

systematic review, and the entirety of the adopted evidence must be evaluated and integrated as a body of evidence. Since the primary requirement for a clinical practice guideline is its reliability, it is important that scientific judgments are made based on evidence, and that unbiasedness is ensured in the development process so that the influence of biased judgments is within acceptable limits. However, since apheresis therapy targets many intractable and rare diseases and the course of treatment differs in each case, it is difficult to conduct large-scale randomized controlled trials and secure high-quality evidence. Therefore, in cases where there is no evidence, we collected as much information as possible on the evidence and indicated the evidence recommendation level and recommendation category.

In addition, to ensure the universality of the development process, we asked specialists in the fields of emergency medicine, hematology, collagen diseases/rheumatology, respiratory medicine, cardiovascular medicine, gastroenterology, neurology, nephrology, and dermatology, who are actively engaged in apheresis therapy as well as drug therapy, to participate in the organization. To eliminate the variation in the literature search due to the involvement of various departments, we submitted keywords to the Japan Medical Library Association and conducted a literature search.

This guideline does not use the clinical question (CQ) format because it is regarding a unified CQ about whether apheresis therapy is effective for a certain disease. In addition, a "Device Manual" is included to unify apheresis techniques in clinical practice.

Compared to Europe and the United States, apheresis using hollow-fiber devices and adsorption-type devices is more advanced in Japan, and new therapeutic devices are being developed daily. New treatment methods using membrane technology include plasma filtration with dialysis (PDF) and selective plasma exchange (SePE). New therapies using adsorption technology include a column for removing blood cells using polyacrylate beads for ulcerative colitis and a direct blood perfusion adsorber used to improve ulcers in atherosclerosis obliterans that are not amenable to revascularization. In this guideline, we have highlighted the PDF that has been reported to have clinical efficacy for various diseases. The clinical efficacy of SePE and newer adsorption columns will be included in future guidelines as soon as they are finalized.

2 | DEVELOPMENT PROCEDURE

For this guideline, we established (1) a guideline preparation committee, (2) a guideline working group (WG), and (3) an organization in charge of the technical area.

The guideline preparation committee determined and summarized the guideline development policies, determined the disease areas, and selected the WG members. The WG for guideline development in the following disease areas: emergency medicine, hematology, collagen diseases/rheumatology, respiratory medicine, cardiovascular medicine, gastroenterology, neurology, nephrology, and dermatology and selected target diseases and extracted keywords for each disease. We also prepared a worksheet based on the list of references submitted by the Japan Medical Library Association based on keywords for each disease. The technical area examined aspects of the implementation of apheresis therapy in clinical practice. For the literature search, English keywords were set for each disease, and articles published by December 31, 2018, mainly in PubMed, were targeted.

3 | RECORDS OF COMMITTEE MEETINGS AND INTERIM REPORTING

- First meeting: February 8, 2017
  - Confirmation of guideline development procedures.
  - Determination of disease areas.
  - Working on guideline development for each disease area guideline WG inauguration.
- Second meeting: July 20, 2017.
  - Request for WG members in each disease area.
  - Request for selection of target diseases for each disease area.
  - Confirmation of conflict of interest (COI) contents.
- Third meeting: October 19, 2017.
  - Determination of WG members for each disease area.
- Fourth meeting: February 7, 2018.
  - Determination of the format using the worksheet.
- Fifth meeting: July 18, 2018.
  - Selection of target diseases by disease area.
- Sixth meeting: October 3, 2018.
  - Review of literature search methods.
  - Decided to request the Japan Medical Library.
  - Association for uniformity in each disease area.
- Seventh meeting: October 25, 2018.
  - Request the Japan Association of Medical Libraries to conduct a literature search.
- Eighth Meeting: February 20, 2019.
  - Submitted the "Memorandum of Agreement for Support of the Development of Medical Guideline" with Japan Medical Library Association and received approval.

Thereafter, a worksheet was prepared based on the search results of the Japan Medical Library Association. The completed worksheet was peer-reviewed by the members of each guideline preparation committee.

4 | ASSESSED THE STRENGTH OF EVIDENCE AND RECOMMENDATIONS

The recommended level of evidence (Table 1) and recommended categories (Table 2) of apheresis therapy for each disease were based on the "Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue" [1] developed by the American Society for Apheresis. The WG members in each disease area reviewed and made decisions.

TABLE 2 The recommended categories [1]

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision-making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

Abbreviation: IRB, institutional review board.

TABLE 1 The recommended level of evidence [1]

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade2A	Weak recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or social values
Grade2B	Weak recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodologicalflaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or social values
Grade2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Abbreviation: RCTs, randomized controlled trials.

TABLE 3 Category and grade recommendations for TA

Disease	Therapeutic tool	Grade	Category
ABO-incompatible kidney transplantation	PE, DFPP, IAPP	1C	I
Acute autonomic sensory neuropathy	PE	2C	III
Acute disseminated encephalomyelitis (ADEM)	PE, IAPP	2C	II
Acute exacerbation of interstitial pneumonia	PMX-DHP	2C	III
Acute liver failure	PE, online HDF, CHDF	1C	I
Acute pancreatitis (acute pancreatitis associated with hypertriglyceridemia is described separately)	CHDF, PDF	2B	II
Acute pancreatitis associated with hypertriglyceridemia	PE, CHDF	2C	III
Acute respiratory distress syndrome (ARDS) (CHDF)	CHDF	2C	III
Acute respiratory distress syndrome (ARDS) (Lixelle)	Lixille	2C	III
Acute respiratory distress syndrome (ARDS) (PE)	PE	2C	III
Acute respiratory distress syndrome (ARDS) (PMX-DHP)	PMX-DHP	2C	III
Amyopathic dermatomyositis and polymyositis with complications of interstitial pneumonia	PMX-DHP, LCAP	2B/3C	III
Amyotrophic lateral sclerosis (ALS)	PE	1C	IV
ANCA-associated glomerulonephritis(CAP)	CAP	2B	III
ANCA-associated glomerulonephritis(DFPP)	DFPP	2C	III
ANCA-associated glomerulonephritis(PE)	PE	1B	II
Anti-GBM RPGN (dialysis-independent, dialysis-dependent, complicated with alveolar hemorrhage) (DFPP)	DFPP	2C/2C/2C	I/I/III
Anti-GBM RPGN (dialysis-independent, dialysis-dependent, complicated with alveolar hemorrhage) (IAPP)	IAPP	2C/2C/2C	I/I/III
Anti-GBM RPGN (dialysis-independent, dialysis-dependent, complicated with alveolar hemorrhage) (PE)	PE	1B/2B/1C	I/III/I
Anti-GBM RPGN (CAP)	CAP		
Anti-VGKC antibody-related diseases	PE, IAPP	1B	II
Arteriosclerosis obliterans	LDL-A	1C	II
Ascites	CART	1C	II
Autoimmune autonomic ganglionopathy	PE	2C	III
Autoimmune encephalitis/cerebellitis LGI1/Caspr2/GABAbR/AMPAR/GAD/GlyR/NAE	PE, IAPP, CAP	2C	III
Bickerstaff brainstem encephalitis	PE, IAPP	2C	III
Blood type incompatible pregnancy	PE, IAPP, DFPP	2C	II
Buerger's disease	LDL-A	1C	II
Calciphylaxis	LDL-A, PE, CF	2C	III
Cholesterol crystal embolism	LDL-A	2C	II or III
Chronic focal encephalitis (Rasmussen encephalitis)	PE, IAPP	2C	III

TABLE 3 (Continued)

Disease	Therapeutic tool	Grade	Category
Chronic hepatitis C	DFPP	2C	III
Chronic inflammatory demyelinating polyneuropathy	PE, IAPP	1A	I
Combined central and peripheral demyelination	PE	1D	III
Complex regional pain syndrome (CRPS)	PE	2C	III
Crohn's disease	GMA	2B	II
Cryoglobulinemia	PE	2A	II
Cutaneous T-cell lymphoma	ECP	1B/1C	I/II
Dermatomyositis (DM) and polymyositis (PM)	PE, IAPP, CAP	2B/2C	IV
Diabetic nephropathy	LDL-A	1C	III
Dialysis-associated amyloidosis	Lixille	2B	II
Dilated cardiomyopathy	IAPP/PE/DFPP	1B/1C/2B	II/II/III
Drug-induced lung damage	PMX-DHP	2C	III
DSA-positive kidney transplant	PE, DFPP	1C	I
Fisher syndrome	PE, DFPP, IAPP	2C	III
Guillain-Barré syndrome	PE, IAPP	1A	I
Hashimoto's encephalopathy	PE, IAPP	2C	II
(Atypical, complement-mediated) hemolytic uremic syndrome (aHUS)	PE	2C/2C	III/I
Hemophilia with inhibitors	IAPP, PE, DFPP	2C/2B	III/II
Heterozygous familial hypercholesterolemia	LDL-A, DFPP, PE	1C	II
Homozygous familial hypercholesterolemia	LDL-A	1B	I
HTLV-1 associated myelopathy (HAM)	PE, IAPP, LCAP	2C	III
Hyper Lp(a)-emia	LDL-A, DFPP, PE	1C	II
Hyperleukocytosis	CFLA	1B/2C	II/III
Hypertrophic pachymeningitis	LCAP	2C	III
Hyperviscosity syndrome	PE, DFPP	1B	I
Inclusion body myositis (IBM)	PE, LDL-A	2C	IV
Isaacs' syndrome	PE, DFPP	2B	III
Lambert-Eaton myasthenic syndrome	PE	2C	II
Multifocal motor neuropathy	PE	1C	IV
Multiple sclerosis	PE, IAPP	PE1A/IAPP1B	RR-MSII/SP-MS, PP-MSIII
Myasthenia gravis	PE, IAPP, DFPP	1B	I
Necrotizing myopathy	PE, IAPP, CAP	2C	IV
Neuro-Behçet's disease	PE	2C	IV
Neuromyelitis optica spectrum disorders (NMOSD)	PE, IAPP	1B	II
Neuropsychiatric SLE (NPSLE)	IAPP, PE, DFPP	2C	II
NMDAR encephalitis	PE, IAPP	1C	I
Palmoplantar pustulosis	GMA	1C	III
PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection)/Sydenham's chorea	PE, IAPP	1B/2B	II/II
Paraneoplastic neurological syndrome (PNS)	PE	2C	III

(Continues)

5 | CATEGORY AND GRADE RECOMMENDATIONS FOR TA

This guideline covers 86 diseases. The TA, recommended level of evidence, and recommended categories of these diseases are summarized in Table 3.

6 | FUTURE PLANS

New therapeutic methods and modalities are being developed on a daily basis, and treatment policies are undergoing daily changes. Therefore, it is necessary to review the contents of the guidelines as appropriate in accordance with

TABLE 3 (Continued)

Disease	Therapeutic tool	Grade	Category
Paraproteinemic demyelinating polyneuropathies/chronic acquired demyelinating polyneuropathies (CADP)	PE, IAPP	1B/1C/2C	I/I/III
Pemphigoid	PE, DFPP	1C	II
Pemphigus	PE, DFPP	1C	II
POEMS syndrome	PE	2C	IV
Polycythemia vera	RBCX	1B	I
Post-transplantation recurrent focal segmental glomerulosclerosis (FSGS) (Prevention)	PE	2C	III
Post-transplantation recurrent focal segmental glomerulosclerosis (FSGS) (Treatment)	PE	1B	I
Progressive multifocal leukoencephalopathy (PML) associated with natalizumab	PE	1C	III
Psoriatic arthritis	GMA	1C	II
Pustular psoriasis	GMA	1C	II
Pyoderma gangrenosum	GMA	2C	III
Rapidly progressive interstitial pneumonia associated with anti-MDA5 antibody-positive dermatomyositis	PE	2C	III
Refractory nephrotic syndrome	PE, DFPP, LDL-A	無/2C	III/III
Refsum's disease	PE, DFPP	2C	II
Renal failure with unstable hemodynamics	CHDF	なし	I
Rheumatoid arthritis (RA)/malignant RA (MRA)	LCAP, PE, DFPP, IAPP	2B	II
Severe sepsis and septic shock	CHDF (without AN-69ST)	なし	I
Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome (STEC-HUS)	PE	2C/1C	III/IV
Sjogren syndrome	PE, DFPP	2C	III
Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)	PE, DFPP	1C	II
Stiff-person syndrome (SPS)	PE	2C	III
Systemic lupus erythematosus (SLE)	PE, DFPP, IAPP	2C/2B	II/II
Thrombotic thrombocytopenic purpura (TTP)	PE	1A	I
Tumefactive demyelinating disease	PE	2C	III
Ulcerative colitis	GMA, LCAP	1B	II
Drug poisoning	PDF	2C	III
Liver failure	PDF	1C	II
Sepsis	PDF	2B	III
Severe acute pancreatitis	PDF	2C	III

TABLE 4 Abbreviations

AAG	autoimmune autonomic ganglionopathy
AASN	acute autonomic and sensory neuropathy
AAV	antineutrophil cytoplasmic antibody associated vasculitis
ACD-A	Acid-citrate-dextrose Formula A
ACE	angiotensin convertase enzyme
AChR	acetylcholine receptor
ACS	abdominal compartment syndrome
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ADEM	acute disseminated encephalomyelitis
aHUS	atypical hemolytic uremic syndrome
ALL	acute lymphoblastic leukemia
ALS	amyotrophic lateral sclerosis
AME	antibody-mediated encephalitis
AML	acute myelogenous leukemia
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPAR	α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor
ANCA	antineutrophil cytoplasmic antibody
AN69ST	acrylonitrile-co-methallyl sulfonate surface-treated
AN69ST-CHDF	continuous hemodiafiltration with acrylonitrile-co-methallyl sulfonate surface-treated hemofilter
aPCC	activated prothrombin complex concentrate
AQP4	aquaporin-4
ARB	angiotensin II receptor blocker
ARDS	acute respiratory distress syndrome
5-ASA	5-aminosalicylic acid
ASO	arteriosclerosis obliterans
ATG	antithymocyte globulin
BBE	Bickerstaff brainstem encephalitis
CAP	cytapheresis
Caspr2	Contactin-associated protein-like 2
CART	cell-free and concentrated ascites reinfusion therapy
CCPD	combined central and peripheral demyelination
CF	cryofiltration
CGRP	calcitonin gene-related peptide
CHDF	continuous hemodiafiltration
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CIS	clinically isolated syndrome
CNI	calcineurin inhibitor
CRT-D	cardiac resynchronization therapy defibrillator
CRMP5	collapsin response mediator protein 5
CRPS	complex regional pain syndrome
csDMARDs	conventional synthetic disease-modifying antirheumatic drugs
CTCL	cutaneous T-cell lymphoma
DAAs	direct acting antivirals
DAD	diffuse alveolar damage
DAH	diffuse alveolar hemorrhage
DFPP	double filtration plasmapheresis
DHP	direct hemoperfusion
DIC	disseminated intravascular coagulation syndrome
DM	dermatomyositis
DSA	donor specific alloantibody
ECP	extracorporeal photopheresis
ECT	early combined therapy
EFT	early fast-active treatment
FFP	fresh frozen plasma
FS	Fisher syndrome
FSGS	focal segmental glomerulosclerosis
GABA	γ-aminobutyric acid
GABAB	γ aminobutyric acid B
GABHS	group A β-hemolytic streptococcus
gAChR	ganglionic acetylcholine receptor
GAD	glutamic acid decarboxylase
GBM	glomerular basement membrane
GBS	Guillain-Barré syndrome
GluR3	glutamate receptor 3
GlyR	glycine receptor
GMA	granulocyte and monocyte adsorption apheresis
GVHD	graft vs. host disease
HAM	human T-cell leukemia virus type 1 associated myelopathy
HDF	hemodiafiltration
HE	Hashimoto encephalopathy
HGF	hepatocyte growth factor
HL	hyperleukocytosis
HLA	human leukocyte antigen
HMGCR	hydroxymethylglutaryl-coenzyme A reductase
HP	hypertrophic pachymeningitis
HRCT	high-resolution CT
HTLV-1	human T-cell leukemia virus type 1
HU	hydroxycarbamide
HUS	hemolytic uremic syndrome

(Continues)

(Continues)

TABLE 4 (Continued)

IAPP	immunoadsorption plasmapheresis
IBM	inclusion body myositis
ICAM-1	intercellular adhesion molecule-1
IRIS	Immune reconstitution inflammatory syndrome
IS	Isaacs syndrome
IVIG	intravenous immunoglobulin
JAK	Janus Kinase
LCAP	leukocytapheresis
LDL	low density lipoprotein
LDL-A	LDL apheresis
LEMS	Lambert-Eaton myasthenic syndrome
LGI1	leucine-rich glioma-inactivated 1
LMN	lower motor neuron
Lp(a)	lipoprotein (a)
Lrp4	low-density lipoprotein receptor-related protein 4
LVP	large volume paracentesis
MAG	myelin-associated glycoprotein
MDA5	melanoma differentiation associated gene 5
MF	mycosis fungoides
MG	myasthenia gravis
β2MG	β2-microglobulin
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MMF	mycophenolate mofetil
MMN	multifocal motor neuropathy
MOG	myelin oligodendrocyte glycoprotein
8-MOP	8-methoxypsoralen
MRA	malignant rheumatoid arthritis
MS	multiple sclerosis
MTX	Methotrexate
MuSK	muscle specific(tyrosine) kinase
MVS	Morvan syndrome
NAE	NH2-terminal of α-enolase
NF155	neurofascin 155
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorders
NMT	neuromyotonia
NPSLE	neuropsychiatric systemic lupus erythematosus
NTZ	natalizumab

TABLE 4 (Continued)

NTZ-PML	natalizumab-associated progressive multifocal leukoencephalopathy
on-line HDF	online hemodiafiltration
PAN	polyacrylonitrile
PANDAS	pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections
PCSK9	proprotein convertase subtilisin/kexin type9
PDE4	phosphodiesterase 4
PDF	plasma filtration with dialysis
PE	plasma exchange
PED	plasma exchange with dialysis
phyH	phytanic-CoA hydroxylase
PICD	paracentesis induced circulatory dysfunction
PM	polymyositis
PML	progressive multifocal leukoencephalopathy
PMMA	polymethyl methacryrate
PMX,PMX-DHP	polimyxin B immobilized fiber column direct hemoperfusion
PNS	paraneoplastic neurological syndrome
POTS	postural orthostatic tachycardia syndrome
PP-MS	primary progressive multiple sclerosis
PUVA	psoralen ultra violet A
RA	rheumatoid arthritis
RE	Rasmussen encephalitis
RPGN	rapidly progressive glomerulonephritis
RR-MS	relapsing–remitting multiple sclerosis
SAP	severe acute pancreatitis
SCLC	small cell lung cancer
SePE	selective plasma exchange
SGPG	sulfated glucuronyl paragloboside
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SOX-1	SRY-related HMG-box gene 1
SP-MS	secondary progressive multiple sclerosis
SPS	stiff-person syndrome
SRP	signal recognition particle
STEC	Shiga toxin producing-*Escherichia coli*
STEC-HUS	Shiga toxin-producing *Escherichia coli* hemolytic-uremic syndrome
TDD	tumefactive demyelinating disease
TDL	tumefactive demyelinating lesion
TEN	toxic epidermal necrolysis

TABLE 4 (Continued)

TG	triglyceride
TIPS	transjugular intrahepatic portosystemic shunt
TLS	tumor lysis syndrome
TMA	thrombotic microangiopathy
TPO	thyroid peroxidase
TTP	thrombotic thrombocytopenic purpura
ULvWFM	unusually large von Willebrand factor multimer
UMN	upper motor neuron
UVB	ultraviolet B
VAD	ventricular assist device
VEGF	vascular endothelial growth factor
VLDL	very low density lipoprotein
VGCC	voltage-gated calcium channel
VGKC	voltage-gated potassium channel
WON	walled-off pancreatic necrosis

changes in actual clinical practice, such as the emergence of new apheresis therapies and the accumulation of new evidence.

This guideline will be reviewed and revised every few years.

The Japanese Society for Apheresis Guideline Preparation Committee is responsible for the contents of this guideline; however, the physician who actually treats the patient bears full responsibility for the application in actual clinical practice and the resulting liability (Table 4).

7 | INTENDED AUDIENCE

The audience for this guideline is not only intended for the medical staff (physicians, clinical engineers, nurses, and nutritionists) who actually perform apheresis therapy or are considering it as a treatment option, but also for patients who are undergoing apheresis therapy.

TABLE OF CONTENTS

8 | THE JSFA CLINICAL PRACTICE GUIDELINE FOR TA

8.1 | Worksheet 1

Diseases: ABO-incompatible kidney transplantation
Procedure: PE*DFPP*IAPP
Purpose: Removal of anti-blood type antibodies
Recommendation: 1C
Category: I
The number of references: RCT 0, CT 0, CS 21, CR 1

Description of the disease

ABO-incompatible kidney transplantation designates kidney transplantation where the donor and recipient blood types are different and where the recipient has anti-blood type antibodies (anti-A antibodies, anti-B antibodies) against the donor's blood group carbohydrate antigen. The number of ABO-incompatible kidney transplantations is increasing because of the scarcity of donors in Japan; based on recent Japanese statistics, ABO-incompatible kidney transplantations account for approximately 30% of living-donor kidney transplantations. The graft survival and patient survival in these procedures are comparable with those of ABO-compatible kidney transplantations.

Description of the disease

Many protocols include antibody removal with apheresis, rituximab administration aimed at controlling antibody production, and initiating immunosuppressants prior to kidney transplantation as desensitization therapies prior to kidney transplantation. Splenectomy was conducted in the past, but rituximab administration has become the main method since the 2000s; presently, splenectomies are rarely selected as an option. The other immunosuppressants are similar to those used for the ABO-compatible kidney transplantation, including drugs, such as methylprednisolone, calcineurin inhibitors, mycophenolate mofetil, and basiliximab.

Rationale for apheresis

In the ABO-incompatible kidney transplantation, the blood group carbohydrate antigens expressed in the vascular endothelial cells of the transplanted kidney react with the recipient's anti-blood type antibodies, resulting in antibody-mediated rejection. Apheresis removes the anti-blood type antibodies and should be conducted to prevent rejection in the early stage following transplantation. PE, DFPP, and IAPP are selected as removal methods. IAPP is often selected outside of Japan; however, adsorption columns for blood group antigens are not commercially available in Japan. Thus, PE or DFPP are usually used. There are no RCTs investigating the methods, number of implementations, or therapeutic performance of apheresis.

Technical notes

A volume of 1–1.5 times the circulating plasma volume is processed in PE or DFPP and is supplemented with either albumin solution or FFP. It is desirable to monitor the blood coagulation time and to replace coagulation factors with FFP immediately before surgery to avoid bleeding complications during the kidney transplantation procedure. FFP from the AB-type donor is used to avoid infusing anti-blood-type antibodies.

Technical notes

The insurance coverage in Japan includes up to four times prior to the surgery and up to two times after the surgery. The target antibody titer of the anti-A/B-type humoral IgG antibody prior to kidney transplantation ranges between less than four times to less than 32 times according to the available reports; however, attention should be given to the fact that variations due to measurement methods may exist. The number of implementations of apheresis to attain the target antibody titer is correlated with the antibody titer prior to the apheresis course.

References

1. Takahashi K, Saito K, Takahara S, Fuchinoue S, Yagisawa T, Aikawa A, et al. IDEC-C2B8 ABO-I KTx Study Group. Results of a multicenter prospective clinical study in Japan for evaluating efficacy and safety of desensitization protocol based on rituximab in ABO-incompatible kidney transplantation. Clin Exp Nephrol. 2017;21(4):705–13.

2.. Chow KV, Flint SM, Shen A, Landgren A, Finlay M, Murugasu A, et al. Histological and extended clinical outcomes after ABO-incompatible renal transplantation without splenectomy or rituximab. Transplantation. 2017;101(6):1433–40.

3. Masutani K, Tsuchimoto A, Kurihara K, Okabe Y, Kitada H, Okumi M, et al. Academic Consortium of Kidney Transplantation (JACK) investigators. Histological analysis in ABO-compatible and ABO-incompatible kidney transplantation by performance of 3- and 12-month protocol biopsies. Transplantation. 2017;101(6):1416–22.

4. Kauke T, Klimaschewski S, Schoenermarck U, Fischereder M, Dick A, Guba M, et al. Outcome after desensitization in HLA or ABO-incompatible kidney transplant recipients: a single center experience. PLoS One. 2016;11(1):e0146075.

5. Gelpi R, Cid J, Lozano M, Revuelta I, Sanchez-Escuredo A, Blasco M, et al. Desensitization in ABO-incompatible kidney transplantation with low ABO iso-agglutinin titers. Transplant Proc. 2015;47(8):2340–43.

6. Won DI, Ham JY, Kim CD, Suh JS, Kim BC. Benefits of fresh-frozen plasma as a replacement fluid to neutralize ABO antibodies. J Clin Apher. 2015;30(5):288–96.

7. de Weerd AE, van Agteren M, Leebeek FW, Ijzermans JN, Weimar W, Betjes MG. ABO-incompatible

kidney transplant recipients have a higher bleeding risk after antigen-specific immunoadsorption. Transpl Int. 2015;28(1):25–33.

8. Opelz G, Morath C, Susal C, Tran TH, Zeier M, Dohler B. Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers. Transplantation. 2015;99(2):400–4.

9. Shishido S, Hyodo YY, Aoki Y, Takasu J, Kawamura T, Sakai KK, et al. Outcomes of pediatric ABO-incompatible kidney transplantations are equivalent to ABO-compatible controls. Transplant Proc. 2012 Jan;44(1):214–6.

10. Lawrence C, Galliford JW, Willicombe MK, McLean AG, Lesabe M, Rowan F, et al. Antibody removal before ABO-incompatible renal transplantation: how much plasma exchange is therapeutic? Transplantation. 2011;92(10):1129–33.

11. Tyden G, Kumlien G, Berg UB. ABO-incompatible kidney transplantation in children. Pediatr Transplant. 2011;15(5):502–4.

12. Chung BH, Lee JY, Kang SH, Sun IO, Choi SR, Park HS, et al. Comparison of clinical outcome between high and low baseline anti-ABO antibody titers in ABO-incompatible kidney transplantation. Ren Fail. 2011;33(2):150–8.

13. Fuchinoue S, Ishii Y, Sawada T, Murakami T, Iwadoh K, Sannomiya A, et al. The 5-year outcome of ABO-incompatible kidney transplantation with rituximab induction. Transplantation. 2011;91(8):853–7.

14. Wilpert J, Fischer KG, Pisarski P, Wiech T, Daskalakis M, Ziegler A, et al. Long-term outcome of ABO-incompatible living donor kidney transplantation based on antigen-specific desensitization. An observational comparative analysis. Nephrol Dial Transplant. 2010;25(11):3778–86.

15. Tobian AA, Shirey RS, Montgomery RA, Cai W, Haas M, Ness PM, et al. ABO antibody titer and risk of antibody-mediated rejection in ABO-incompatible renal transplantation. Am J Transplant. 2010;10(5):1247–53.

16. Sivakumaran P, Vo AA, Villicana R, Peng A, Jordan SC, Pepkowitz SH, et al. Therapeutic plasma exchange for desensitization prior to transplantation in ABO-incompatible renal allografts. J Clin Apher. 2009;24(4):155–60.

17. Tobian AA, Shirey RS, Montgomery RA, Tisch DJ, Ness PM, King KE. Therapeutic plasma exchange reduces ABO titers to permit ABO-incompatible renal transplantation. Transfusion. 2009;49(6):1248–54.

18. Genberg H, Kumlien G, Wennberg L, Berg U, Tyden G. ABO-incompatible kidney transplantation using antigen-specific immunoadsorption and rituximab: a 3-year follow-up. Transplantation. 2008; 85(12):1745–54.

19. Tyden G, Donauer J, Wadstrom J, Kumlien G, Wilpert J, Nilsson T, et al. Implementation of a protocol for ABO-incompatible kidney transplantation—a three-center experience with 60 consecutive transplantations. Transplantation. 2007;83(9):1153–55.

20. Tanabe K. Double-filtration plasmapheresis. Transplantation. 2007;84(12 Suppl):S30–2.

21. Segev DL, Simpkins CE, Warren DS, King KE, Shirey RS, Maley WR, et al. ABO incompatible high-titer renal transplantation without splenectomy or anti-CD20 treatment. Am J Transplant. 2005;5(10): 2570–5.

22. Tydén G, Kumlien G, Genberg H, Sandberg J, Lundgren T, Fehrman I. ABO incompatible kidney transplantations without splenectomy, using antigen-specific immunoadsorption and rituximab. Am J Transplant. 2005 Jan;5(1):145–8.

8.2 | Worksheet 2

Diseases: Acute autonomic sensory neuropathy

Procedure: PE

Purpose: Removal of immunity-related substances, improvement of pathological condition

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 0, CR 6

Description of the disease

Acute autonomic and sensory neuropathy (AASN) is a neuropathy with severe acute-onset autonomic neuropathy and sensory dysfunction without dyskinesia. AASN often develops due to previous infection such as upper respiratory tract inflammation; therefore, involvement an autoimmune mechanism such as that involved in Guillain-Barré syndrome is presumed. However, no autoantibodies associated with this pathological condition have been identified.

Current management/treatment

Intravenous immunoglobulin therapy, PE, and corticosteroid therapy have been reported to be effective; however, there is no consensus on their effectiveness.

Rationale for apheresis

Involvement an autoimmune mechanism such as that involved in Guillain-Barré syndrome is presumed. Some case reports have reported the effectiveness of PE, reporting that simple PE significantly stabilized autonomic symptoms, including orthostatic hypertension.

Technical notes

Attention should be paid to blood pressure fluctuations as a form of autonomic neuropathy. Apheresis therapy for this disease is not covered by insurance.

Duration and discontinuation/number of procedures

This procedure should be performed 3–4 times a week while observing the clinical course of the disease.

References

1. Koike H, Atsuta N, Adachi H, Iijima M, Katsuno M, Yasuda T, et al. Clinicopathological features of acute autonomic and sensory neuropathy. Brain. 2010;133:2881–96.

2. Koike H, Watanabe H, Sobue G. The spectrum of immunemediated autonomic neuropathies: insights from the clinicopathological features. J Neurol Neurosurg Psychiatry. 2013;84:98–106.

3. Koike H, Sobue G. The wide range of clinicopathological features in immune-mediated autonomic neuropathies. Clin Exp Neuroimmunol. 2013;4:46–59.

4. Gibbons CH, Vernino SA, Freeman R. Combined immunomodulatory therapy in autoimmune autonomic ganglionopathy. Arch Neurol. 2008;65:213–7.

8.3 | Worksheet 3

Diseases: Acute disseminated encephalomyelitis (ADEM)

Procedure: PE, IAPP

Purpose: Removal of autoantibodies and inflammatory cytokines

Recommendation: 2C

Category: II

The number of references: RCT 0, CT 0, CS 7, CR 29

Description of the disease

Acute disseminated encephalomyelitis (ADEM) is an acute developing monophasic demyelinating disease. It typically occurs after viral/bacterial infection or vaccination. It can develop at any age, but it is common during childhood. Its etiologies are thought to include multifocal inflammation and demyelinating lesions due to transient autoimmune abnormalities against myelin oligodendrocyte glycoprotein (MOG) and other neural autoantigens. MRI is useful for diagnosis, and the lesions are present as patchy high-intensity signals in the deep white matter, subcortical white matter, basal ganglia, gray-white matter boundary, brain stem, cerebrum, and spinal cord. Prognosis is favorable; complete recovery within a few weeks or months is observed in 55%–95% of cases, with only a few deaths.

Current management/treatment

ADEM should be treated as early as possible after diagnosis. Corticosteroids are widely used as first-line treatments (methylprednisolone, 20–30 mg/kg/day, maximum of 1 g/day, 3–5 days). For adults, 1000 mg/day of methylprednisolone is administered continuously over 3–5 days as intravenous infusion. Corticosteroid treatment is effective due to its anti-inflammatory/immunomodulatory effects. IVIG is also administered for cases with a poor response to corticosteroid treatment; it is rarely administered as initial treatment.

Rationale for apheresis

PE is performed to remove humoral factors and autoantibodies. It is used as second-line treatment for cases with a poor response to corticosteroid treatment. A large-scale retrospective study reported that PE was required for 17 of 228 cases of ADEM (7%).

Technical notes

There is no standard protocol for PE in ADEM. PE is recommended within 15 days of onset, and improvements in neurological symptoms have been reported a few days after administering treatment 2–3 times. The amount of processed plasma during PE was approximately 1.1–1.4, and an albumin solution and FFP are used as replenishment solutions.

Duration and discontinuation/number of procedures

PE is mainly used as apheresis therapy for ADEM. Case reports on PE for moderate to severe ADEM reported improvements in 40% of cases. Several case reports have indicated that PE was conducted 5–7 times.

References

1. Alper G. Acute disseminated encephalomyelitis. J Child Neurol. 2012;27:1408–25.

2. Koelman DL, Mateen FJ. Acute disseminated encephalomyelitis: current controversies in diagnosis and outcome. J Neurol. 2015;262:2013–24.

3. Bigi S, Banwell B, Yeh EA. Outcomes after early administration of plasma exchange in pediatric central nervous system inflammatory demyelination. J Child Neurol. 2015;30:874–80.

4. Borras-Novell C, Rey EG, Baena LFP, Carcia IJ, Cahiz DC, Cambra F. Theraputic plasma exchange in acute disseminated encephalomyelitis in children. J Clin Apher. 2015;30:335–9.

5. Koerlman DLH, Chabin S, Mar SS, Venkatesan A, Hoganson GM, Yeshokumar AK, et al. Acute disseminated encephalomyelitis in 228 patients: a retrospective, multicenter US study. Neurology. 2016;86:2085–93.

6. Keegan M, Pineda AA, McClelajd RL, Darby CH, Rodorigues M, Weinschenkaer BG. Plasma exchanges for severe attacks of CNS demyekination: predictors of response. Neurology. 2002;58:143–6.

7. Khurana DS, Melvin JJ, Kothare SV, Valencia I, Hardison HH, Yum S, et al. Acute disseminated encephalomyelitis in children: discordant neurologic and neuroimaging abnormalities and response to plasmapheresis. Pediatrics. 2005;116:431–6.

8.4 | Worksheet 4

Diseases: Acute exacerbation of interstitial pneumonia

Procedure: PMX-DHP

Purpose: Oxygenation/vital prognosis improvement

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 17, CR 0

Description of the disease

A condition where all of the following items were observed within a month during the course of interstitial pneumonia:

1. Increased dyspnea
2. Newly developed ground-glass shadow/infiltrative shadow on HRCT
3. Decreased arterial partial pressure of oxygen (PaO_2 of over 10 Torr under the same conditions)

The mortality rate is 50%–80% and the median survival time (MST) is 1.3 months.

It is a pathological condition with extremely poor prognosis.

Current management/treatment

There are no comparative studies that have provided evidence regarding treatment methods for acute exacerbations.

Steroid pulse therapy, immunosuppressants (e.g., cyclophosphamide), and recombinant thrombomodulin have been used; however, it is difficult to determine whether the therapeutic responses have been favorable.

Rationale for apheresis

A retrospective study reported that PMX-DHP improved oxygenation (PaO_2/FiO_2) and the survival rate in cases of worsening respiratory status associated with acute exacerbations.

PMX-DHP has also been reported to significantly decrease inflammatory cytokines and mediators (e.g., blood IL-9, IL-12, IL-17, PDGF, VEGF, HMGB1, IL-18).

Technical notes

No serious complications have been reported in the conventional literature; however, the pressure in the thoracic cavity has often been excessively negative during the deterioration of respiratory conditions. Therefore, there is a risk of air embolism when inserting a catheter for vascular access from the internal jugular vein. Efforts should be made for catheter removal in the supine position (ideally by raising the lower limbs or placing the patient in the Trendelenburg position).

Duration and discontinuation/number of procedures

Perform the treatment two to three times. Favorable prognosis has been reported in cases of early introduction (within 3 days of onset) relative to later introduction (after 4 days of onset); therefore, treatment is preferable in the early stage.

Comparison between the 6 h/session and 12 h/session duration showed that treatment performed over longer periods had a higher effect. Therefore, the procedure is currently performed over longer periods (i.e., around 18–24 h).

References

1. Seo Y, Abe S, Kurahara M, Okada D, Saito Y, Usuki J, et al. Beneficial effect of polymyxin B-immobilized fiber column (PMX) hemoperfusion treatment on acute exacerbation of idiopathic pulmonary fibrosis. Intern Med. 2006;45(18):1033–8.

2. Noma S, Matsuyama W, Mitsuyama H, Suetsugu T, Koreeda Y, Mizuno K, et al. Two cases of acute exacerbation of interstitial pneumonia treated with polymyxin B-immobilized fiber column hemoperfusion treatment. Intern Med. 2007;46(17):1447–54.

3. Enomoto N, Suda T, Uto T, Kato M, Kaida Y, Ozawa Y, et al. Possible therapeutic effect of direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) on pulmonary oxygenation in acute exacerbations of interstitial pneumonia. Respirology. 2008;13(3):452–60.

4. Abe S, Seo Y, Hayashi H, Matsuda K, Usuki J, Azuma A, et al. Neutrophil adsorption by polymyxin B-immobilized fiber column for acute exacerbation in patients with interstitial pneumonia: a pilot study. Blood Purif. 2010;29(4):321–6.

5. Tachibana K, Inoue Y, Nishiyama A, Sugimoto C, Matsumuro A, Hirose M, et al. Polymyxin-B hemoperfusion for acute exacerbation of idiopathic pulmonary fibrosis: serum IL-7 as a prognostic marker. Sarcoidosis Vasc Diffuse Lung Dis. 2011;28(2):113–22.

6. Abe S, Hayashi H, Seo Y, Matsuda K, Kamio K, Saito Y, et al. Reduction in serum high mobility group box-1 level by polymyxin B-immobilized fiber column in patients with idiopathic pulmonary fibrosis with acute exacerbation. Blood Purif. 2011;32(4):310–6.

7. Hara S, Ishimoto H, Sakamoto N, Mukae H, Kakugawa T, Ishimatsu Y, et al. Direct hemoperfusion using immobilized polymyxin B in patients with rapidly progressive interstitial pneumonias: a retrospective study. Respiration. 2011;81(2):107–17.

8. Kono M, Suda T, Enomoto N, Nakamura Y, Kaida Y, Hashimoto D, et al. Evaluation of different perfusion durations in direct hemoperfusion with polymyxin B-immobilized fiber column therapy for acute

exacerbation of interstitial pneumonias. Blood Purif. 2011;32(2):75–81.

9. Tachikawa R, Tomii K, Murase K, Ueda H, Harada Y, Kida Y, et al. Therapeutic effect of direct hemoperfusion with a polymyxin B-immobilized fiber column in the treatment of HIV-negative severe pneumocystis pneumonia. Respiration. 2011;81(4): 318–24.

10. Abe S, Azuma A, Mukae H, Ogura T, Taniguchi H, Bando M, et al. Polymyxin B-immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis. Intern Med. 2012;51(12):1487–91.

11. Oishi K, Mimura-Kimura Y, Miyasho T, Aoe K, Ogata Y, Katayama H, et al. Association between cytokine removal by polymyxin B hemoperfusion and improved pulmonary oxygenation in patients with acute exacerbation of idiopathic pulmonary fibrosis. Cytokine. 2013;61(1):84–9.

12. Sato N, Kojima K, Horio Y, Goto E, Masunaga A, Ichiyasu H, et al. Successful treatment of severe amiodarone pulmonary toxicity with polymyxin B-immobilized fiber column direct hemoperfusion. Chest. 2013;143(4):1146–50.

13. Takada T, Asakawa K, Sakagami T, Moriyama H, Kazama J, Suzuki E, et al. Effects of direct hemoperfusion with polymyxin B-immobilized fiber on rapidly progressive interstitial lung diseases. Intern Med. 2014; 53(17):1921–6.

14. Enomoto N, Mikamo M, Oyama Y, Kono M, Hashimoto D, Fujisawa T, et al. Treatment of acute exacerbation of idiopathic pulmonary fibrosis with direct hemoperfusion using a polymyxin B-immobilized fiber column improves survival. BMC Pulm Med. 2015;15:15.

15. Itai J, Ohshimo S, Kida Y, Ota K, Iwasaki Y, Hirohashi N, et al. A pilot study: a combined therapy using polymyxin-B hemoperfusion and extracorporeal membrane oxygenation for acute exacerbation of interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis. 2015;31(4):343–9.

16. Oishi K, Aoe K, Mimura Y, Murata Y, Sakamoto K, Koutoku W, et al. Survival from an acute exacerbation of idiopathic pulmonary fibrosis with or without direct hemoperfusion with a polymyxin B-immobilized fiber column: a retrospective analysis. Intern Med. 2016;55(24):3551–9.

17. Furusawa H, Sugiura M, Mitaka C, Inase N. Direct hemoperfusion with polymyxin B-immobilized fibre treatment for acute exacerbation of interstitial pneumonia. Respirology. 2017;22(7):1357–62.

18. Ichiyasu H, Horio Y, Masunaga A, Migiyama Y, Sakamoto Y, Jodai T, et al. Efficacy of direct hemoperfusion using polymyxin B-immobilized fiber column (PMX-DHP) in rapidly progressive interstitial pneumonias: results of a historical control study and a review of previous studies. Ther Adv Respir Dis. 2017;11(7):261–75.

19. Komatsu M, Hachiya T, Takahashi H, Yoshikawa S, Honda T. Direct hemoperfusion with polymyxin B-immobilized fiber for the treatment of the acute exacerbation of idiopathic pulmonary fibrosis in patients requiring invasive mechanical ventilation. Respir Investig. 2017;55(5):318–22.

8.5 | Worksheet 5

Diseases: Acute liver failure

Procedure: PE, on-line HDF, CHDF

Purpose: Replenishment of deficient plasma factors/awakening from coma by removing coma-inducing substances

Recommendation: 1C

Category: I

The number of references: RCT 1, CT 0, CS 18, CR 1

Description of the disease

Acute liver failure is a syndrome involving hepatic coma and bleeding tendencies, due to extensive hepatocellular necrosis, as the main symptoms. Liver transplantation is the last resort in cases where the liver does not regenerate with intensive care centered on blood purification. According to Japanese diagnostic criteria, "acute liver failure" is defined as when a liver with normal hepatic reserve is impaired, and where a prothrombin time of 40% or less, or INR value of 1.5 or more, is present within 8 weeks of onset. A hepatic encephalopathy degree of I or below is "non-coma type"; a degree of II or higher is "coma type"; a time period of less than 10 days from initial onset to the appearance of encephalopathy degree II is "acute type"; and longer periods of time are "sub-acute type." The lifesaving rates for the acute and sub-acute types are 43.7% and 27.2%, respectively.

Current management/treatment

The most reliable treatment worldwide is liver transplantation. Living-donor transplantation accounts for the majority of transplantations in Japan, due to a serious shortage of donors in the country. Intensive medical care is the central treatment for adults. The main components of intensive medical care are PE and blood purification therapies (e.g., HDF, CHDF, on-line HDF), as well as the administration and tapering of steroid pulse therapy.

Rationale for apheresis

PE is a safe and convenient method for replenishing plasma components (e.g., deficient coagulation factors). However, its limitations regarding awakening effects were first indicated in the 1980s. Since the introduction of PAN membrane dialysis by Opolon in Japan, methods such as HDF, high-flow CHDF, and on-line HDF have been used as blood purification therapies using high-performance membranes. In this way, a high coma-awakening rate has been achieved.

Technical notes

Confirm that the general condition of the patient is such that blood purification therapy could be conducted, and then insert the vascular access at a position where sufficient blood flow can be obtained. FFP is used as a replenishment solution in PE, so calcium replenishment should be conducted as appropriate since citric acid in FFP causes hypocalcemia. Complications of electrolyte abnormalities and metabolic alkalosis may occur, so combining the use of blood purification methods such as HD may be an effective measure. Blood purification therapy is for renal failure in both dialysate and replenishment solution, so potassium and phosphorus replenishment is necessary.

Duration and discontinuation/number of procedures

PE should be implemented so that the prothrombin time can be maintained to the extent that bleeding does not occur the day after implementation. Tapering and withdrawal become possible as the liver regenerates. When bridging to transplantation, be conscious of the limit of 10 administrations, and provide FFP at intervals. HDF should be performed daily until the patient gains consciousness. It should then be gradually stopped when his or her condition improves.

References

1. Yoshiba M, Sanjo T, Inoue N, Sakai T, Okada T, Wada T. Plasma exchange therapy of fulminant hepatic failure. Nippon Shokakibyo Gakkai Zasshi. 1980;77:1397–1402.

2. Yoshiba M, Yamada H, Yoshikawa Y, Fujiwara K, Toda G, Oka H, et al. Hemodiafiltration treatment of deep hepatic coma by protein passing membrane: case report. Artif Organs. 1986;10:417–9.

3. Yoshiba M, Inoue K, Sekiyama K, Koh I. Favorable effect of new artificial liver support on survival of patients with fulminant hepatic failure. Artif Organs. 1996;20:1169–72.

4. De Silvestro G, Marson P, Brandolese R, Pittoni G, Ongaro G. A single institution's experience (1982–1999) with plasma-exchange therapy in patients with fulminant hepatic failure. Int J Artif Organs. 2000;23:454–61.

5. Sadahiro T, Hirasawa H, Oda S, Shiga H, Nakanishi K, Kitamura N, et al. Usefulness of plasma exchange plus continuous hemodiafiltration to reduce adverse effects associated with plasma exchange in patients with acute liver failure. Crit Care Med. 2001;29:1386–92.

6. Arata S, Iwashita M, Ishikawa J, et al. Use of on-line hemodiafiltration for fulminant hepatic failure. J Abdom Emerg Med. 2003;23:865–73.

7. Akdogan M, Camci C, Gurakar A, Gilcher R, Alamian S, Wright H, et al. The effect of total plasma exchange on fulminant hepatic failure. J Clin Apher. 2006;21:96–9.

8. Hirasawa H, Oda S, Matsuda K. Continuous hemodiafiltration with cytokine-adsorbing hemofilter in the treatment of severe sepsis and septic shock. Contrib Nephrol. 2007;156:365–70.

9. Inoue K, Kourin A, Watanabe T, Yamada M, Yoshiba M. Artificial liver support system using large buffer volumes removes significant glutamine and is an ideal bridge to liver transplantation. Transplant Proc. 2009;41:259–61.

10. Inoue K, Yoshiba S. Effective artificial liver support system is a prerequisite for the intensive medical care and liver transplantation. J Abdom Emerg Med. 2009;29:603–8.

11. Inoue K, Watanabe T, Maruoka N, Kuroki Y, Takahashi H, Yoshiba M. Japanese-style intensive medical care improves prognosis for acute liver failure and the perioperative management of liver transplantation. Transplant Proc. 2010;42:4109–12.

12. O'Grady J. Liver transplantation for acute liver failure. Best Pract Res Clin Gastroenterol. 2012;26:27–33.

13. Sugawara K, Nakayama N, Mochida S. Acute liver failure in Japan: definition, classification, and prediction of the outcome. J Gastroenterol. 2012;47:849–61.

14. Fujiwara K, Yokosuka O, Oda S, Arata S, Inoue K, Takikawa Y, et al. Present status of artificial liver support for acute liver failure in Japan. Kanzo. 2012;53:530–3.

15. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369:2525–34.

16. Fujiwara K, Oda S, Inoue K, Arata S, Abe R, Takikawa Y, et al. Proposal of standardization of artificial liver supports for acute liver failure in Japan. Kanzo. 2014;55:79–81.

17. Ichida T, Genda T, Hirano K. Current issues and problems of deceased donor liver transplantation in Japan. Kanzo. 2015;56:79–87.

18. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol. 2016;64:69–78.

19. Yue-Meng W, Yang L-H, Yang J-H, Xu Y, Yang J, Song G-B. The effect of plasma exchange on entecavir-treated chronic hepatitis B patients with hepatic decompensation and acute-on-chronic liver failure. Hepatol Int. 2016;10:462–9.

20. Mochida S. The cutting-edge of medicine; acute liver failure in Japan. Nichinaikaishi. 2016;105:1463–71.

8.6 | Worksheet 6

Diseases: Acute pancreatitis (acute pancreatitis associated with hypertriglyceridemia is described separately)

Procedure: CHDF, other (e.g., PDF)

Purpose: Body fluid management, removal of pathogenic substances

Recommendation: 2B

Category: II

The number of references: RCT 8, CT 19, CS 12, CR 90

Description of the disease

Acute pancreatitis is an acute inflammation of the pancreas due to the disruption of pancreatic function. Causes include alcohol, gallstones, and hypertriglyceridemia (separately described). Severe acute pancreatitis affects other adjacent organs and induces abdominal compartment syndrome (ACS). Overproduction of humoral factors (e.g., inflammatory cytokines) causes vascular hyperpermeability and distant organ damage, necessitating systemic management in ICU and resulting in high mortality and complication rates. Necrotic areas often develop into walled-off pancreatic necrosis (WON), with secondary pancreatic infections affecting vital prognosis.

Current management/treatment

Sufficient infusion under ICU control, various organ failures such as ventilator management and blood purification, and ACS measures should be taken for severe cases. The usefulness of early-stage enteral nutrition (starting within 48 h) has been proven. There is limited evidence supporting prophylactic antibiotics, proteolytic enzyme inhibitors, and intra-arterial infusion therapy (not covered by insurance). Consider endoscopic papilla treatment for gallstone pancreatitis. Treatment with minimally invasive procedures under endoscopes has become the primary method for secondary pancreatic infections.

Rationale for apheresis

CHDF is performed for the purposes of renal support and mediator removal in Japan, and its usefulness for ACS has been suggested, though there are no RCTs. PDF is also being attempted in more severe cases.

Technical notes

The PMMA membrane, which is a hemofilter that is capable of adsorbing cytokines, is often selected for CHDF, but the AN69ST membrane may be selected in future. The recommendations for implementation conditions are not fixed, but the amount of dialysis/replenishment fluid use is limited to 15–16 L/day in terms of insurance, so other infusion preparations may be used as replenishment fluids. Note that PDF is not covered by insurance for acute pancreatitis itself.

Duration and discontinuation/number of procedures

Regardless of whether "acute renal failure" is present, in terms of insurance, up to eight sessions per treatment series are allowed under the disease name of "severe acute pancreatitis." Treatment is normally withdrawn when decreases in inflammatory mediators (IL-6 values used as a reference in some facilities) and improvements in vascular permeability are seen, hemodynamics stabilize, and organ disorders (e.g., renal disorders) improve.

References

1. Hu Y, Xiong W, Li C, Cui Y. Continuous blood purification for severe acute pancreatitis: a systematic review and meta-analysis. Medicine. 2019;98:e14873.

2. Wang G, Liu H, Xu L, Wen P, Wen J, Zhou SF, et al. Effect of laparoscopic peritoneal lavage and drainage and continuous venovenous diahemofiltration on severe acute pancreatitis. J Laparoendosc Adv Surg Tech A. 2017;27:1145–50.

3. Guo H, Suo DW, Zhu HP, Sun XM, Chen J. Early blood purification therapy of severe acute pancreatitis complicated by acute lung injury. Eur Rev Med Pharmacol Sci. 2016;20:873–8.

4. Chu LP, Zhou JJ, Yu YF, Huang Y, Dong WX. Clinical effects of pulse high-volume hemofiltration on severe acute pancreatitis complicated with multiple organ dysfunction syndrome. Ther Apher Dial. 2013;17:78–83.

5. Zhang J, Yuan C, Hua G, Tong R, Luo X, Ying Z. Early gut barrier dysfunction in patients with severe acute pancreatitis: attenuated by continuous blood purification treatment. Int J Artif Organs. 2010;33:706–15.

6. Yang C, Guanghua F, Wei Z, Zhong J, Penghui J, Xin F, et al. Combination of hemofiltration and peritoneal dialysis in the treatment of severe acute pancreatitis. Pancreas. 2010;39:16–9.

7. Jiang HL, Xue WJ, Li DQ, Yin AP, Xin X, Li CM, et al. Influence of continuous veno-venous hemofiltration on the course of acute pancreatitis. World J Gastroenterol. 2005;11:4815–21.

8. Mao EQ, Tang YQ, Zhang SD. Effects of time interval for hemofiltration on the prognosis of severe acute pancreatitis. World J Gastroenterol. 2003;9:373–6.

9. Pupelis G, Plaudis H, Zeiza K, Drozdova N, Mukans M, Kazaka I. Early continuous veno-venous haemofiltration in the management of severe acute pancreatitis complicated with intra-abdominal hypertension: retrospective review of 10 years' experience. Ann Intensive Care. 2012;2(Suppl 1):S21.

10. Oda S, Hirasawa H, Shiga H, Matsuda K, Nakamura M, Watanabe E, et al. Management of intra-abdominal hypertension in patients with severe acute pancreatitis with continuous hemodiafiltration using a

polymethyl methacrylate membrane hemofilter. Ther Apher Dial. 2005 Aug;9:355–61.

11. Xu J, Tian X, Zhang C, Wang M, Li Y. Management of abdominal compartment syndrome in severe acute pancreatitis patients with early continuous veno-venous hemofiltration. Hepatogastroenterology. 2013;60:1749–52.

12. Moriguchi T, Hirasawa H, Oda S, Shiga H, Matsuda K. CHDF (continuous hemodiafiltration) for severe acute pancreatitis. Jpn J Acute Med. 2002;26:803–808.

13. Saotome T, Eguchi Y. A novel plasmapheresis plasma dia-filtration (PDF) as cytokine apheresis for severe acute pancreatitis. J Biliary Tract Pancreas. 27;2006:45–50.

14. Furuya T. PDF (plasma filtration with dialysis) for acute pancreatitis. Jpn J Apher. 2017;36:171–4.

8.7 | Worksheet 7

Diseases: Acute pancreatitis associated with hypertriglyceridemia

Procedure: PE, CHDF

Purpose: Removal of blood triglycerides

Recommendation: 2C

Category: III

The number of references: RCT 2, CT 5, CS 29, CR 98

Description of the disease

Hypertriglyceridemia (TG) is a condition caused by increased the production and decreased metabolism.

Significantly high TG values are likely to occur when a secondary cause is added to a patient with congenital anomalies related to TG metabolism. Acute pancreatitis can develop when TG exceeds 500–1000 mg/dl.

Current management/treatment

Complete parenteral nutrition, fasting, and calorie restriction are required treatment measures for acute pancreatitis due to hypertriglyceridemia.

Insulin is indicated for diabetic patients since it activates the lipoprotein lipase (LpL).

Heparin promotes LpL secretion and TG degradation, but its use is controversial because it promotes pancreatitis-related bleeding.

Rationale for apheresis

PE can decrease blood TG levels and replace deficient LpL and apoliproproteins.

Multiple case reports, case series, and a single non-randomized CT investigated the therapeutic effects of acute pancreatitis due to hypertriglyceridemia, and it was reported that the rate of TG decrease by a single session of PE was 49%–80%. Blood TG values rapidly decrease due to PE, but these effects are temporary, so appropriate treatment for hyperlipidemia is needed.

A single CT on PE indicated that PE was not associated with mortality rate and complication occurrence rate, but the sample size was small, and there was insufficient information to confirm whether the comparisons between the two groups were valid. Other case series decreased TG when compared to conservative treatment, but there was no association with severity or mortality.

CHDF (AN69HF membrane, filtration rate of 50 ml/kg/h) has also been suggested to reduce blood TG concentrations, but the sample size was small, and no target group has been set, so further studies will need to be conducted in the future.

Neither PE nor CHDF are covered by insurance for use against hypertriglyceridemia and acute pancreatitis associated with hypertriglyceridemia.

Technical notes

PE may be carried out in terms of two methods: the centrifugal separation method and the membrane plasma separation method. Of the two, the former has a higher removal efficiency as TG has a tendency to clog membrane pores. Heparin is used since it not only has an anticoagulant effect, it also promotes LpL secretion and contributes to lowering TG levels.

Duration and discontinuation/number of procedures

The goal is to have blood TG values < 500–1000 mg/dl.

References

1. Basar R, Uzum AK, Canbaz B, Dogansen SC, Kalayoglu-Besisik S, Altay-Dadin S, et al. Therapeutic apheresis for severe hypertriglyceridemia in pregnancy. Arch Gynecol Obstet. 2013;287:839–43.

2. Chen JH, Yeh JH, Lai HW, Liao CS. Therapeutic plasma exchange in patients with hyperlipidemic pancreatitis. World J Gastroenterol. 2004;10:2272–4.

3. Costantini N, Mameli A, Marongiu F. Plasmapheresis for preventing complication of hypertriglyceridemia: a case report and review of literature. Am J Ther. 2016;23:e288–91.

4. Gubensek J, Buturović-Ponikvar J, Marn-Pernat A, Kovac J, Knap B, Premru V, et al. Treatment of hyperlipidemic acute pancreatitis with plasma exchange: a single-center experience. Ther Apher Dial. 2009;13:314–7.

5. Gubensek J, Buturovic-Ponikvar J, Romozi K, Ponikvar R. Factors affecting outcome in acute hypertriglyceridemic pancreatitis treated with plasma exchange: an observational cohort study. PLoS One. 2014;9:e102748.

6. Markota A, Knehtl M, Sinkovic A, Ekart R, Hojs R, Bevc S. Plasma exchange treatment for acute hyperlipidemic pancreatitis with falsely low levels of serum triglycerides - a case report. Transfus Apher Sci. 2014;51:178–80.

7. Ramírez-Bueno A, Salazar-Ramírez C, Cota-Delgado F, de la Torre-Prados MV, Valdivielso P. Plasmapheresis as treatment for hyperlipidemic pancreatitis. Eur J Intern Med. 2014;25:160–3.

8. Seth A, Rajpal S, Saigal T, Bienvenu J, Sheth A, Alexander JS, et al. Diabetic ketoacidosis-induced hypertriglyceridemic acute pancreatitis treated with plasmapheresis-recipe for biochemical disaster management. Clin Med Insights Gastroenterol. 2014;7:51–3.

9. Stefanutti C, Di Giacomo S, Vivenzio A, Labbadia G, Mazza F, D'Alessandri G, et al. Therapeutic plasma exchange in patients with severe hypertriglyceridemia: a multicenter study. Artif Organs. 2009;33:1096–102.

10. Stefanutti C, Labbadia G, Morozzi C. Severe hypertriglyceridemia-related acute pancreatitis. Ther Apher Dial. 2013;17:130–7.

11. Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. Current knowledge of hypertriglyceridemic pancreatitis. Eur J Intern Med. 2014;25:689–94.

12. Yeh JH, Chen JH, Chiu HC. Plasmapheresis for hyperlipidemic pancreatitis. J Clin Apher. 2003;18:181–5.

13. Yeh JH, Lee MF, Chiu HC. Plasmapheresis for severe lipemia: comparison of serum-lipid clearance rates for the plasma exchange and double-filtration variants. J Clin Apher. 2003;18:32–6.

14. Zeitler H, Balta Z, Klein B, Strassburg CP. Extracorporeal treatment in severe hypertriglyceridemia-induced pancreatitis. Ther Apher Dial. 2015;19:405–10.

15. He WH, Yu M, Zhu Y, Xia L, Liu P, Zeng H, et al. Emergent triglyceride-lowering therapy with early high-volume hemofiltration against low-molecular-weight heparin combined with insulin in hypertriglyceridemic pancreatitis: a prospective randomized controlled trial. J Clin Gastroenterol. 2016;50:772–8.

8.8 | Worksheet 8

Diseases: Acute respiratory distress syndrome (ARDS)

Procedure: CHDF

Purpose: Improved oxygenation/improved circulatory dynamics

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 2, CR 0

Description of the disease

Acute respiratory distress syndrome (ARDS) causes cell damage in the lung parenchyma due to systemic invasion (e.g., pneumonia, trauma, surgery, burns, sepsis) and presents with increased pulmonary edema due to extensive damage to pulmonary capillary endothelial cells. It is thought that monocytes and macrophages are activated by some stimulus, which results in the production and release of inflammatory mediators such as cytokines, in turn causing ARDS, which is a subtype of multiple organ failure syndrome.

Following accumulation of activated neutrophils in the lungs, the inflammatory mediators express adhesion molecules such as CD11b on the surface of the neutrophils, which in turn results in adhesion factors such as the intercellular adhesion molecule-1 (ICAM-1) being expressed on pulmonary vascular endothelial cells. This results in migration of the accumulated neutrophils from the lung capillaries into the alveolar septum and alveolar space. Subsequently, neutrophil elastase and reactive oxygen species are released from the activated neutrophils, which in turn extensively damages the pulmonary vascular endothelial and alveolar epithelial cells. Ultimately, patients present with increased permeability pulmonary edema.

Current management/treatment

Currently, there is no recommended drug therapy. Low tidal volume ventilation is recommended, and favorable results have been reported in some patients with prone position therapy. It has also been predicted that improvements in PEEP may be observed with a pressure that causes the affected lung to collapse.

Rationale for apheresis

The objective of CHDF is to remove low-molecular-weight inflammatory cytokines and water from the body. CHDF has minimal influence on extracorporeal circulation and is useful for systemic management. CHDF with a PMMA membrane is expected to improve oxygenation by eliminating inflammatory mediators; however, there are no reports to prove its benefits in ARDS.

Technical notes

The apheresis procedure is generally covered by insurance for cases of ARDS accompanying renal failure; however, other cases where this treatment was implemented have been recognized in Japanese publications.

Duration and discontinuation/number of procedures

There are no established guidelines for the completion of CHDF. Comprehensive judgment is required based on factors such as respiratory status (e.g., improved oxygenation) or increased urine volume in patients with renal failure.

References

1. Sakai M. Efficacy of continuous haemodiafiltration using a polymethylmethacrylate membrane haemofilter in the treatment of sepsis and acute respiratory distress syndrome. Crit Care. 2012;16(Suppl 1): P378. https://doi.org/10.1186/cc10985

2. Nakada T, Oda S, Matsuda K, Sadahiro T, Nakamura M, Abe R, et al. Continuous hemodiafiltration with PMMA hemofilter in the treatment of patients with septic shock. Mol Med. 2008 May-Jun;14(5–6):257–63.

8.9 | Worksheet 9

Diseases: Acute respiratory distress syndrome (ARDS)

Procedure: β2-microglobulin adsorption column (Lixelle)

Purpose: Improved oxygenation/improved circulatory dynamics

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 1, CR 0

Description of the disease

Acute respiratory distress syndrome (ARDS) causes cell damage to the lung parenchyma due to systemic invasion (e.g., pneumonia, trauma, surgery, burns, sepsis) and presents with increased pulmonary edema due to extensive damage to the pulmonary capillary endothelial cells. Monocytes and macrophages are believed to be activated by some type of stimulation, causing the production and release of inflammatory mediators, such as cytokines, which in turn cause ARDS, a subtype of multiple organ failure syndrome.

After the accumulation of activated neutrophils in the lungs, the inflammatory mediators express adhesion molecules such as CD11b on the neutrophil surface, which in turn results in adhesion factors such as the intercellular adhesion molecule-1 (ICAM-1) being expressed on pulmonary vascular endothelial cells. This results in the neutrophils being accumulated in the lung migrating from the lung capillaries into the alveolar septum and alveolar space. Neutrophil elastase and reactive oxygen species are released from the activated and migrated neutrophils, which in turn extensively damage pulmonary vascular endothelial cells and alveolar epithelial cells. The patient then presents with increased-permeability pulmonary edema.

Current management/treatment

No recommended drug therapy is currently available. Ventilator management with low tidal volume is recommended, and favorable results, such as prone position therapy, have currently been reported in some patients. It is also predicted that improvements PEEP pressure-related improvements could be seen with a pressure that causes the affected lung to collapse.

Rationale for apheresis

Lixelle is filled with porous and hydrophobic cellulose beads. Therefore, β2MG and inflammatory cytokines are adsorbed by the combination of the two elements with a molecular sieving effect according to pore size, and the hydrophobic interactions that penetrate into the pores.

The use of Lixelle reportedly reduced inflammatory cytokines (IL1b, IL-6, sICAM1) and improved mortality and oxygenation.

Technical notes

There are three types of Lixelle depending on capacity: s-15 (capacity of 150 ml), s-25 (capacity of 250 ml), and s-35 (capacity of 350 ml). Cases with stable hemodynamics should use s-25 or s-35, and cases with hypotension or elderly cases should use s-15.

Duration and discontinuation/number of procedures

There are no established guidelines. Comprehensive decisions based on factors such as respiratory status (e.g., improved oxygenation) are necessary.

References

1. Kono K, Toda S, Hora K, Kiyosawa K. Direct hemoperfusion with a beta2-microglobulin-selective adsorbent column eliminates inflammatory cytokines and improves pulmonary oxygenation. Ther Apher Dial. 2009 Feb; 13(1):27–33. https://doi.org/10.1111/j.1744–9987.2009.00652.x

8.10 | Worksheet 10

Diseases: Acute respiratory distress syndrome (ARDS)

Procedure: PE

Purpose: Improved oxygenation/improved circulatory dynamics

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 0, CR 0

Description of the disease

Acute respiratory distress syndrome (ARDS) causes cell damage to the lung parenchyma due to systemic invasion (e.g., pneumonia, trauma, surgery, burns, sepsis) and presents with increased pulmonary edema due to the extensive damage to the pulmonary capillary endothelial cells. Monocytes and macrophages are believed to be activated by some type of stimulation, causing the production and release of inflammatory mediators, such as cytokines, in turn causing ARDS, a subtype of multiple organ failure syndrome.

After the accumulation of activated neutrophils in the lungs, the inflammatory mediators express adhesion molecules such as CD11b on the neutrophil surface, which in turn results in adhesion factors, such as the intercellular adhesion molecule-1 (ICAM-1) being expressed on pulmonary vascular endothelial cells. This results in the neutrophils being accumulated in the lung, migrating from the lung capillaries into the alveolar septum and alveolar space. Neutrophil elastase and reactive oxygen species are released from the activated and migrated neutrophils, which in turn extensively damage the pulmonary vascular endothelial cells and alveolar epithelial cells. The patient then presents with increased-permeability pulmonary edema.

Current management/treatment

No recommended drug therapy is currently available. Ventilator management with low tidal volume is recommended, and favorable results, such as prone position therapy, have currently been reported in some patients. It is also predicted that improvements PEEP pressure-related improvements could be seen with a pressure that causes the affected lung to collapse.

Rationale for apheresis

PE is expected to improve the pathological conditions by removing pathogenic substances, such as inflammatory cytokines.

Technical notes

More attention should be paid to changes in hemodynamics for PE compared to other apheresis therapies due to the large volume of extracorporeal circulation.

Duration and discontinuation/number of procedures

There are no established guidelines. Comprehensive decisions based on factors such as respiratory status (e.g., improved oxygenation) are necessary.

References

8.11 | Worksheet 11

Diseases: Acute respiratory distress syndrome (ARDS)

Procedure: PMX-DHP

Purpose: Improved oxygenation/improved circulatory dynamics

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 7, CR 7

Description of the disease

Acute respiratory distress syndrome (ARDS) causes cell damage to the lung parenchyma due to systemic invasion (e.g., pneumonia, trauma, surgery, burns, sepsis) and presents with increased-pulmonary edema due to the extensive damage to the pulmonary capillary endothelial cells. Monocytes and macrophages are believed to be activated by some type of stimulation, causing the production and release of inflammatory mediators, such as cytokines, which in turn cause ARDS, a subtype of multiple organ failure syndrome.

After the accumulation of activated neutrophils in the lungs, the inflammatory mediators express adhesion molecules such as CD11b on the neutrophil surface, which in turn results in adhesion factors, such as the intercellular adhesion molecule-1 (ICAM-1) being expressed on pulmonary vascular endothelial cells. This results in the neutrophils accumulated in the lung migrating from the lung capillaries into the alveolar septum and alveolar space. Neutrophil elastase and reactive oxygen species are released from the activated and migrated neutrophils, which in turn extensively damage the pulmonary vascular endothelial cells and alveolar epithelial cells. The patient then presents with increased-permeability pulmonary edema.

Current management/treatment

No recommended drug therapy is currently available. Ventilator management with low tidal volume is recommended, and favorable results, such as prone position therapy, have currently been reported in some patients. It is also predicted that improvements PEEP pressure-related improvements could be seen with a pressure that causes the affected lung to collapse.

Rationale for apheresis

PMX-DHP is used in patients with sepsis due to gram-negative bacillus infection. Clinical trials across eight institutions in Japan on sepsis patients showed that this was effective, with improved hemodynamics and increased survival rate. It has since been reported that oxygenation was improved when introduced to ARDS, which is a pathological condition of sepsis. However, there are no comparative studies that prove its usefulness.

Technical notes

Effects cannot be seen unless used for at least 2 h. However, caution is required as blood flow tends to become clogged in the column when coagulation is hyperactive.

Duration and discontinuation/number of procedures

This can be used up to two times under insured coverage for septic shock. The required implementation time is at least 2 h. It has been reported that long-term implementation until the column blood flow pressure becomes high (maximum working pressure is 66 kPa = 50 cmHg) is beneficial.

References

1. Tsushima K, Kubo K, Koizumi T, Yamamoto H, Fujimoto K, Hora K, et al. Direct hemoperfusion using a polymyxin B immobilized column improves acute respiratory distress syndrome. J Clin Apher. 2002;17:97–102. (CS)

2. Nakamura T, Kawagoe Y, Matsuda T, Shoji H, Ueda Y, Tamura N, et al. Effect of polymyxin B-immobilized fiber on blood metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 levels in acute respiratory distress syndrome patients. Blood Purif. 2004;22:256–60. (CS)

3. Tsushima K, Kubo K, Yoshikawa S, Koizumi T, Yasuo M, Furuya S, et al. Effects of PMX-DHP treatment for patients with directly induced acute respiratory distress syndrome. Ther Apher Dial. 2007;11:138–45. (CS)

4. Suyama H, Kawasaki Y, Morikawa S, Kaneko K, Yamanoue T. Early induction of PMX-DHP improves oxygenation in severe sepsis patients with acute lung injury. Hiroshima J Med Sci. 2008;57:79–84. (CS)

5. Takezono T, Izumikawa K, Tsurutani J, Tanaka A, Kakugawa T, Fukuda Y, et al. Lemierre's syndrome followed by acute respiratory distress syndrome successfully rescued by antibiotics and hemoperfusion with polymyxin B-immobilized fiber. Jpn J Infect Dis. 2009 Mar;62:133–6. (CR)

6. Nakamura T, Fujisawa N, Sato E, Kawagoe Y, Ueda Y, Yamada S, et al. Effect of polymyxin B-immobilized fiber hemoperfusion on serum high mobility group box-1 protein levels and oxidative stress in patients with acute respiratory distress syndrome. ASAIO J. 2009;55:395–9. (CS)

7. Yokoyama T, Tateishi K, Tsushima K, Agatsuma T, Yamamoto H, Koizumi T, et al. A case of severe ARDS caused by novel swine-origin influenza (A/H1N1pdm) virus: a successful treatment with direct hemoperfusion with polymyxin B-immobilized fiber. J Clin Apher. 2010;25:350–3. (CR)

8. Yatera K, Yamasaki K, Kawanami T, Tokuyama S, Ogoshi T, Kouzaki M, et al. A case of successful treatment with polymyxin B-immobilized fiber column direct hemoperfusion in acute respiratory distress syndrome after influenza A infection. Intern Med. 2011;50:601–5. (CR)

9. Binh NG, Manabe T, Co DX, Tuan ND, Thach PT, Kudo K. Polymyxin-B-immobilized-fiber column hemoperfusion with oseltamivir treatment for ARDS due to influenza H1N1/09. Respirol Case Rep. 2015;3:57–60. (CR)

10. Yamashita C, Hara Y, Kuriyama N, Nakamura T, Nishida O. Clinical effects of a longer duration of polymyxin B-immobilized fiber column direct hemoperfusion therapy for severe sepsis and septic shock. Ther Apher Dial. 2015;19:316–23. (CS)

11. Ishibe Y, Shibata S, Takahashi G, Suzuki Y, Inoue Y, Endo S. Association of type II secretory phospholipase A2 and surfactant protein D with the pulmonary oxygenation potential in patients with septic shock during polymyxin-B immobilized fiber-direct hemoperfusion. J Clin Apher. 2017;32:302–10. (CS)

12. Kawano Y, Nagashima R, Morimoto S, Izutani Y, Yamasaki R, Nishida T, et al. Efficacy of direct hemoperfusion with a polymyxin B-immobilized fiber column in miliary tuberculosis. Acute Med Surg. 2016;26:311–5. (CR)

8.12 | Worksheet 12

Diseases: Amyopathic dermatomyositis and polymyositis with complications of interstitial pneumonia

Procedure: PMX-DHP and LCAP

Purpose: Introduction of remission

Recommendation: 2B/2C

Category: III

The number of references: RCT 1, CT 1, CS 3, CR 12

Description of the disease

PM/DM causes the complication of interstitial pneumonia in approximately 40% of cases and may rapidly progress and worsen, but steroid pulse therapy is effective. Cases resistant to corticosteroids are responsive to immunosuppressants, such as cyclophosphamide pulse therapy and cyclosporine. However, cases with poor or no myoinflammatory symptoms, in which CK is not elevated despite the presence of typical cutaneous symptoms of dermatomyositis (i.e., amyopathic dermatomyositis), rapidly worsens when interstitial pneumonia develops. Such cases are resistant to the aforementioned treatments and have a poor prognosis. Many cases are positive for anti-melanoma differentiation-associated gene 5 (MDA5) antibodies.

Current management/treatment

The prognosis improves in treatment-resistant cases of interstitial pneumonia complicated with dermatomyositis with poor myoinflammatory symptoms when PMX-DHP is combined with cyclosporine and cyclophosphamide pulse therapy. Many studies have shown the ineffectiveness of LCAP in interstitial pneumonia with polymyositis, but LCAP has also been effective in some cases.

Rationale for apheresis

Polymyxin B has a high affinity for endotoxins produced in the circulating blood during sepsis (outer membrane component of Gram-negative bacteria). The mechanism of PMX-DHP is speculated to be the removal of activated neutrophils and monocytes and that of cytokines and autoantibodies. Further, interstitial pneumonia improves with PMX-DHP. Additionally, LCAP is thought to improve pneumonia by removing a large number of CD8+ T lymphocytes and plasma cells present in the interstitial tissue of the lungs. Uncontrolled trials reported that LCAP was effective, but double-blind trials did not.

Technical notes

Investigations with small sample sizes and case reports have shown apheresis to be effective, but comparative trials with other treatment methods using a large sample size have not shown clear therapeutic effects; therefore, apheresis should be considered only for refractory cases with resistivity to various other treatments.

Duration and discontinuation/number of procedures

It is not covered by insurance. PMX-DHP, an endotoxin adsorption therapy using polymyxin B-immobilized fiber, should be performed twice over 2 h in one session (for two consecutive days). LCAP is a method of adsorbing and removing white blood cells, including lymphocytes, in the patient's blood using extracorporeal circulation. It is performed according to the insurance-covered treatment for drug-resistant rheumatoid arthritis and ulcerative colitis. The removal of 5–10 $\times$ 10^9 lymphocytes has been achieved in previously reported cases.

References

1. Euwer RL, Sontheimer RD. Amyopathic dermatomyositis: a review. J Invest Dermatol. 1993;100:124–7.

2. Sontheimer RD. Cutaneous features of classic dermatomyositis and amyopathic dermatomyositis. Curr Opin Rheumatol. 1999;11:475–82.

3. Kakugawa T, Mukae H, Saito M, Ishii K, Ishimoto H, Sakamoto N, et al. Rapidly progressive interstitial pneumonia associated with clinically amyopathic dermatomyositis successfully treated with polymyxin B–immobilized fiber column hemoperfusion. Intern Med. 2008;47:785–90.

4. Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Doanti A, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA. 2009;301:2445–52.

8.13 | Worksheet 13

Diseases: Amyotrophic lateral sclerosis (ALS)
Procedure: PE
Purpose: Improving clinical symptoms
Recommendation: Grade 1C
Category: IV
The number of references: RCT 0, CT 2, CS 25, CR 23

Description of the disease

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease in which upper motor neuron (UMN) and lower motor neuron (LMN) cell bodies undergo sporadic and progressive degeneration and deficit. A majority of cases are sporadic ALS, while some are familial ALS. The clinical manifestations of classical ALS consist of the three symptoms of LMN symptoms, bulbar palsy symptoms, and UMN symptoms. Symptoms often progress in a nodular and horizontal manner and was anatomically continuous, from a local part of the spinal cord on one side to the other. The revised El Escorial diagnostic criteria, which incorporates neurological findings and medical history in the electrophysiological criteria, were proposed for the diagnosis of ALS. In 2008, the Awaji criteria, which was a revision proposed by the International Federation of Clinical Neurophysiology, was established in order to emphasize EMG abnormalities while following the principles of the El Escorial criteria.

Current management/treatment

Oral riluzole prolongs survival by 2–3 weeks. However, this did not improve motor function or muscle strength, nor did it control progression of the disease. Edaravone significantly improved the 24-week revised ALS function rating scale in patients with relatively mild ALS with an ALS severity of 1 or 2 and effort lung activity of 80% or higher. Doctor-initiated ALS clinical trials in Japan include trials on intramuscular administration of high-dose mecobalamin, oral administration of perampanel (glutamate AMPA receptor antagonist), and intrathecal administration of hepatocyte growth factor (HGF). Some improvements in neurological symptoms have been observed.

Rationale for apheresis

There are some reports where PE was conducted for ALS, but symptoms progressed regardless of PE, and progress was not controlled.

Technical notes

The effectiveness of apheresis has currently not been supported.

Duration and discontinuation/number of procedures

The effectiveness of apheresis has currently not been supported.

References

1. de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol. 2008;119:497–503.

2. Oyama G, Izawa N, Fujishima K, et al. Familial amyotrophic lateral sclerosis with rapid progression. No To Shinkei. 2005;57:1003–6.

3. Vannucci P, Castiglioni M, Filidei M, Riccioni N. Amyotrophic lateral sclerosis in a patient with Waldemstrom's macroglobulinemia. Minerva Med. 1997;88:167–70.

4. Rudnicki S, Chad DA, Drachman DA, Smith TW, Anwer UE, Levitan N. Motor neuron disease and paraproteinemia. Neurology. 1987;37:335–7.

5. Vincenzo S, Guglielmo S, Giorgio V. Plasma exchange ineffective in amyotriphic lateral sclerosis. Arch Neurol. 1980;37:511–3.

6. Monstad I, Dale I, Petlund CF, Sjaastad O. Plasma exchange in motor neuron disease. A controlled study. J Neurol. 1979;221:59–66.

8.14 | Worksheet 14

Diseases: ANCA-associated glomerulonephritis
Procedure: CAP
Purpose: Removal of activated leukocytes
Recommendation: 2B
Category: III
The number of references: RCT 1, CT 1, CS 1, CR 0

Description of the disease

Small-sized vasculitis that develops by a disease-specific antibody called antineutrophil cytoplasmic antibody (ANCA) without the involvement of immune complexes is collectively referred to as ANCA-associated vasculitis (AAV). AAV frequently affects renal vasculature, which is collectively referred to as ANCA-associated glomerulonephritis.

Current management/treatment

Corticosteroids, cyclophosphamide, azathioprine, and rituximab

Rationale for apheresis

Inflammatory cytokines may decrease by CAP.

Technical notes

Not covered by the insurance in Japan.

A clinical study demonstrated that a use of CAP may be similarly effective on renal survival as methylprednisolone pulse therapy. Steroid sparing effects by CAP may lessen the incidence of infectious diseases.

Duration and discontinuation/number of procedures

LCAP (with Cellsorba, 4–10 times)
GMA (with Adacolumn, 5–10 times)

References

1. Hasegawa M, Watanabe A, Takahashi H, Takahashi K, Kasugai M, Kawamura N, et al. Treatment with cytapheresis for antineutrophil cytoplasmic antibody-associated renal vasculitis and its effect on anti-inflammatory factors. Ther Apher Dial. 2005;9:297–302.

2. Hasegawa M, Kawamura N, Kasugai M, Koide S, Murase M, Asano S, et al. Cytapheresis for the treatment of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis: report of five cases. Ther Apher. 2002;6:443–9.

3. Furuta T, Hotta O, Yusa N, Horigome I, Chiba S, Taguma Y. Lymphocytapheresis to treat rapidly progressive glomerulonephritis: a randomised comparison with steroid-pulse treatment. Lancet. 1998;352:203–4.

8.15 | Worksheet 15

Diseases: ANCA-associated glomerulonephritis

Procedure: DFPP

Purpose: Removal of antibodies

Recommendation: 2C (for ANCA-associated glomerulonephritis complicated with severe renal impairment)

Category: III

The number of references: RCT 0, CT 0, CS 1, CR 3

Description of the disease

Small-sized vasculitis that develops by a disease-specific antibody called antineutrophil cytoplasmic antibody (ANCA) without the involvement of immune complexes is collectively referred to as ANCA-associated vasculitis (AAV). AAV frequently affects renal vasculature, which is collectively referred to as ANCA-associated glomerulonephritis.

Current management/treatment

Corticosteroids, cyclophosphamide, azathioprine, and rituximab

Rationale for apheresis

ANCA, the pathogenic antibody, can be removed by DFPP.

Technical notes

Covered by insurance since April 2018. DFPP can be implemented up to seven times in a single course (up to 2 weeks), with up to two courses in a series, for ANCA-positive patients with rapidly progressive glomerulonephritis (RPGN).

DFPP should be considered for ANCA-associated glomerulonephritis especially with a severe renal impairment (serum Cr > 5.8 mg/dl) at the time of diagnosis or dialysis-dependent to improve renal survival.

Duration and discontinuation/number of procedures

Number of implementations: seven times in 14 days

Processed plasma volume: 60 ml/kg

Replacement fluid: albumin solution

References

1. Chen Y, Yang L, Li K, Liu Z, Gong D, Zhang H, et al. Double filtration plasmapheresis in the treatment of antineutrophil cytoplasmic autoantibody associated vasculitis with severe renal failure: a preliminary study of 15 patients. Ther Apher Dial. 2016;20:183–8.

2. Iwatani H, Uzu T, Kakihara M, Nakayama Y, Kanasaki K, Yamato M, et al. A case of Wegener's granulomatosis with pulmonary bleeding successfully treated with double filtration plasmapheresis (DFPP). Clin Exp Nephrol. 2004;8:369–74.

3. Yorioka N, Taniguchi Y, Amimoto D, Katsutani M, Kumagai J, Yamakido M. Plasmapheresis for removal of myeloperoxidase antineutrophil cytoplasmic antibodies: a case report. Ther Apher. 1998;2:314–6.

4. Omote A, Muramatsu M, Sugimoto Y, Hosono S, Murakami R, Tanaka H, et al. Myeloperoxidase-specific anti-neutrophil cytoplasmic autoantibodies – related scleroderma renal crisis treated with double-filtration plasmapheresis. Intern Med. 1997;36:508–13.

8.16 | Worksheet 16

Diseases: ANCA-associated glomerulonephritis

Procedure: PE

Purpose: Removal of antibodies, etc.

Recommendation: 1B (for ANCA-associated glomerulonephritis complicated with severe renal impairment)

Category: II

The number of references: RCT 7, CT 8, CS 54, CR 73

Description of the disease

Small-sized vasculitis that develops by a disease-specific antibody called antineutrophil cytoplasmic antibody (ANCA) without the involvement of immune complexes is collectively referred to as ANCA-associated vasculitis (AAV). AAV frequently affects renal vasculature, which is collectively referred to as ANCA-associated glomerulonephritis.

Current management/treatment

Corticosteroids, cyclophosphamide, azathioprine, and rituximab

Rationale for apheresis

ANCA, the pathogenic antibody, can be removed by PE.

Technical notes

Covered by insurance since April 2018. PE can be implemented up to seven times in a single course (up to 2 weeks), with up to two courses in a series, for ANCA-positive patients with rapidly progressive glomerulonephritis (RPGN).

PE should be considered for ANCA-associated glomerulonephritis especially with a severe renal impairment (serum Cr > 5.8 mg/dl) at the time of diagnosis or dialysis-dependent to improve renal survival.

Duration and discontinuation/number of procedures

Number of implementations: seven times in 14 days

Processed plasma volume: 60 ml/kg

Replacement fluid: 5% albumin solution

References

1. Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. Cochrane Database Syst Rev. 2015;24:CD003232. (レベル1)

2. Walsh M, Catapano F, Szpirt W, Thorlund K, Bruchfeld A, Guillevin L, et al. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. Am J Kidney Dis. 2011;57:566–74.

3. Walsh M, Casian A, Flossmann O, Westman K, Höglund P, Pusey C, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int. 2013;84:397–402.

4. Szpirt WM, Heaf JG, Petersen J. Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis—a clinical randomized controlled trial. Nephrol Dial Transplant. 2011;26:206–13.

5. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol. 2007;18:2180–8.

6. Cole E, Cattran D, Magil A, Greenwood C, Churchill D, Sutton D, et al. A prospective randomized trial of plasma exchange as additive therapy in idiopathic crescentic glomerulonephritis. The Canadian Apheresis Study Group. Am J Kidney Dis. 1992;20:261–9.

7. Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int. 1991;40:757–63.

8. Glöckner WM, Sieberth HG, Wichmann HE, Backes E, Bambauer R, Boesken WH, et al. Plasma exchange and immunosuppression in rapidly progressive glomerulonephritis: a controlled, multi-center study. Clin Nephrol. 1988;29:1–8.

9. Rifle G, Chalopin JM, Zech P, Deteix P, Ducret F, Vialtel P, et al. Treatment of idiopathic acute crescentic glomerulonephritis by immunodepression and plasma-exchanges. A prospective randomised study. Proc Eur Dial Transplant Assoc. 1981;18:493–502.

8.17 | Worksheet 17

Diseases: Anti-GBM RPGN (dialysis-independent, dialysis-dependent, complicated with alveolar hemorrhage)

Procedure: DFPP

Purpose: Removal of antibodies

Recommendation: (1) Dialysis-independent (for renal survival) 2C; (2) Dialysis-dependent (for renal survival) 2C; (3) Alveolar hemorrhaging present (for patient survival) 2C

Definition of dialysis-dependent:

serum creatinine > 6 mg/dl + oliguria-anuria

Category: ① I; ② III; ③ I

The number of references: RCT 0, CT 1, CS 0, CR 4

Description of the disease

Anti-glomerular basement membrane (GBM) disease has a poor prognosis and causes rapid and severe organ damage to the kidneys (rapidly progressive glomerulonephritis [RPGN]) and lungs (alveolar hemorrhage). Goodpasture syndrome, which damages both the kidneys and lungs, is an autoimmune disease that develops when the α chain (almost the α3 chain) of the C terminal of the noncollagen region in Type IV collagen, a common antigen expressed on the basement membrane of the kidneys and lungs. The antigen is exposed to the immune system and autoantibodies (i.e., anti-GBM antibodies) are produced against it. The anti-GBM antibody induces inflammation by binding at the same site, rupturing the glomerular and lung basement membranes, and inducing rapidly progressive glomerulonephritis and alveolar hemorrhage.

Current management/treatment

Combined use of plasma exchange (PE) + corticosteroid + immunosuppressants (mainly cyclophosphamide)

Rationale for apheresis

Since the anti-GBM antibody, a pathogenic substance, is classified in the immunoglobulin G class, DFPP can efficiently remove the antibody. However, there is currently insufficient evidence about whether this improves patient survival or renal survival.

Technical notes

Start treatment as soon as possible in dialysis-independent cases since renal function at the start of treatment and the proportion of crescent formation affect prognosis. The possibility of the recovery of renal function significantly decreases by antibody removal once the patient reaches a dialysis-dependent state. Treatment should be started as soon as possible because alveolar hemorrhage can be fatal. Side effects of DFPP include hypotension, fever due to infection or an allergic reaction, hemorrhagic events due to a fibrinogen reduction, allergic reactions, muscle cramps, vascular access catheter-related complications (thrombosis and infection), and hemolysis.

Duration and discontinuation/number of procedures

Number of implementations: insurance coverage in Japan is 7 times during 14 days over two courses.

Implement as often as possible (every day to every other day) and aim to make an anti-GBM antibody negative.

Loss of coagulation factors such as fibrinogen is problematic in frequent procedures.

References

1. Zhang YY. Comparison of double filtration plasmapheresis with immunoadsorption therapy in patients with anti-glomerular basement membrane nephritis. BMC Nephrol. 2014 Aug 3;15:128. https://doi.org/10.1186/1471-2369-15-128

2. Iwamoto I. Case of anti-glomerular basement membrane antibody nephritis in a patient who was able to withdraw from dialysis and gave birth twice but underwent living renal transplantation due to progression to end-stage renal failure 15 years after onset. Nihon Jinzo Gakkai Shi. 2009;51(8):1080–5. [Japanese].

3. Nagasu H. A case report of efficiency of double filtration plasmapheresis in treatment of Goodpasture's syndrome. Ther Apher Dial. 2009 Aug;13(4):373–7. https://doi.org/10.1111/j.1744-9987.2009.00687.x

4. Takeda T. An experience of treatment of double positive myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) and anti-glomerular basement membrane antibodies in Goodpasture's syndrome onset of crescentic glomerulonephritis. Nihon Jinzo Gakkai Shi. 1998 Nov;40(8):591–6. [Japanese].

5. Kumazaki S. Double filtration plasmapheresis in case of Goodpasture's syndrome. Nihon Kyobu Shikkan Gakkai Zasshi. 1990 Apr;28(4):628–33. [Japanese].

8.18 | Worksheet 18

Diseases: Anti-GBM RPGN (IAPP) (dialysis-independent, dialysis-dependent, complicated with alveolar hemorrhage)

Procedure: IAPP

Purpose: Removal of antibodies, etc.

Recommendation: (1) Dialysis-independent (for renal survival) 2C; (2) Dialysis-dependent (for renal survival) 2C; (3) Alveolar hemorrhaging present (for patient survival) 2C

Definition of dialysis-dependent:

serum creatinine > 6 mg/dl + oliguria-anuria

Category: ① I; ② III; ③ I

The number of references: RCT 1, CT 1, CS 1, CR 5

Description of the disease

Anti-glomerular basement membrane (GBM) disease has a poor prognosis and causes rapid and severe organ damage to the kidneys (rapidly progressive glomerulonephritis [RPGN]) and lungs (alveolar hemorrhage). Goodpasture syndrome, which damages both the kidneys and lungs, is an autoimmune disease that develops when the α chain (almost the α3 chain) of the C terminal of the noncollagen region in Type IV collagen, a common antigen expressed on the basement membrane of the kidneys and lungs. The antigen is exposed to the immune system and autoantibodies (i.e., anti-GBM antibodies) are produced against it. The anti-GBM antibody induces inflammation by binding at the same site, rupturing the glomerular and lung basement membranes, and inducing rapidly progressive glomerulonephritis and alveolar hemorrhage.

Current management/treatment

Combined use of plasma exchange (PE) + corticosteroid + immunosuppressants (mainly cyclophosphamide)

Rationale for apheresis

Since the anti-GBM antibody, a pathogenic substance, is classified in the immunoglobulin G class, DFPP can efficiently remove the antibody. However, there is currently insufficient evidence about whether this improves patient surivival or renal survival.

Technical notes

Start treatment as soon as possible in dialysis-independent cases since renal function at the start of treatment and the proportion of crescent formation affect prognosis. The possibility of the recovery of renal function significantly decreases by antibody removal once the patient reaches a dialysis-dependent state. Treatment should be started as soon as possible when alveolar hemorrhage is observed because it can be fatal. Attentions should be paid to fibrinogen loss when the treatment is implemented frequently.

Duration and discontinuation/number of procedures

Number of implementations: (IAPP is not covered by insurance in Japan)

There have been cases reports and case series in Europe with a large amount of processed volume (2–3 PV) using proiein-A or anti-IgG antibody conjugated columns, which stringently absorbs IgG1, 2, and 4 than IgG3, and its antibody removal is greater than PEX. There are very few reports in Japan on commercially available adsorptive columns in which tryptophan/phenylalanine were used as a ligand. Reports have indicated that clinical outcomes were not different from those of DFPP even though adsorption characteristics (IgG3 and 1 are more efficiently absorbed than IgG2 and 4 by the columns available in Japan) and the limiation of processing plasma volume differ.

References

1. Stegmayr BG. Plasma exchange or immunoadsorption in patients with rapidly progressive crescentic glomerulonephritis. A Swedish multi-center study. Int J Artif Organs. 1999 Feb;22(2):81–7.

2. Laczika K. Immunoadsorption in Goodpasture's syndrome. Am J Kidney Dis. 2000 Aug;36(2):392–5.

3. Moreso F. Therapeutic immunoadsorption in Goodpasture disease. Med Clin. 1995 Jun 10; 105(2):59–61.

4. Esnault VL. Influence of immunoadsorption on the removal of immunoglobulin G autoantibodies in crescentic glomerulonephritis. Nephron. 1993;65(2):180–4.

5. Bygren P. Goodpasture's syndrome treated with staphylococcal protein A immunoadsorption. Lancet. 1985 Dec 7;2(8467):1295–6.

6. Biesenbach P. Long-term outcome of anti-glomerular basement membrane antibody disease treated with immunoadsorption. PLoS One. 2014 Jul 31;9(7): e103568.

8.19 | Worksheet 19

Diseases: Anti-GBM RPGN (PE) (dialysis-independent, dialysis-dependent, complicated with alveolar hemorrhage)

Procedure: PE

Purpose: Removal of antibodies, etc.

Recommendation: (1) Dialysis-independent (for renal survival) 1B; (2) Dialysis-dependent (for renal survival) 2B; (3) Alveolar hemorrhaging present (for patient survival) 1C

Definition of dialysis-dependent:

serum creatinine > 6 mg/dl + oliguria-anuria

Category: ① I; ② III; ③ I

The number of references: RCT 1, CT 1, CS 4, CR 190

Description of the disease

Anti-glomerular basement membrane (GBM) disease has a poor prognosis and causes rapid and severe organ damage to the kidneys (rapidly progressive glomerulonephritis [RPGN]) and lungs (alveolar hemorrhage). Goodpasture syndrome, which damages both the kidneys and lungs, is an autoimmune disease that develops when the α chain (almost the α3 chain) of the C terminal of the non-collagen region in Type IV collagen, a common antigen expressed on the basement membrane of the kidneys and lungs. The antigen is exposed to the immune system and autoantibodies (i.e., anti-GBM antibodies) are produced against it. The anti-GBM antibody induces inflammation by binding at the same site, rupturing the glomerular and lung basement membranes, and inducing rapidly progressive glomerulonephritis and alveolar hemorrhage.

Current management/treatment

Combined use of plasma exchange (PE) + corticosteroid + immunosuppressants (mainly cyclophosphamide)

Rationale for apheresis

Since the anti-GBM antibody, a pathogenic substance, is classified in the immunoglobulin G class, PE can efficiently remove the antibody. PE reportedly improves both patient and renal survival.

Technical notes

Start treatment as soon as possible in dialysis-independent cases since renal function at the start of treatment and the rate of crescent formation affect prognosis. The possibility of the recovery of renal function significantly decreases by antibody removal once the patient reaches a dialysis-dependent state. PE is useful for improving patient and renal survival in Goodpasture syndrome. Treatment should be started as soon as possible when alveolar hemorrhage is observed because it can be fatal.

Duration and discontinuation/number of procedures

Number of implementations: insurance coverage in Japan is 7 times during 14 days over two courses

Implement as often as possible (every day–every other day) and aim to make an anti-GBM antibody negative.

Plasma processing volume: 60 ml/kg or 1.0–1.5 PV

Replacement fluid: 5% albumin solution or FFP (consider using FFP if serious bleeding such as alveolar hemorrhaging is present)

References

1. Huart A. Outcomes of patients with Goodpasture syndrome: a nationwide cohort-based study from the French Society of Hemapheresis. J Autoimmun. 2016 Sep;73:24–9. https://doi.org/10.1016/j.jaut.2016.05.015

2. Cui Z. Anti-glomerular basement membrane disease: outcomes of different therapeutic regimens in a large single-center Chinese cohort study. Medicine. 2011 Sep;90 (5):303–11. https://doi.org/10.1097/MD.0b013e31822f6f68

3. Cui Z. Characteristics and prognosis of Chinese patients with anti-glomerular basement membrane disease .Nephron Clin Pract. 2005;99(2):c49–55.

4. Johnson JP. Therapy of anti-glomerular basement membrane antibody disease: analysis of prognostic significance of clinical, pathologic and treatment factors. Medicine. 1985 Jul;64(4):219–27.

5. Walker RG. Clinical and morphological aspects of the management of crescentic anti-glomerular basement membrane antibody (anti-GBM) nephritis/Goodpasture's syndrome. Q J Med. 1985 Jan;54(213):75–89.

6. Levy JB. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med. 2001 Jun 5;134(11):1033–42.

8.20 | Worksheet 20

Diseases: Anti-GBM RPGN
Procedure: CAP
Purpose: Removal of antibodies, etc.
Recommendation: No recommendation
Category: None
The number of references: RCT 0, CT 0, CS 0, CR 0

Description of the disease

Anti-glomerular basement membrane (GBM) disease has a poor prognosis and causes rapid and severe organ damage to the kidneys (rapidly progressive glomerulonephritis [RPGN]) and lungs (alveolar hemorrhage). Goodpasture syndrome, which damages both the kidneys and lungs, is an autoimmune disease that develops when the α chain (almost the α3 chain) of the C terminal of the noncollagen region in Type IV collagen, a common antigen expressed on the basement membrane of the kidneys and lungs. The antigen is exposed to the immune system and autoantibodies (i.e., anti-GBM antibodies) are produced against it.

Current management/treatment

Combined use of plasma exchange (PE) + corticosteroid + immunosuppressants (mainly cyclophosphamide)

Rationale for apheresis

Early removal of the anti-GBM antibodies is crucial because the severe damage progresses rapidly.

Technical notes

PE should be started as soon as possible for renal damage and alveolar hemorrhaging in patients independent of dialysis.

Duration and discontinuation/number of procedures

Number of implementations: (not covered by insurance in Japan)

No reports on the pathophysiology of anti-GBM RPGN.

References

8.21 | Worksheet 21

Diseases: Anti-VGKC antibody-related diseases

Procedure: PE、IAPP

Purpose: Control of disease activity and removal of autoantibodies

Recommendation: 2C

Category: II

The number of references: RCT 0, CT 1, CS 7, CR 31

Description of the disease

Anti-voltage-gated calcium channel (VGCC) antibody-related diseases are autoimmune diseases associated with anti-VGKC complex antibodies. This is a disease spectrum that includes acquired neuromyotonia (NMT, Isaacs' syndrome [IS]), antibody-mediated encephalitis (AME), and Morvan's syndrome (MVS). The anti-VGKC complex antibody is a general term for autoantibodies against each molecule that forms a complex with voltage-gated potassium channels (VGKC) expressed in the nervous system. The target antigens are contactin-associated protein (Caspr) 2 and leucine-rich glioma-activated protein (LGI)-1. Autoantibodies may also be associated with systemic neoplastic lesions.

Current management/treatment

Treatment of anti-VGKC antibody-related diseases involves immunotherapy including corticosteroids, IVIG, apheresis therapy (PE, IAPP), immunosuppressants, and rituximab. Among anti-VGKC antibody-related diseases, apheresis therapy is used as the first-line treatment in AME, and these are often combined with the use of corticosteroids. Meanwhile, corticosteroids and IVIG are used as the first-line treatment, and apheresis as the second-line treatment, in NMT/IS and MVS. Apheresis therapy may be used as maintenance therapy in the chronic phase.

Rationale for apheresis

Efficacy is often obtained not through plasmapheresis alone but through combination with other therapies such as corticosteroids and IVIG 7–9. However, it has been reported that a decreased antibody titer was associated with clinical therapeutic effects (7), and pathological conditions are improved by removing the anti-VGKC complex antibody, which is the pathogenic substance, by apheresis.

Technical notes

Attention should be given to hypotension and deep vein thrombosis when implementing apheresis. Coagulation factors such as serum immunoglobulin and fibrinogen decrease nonspecifically, so the implementation interval may need to be adjusted. Apheresis therapy for this disease is not covered by insurance.

Duration and discontinuation/number of procedures

The implementation conditions must be investigated on a case-by-case basis, but the following are set as guidelines. Acute treatment: 5–10 times over 7–14 days.

Chronic maintenance treatment: 10 times over 5 weeks, or once every 3 weeks to 3 months.

References

1. Watanabe O. Neuroimmunological diseases associated with VGKC complex antibodies. Nihon Rinsho 2016;71:915–20. [Japanese]

2. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice - evidence-based approach from the Writing Committee of the American Society for Apheresis: the eighth special issue. J Clin Apher. 2019;34:171–354.

3. Dubey D, Samudra N, Gupta P, Agostini M, Ding K, Van Ness PC, et al. Retrospective case series of the clinical features, management and outcomes of patients with autoimmune epilepsy. Seizure. 2015;29:143–7.

4. Heine J, Ly LT, Lieker I, Slowinski T, Finke C, Prüss H, et al. Immunoadsorption or plasma exchange in the treatment of autoimmune encephalitis: a pilot study. J Neurol. 2016;263:2395–2402.

5. Dogan-Onugoren M, Golombeck KS, Bien C, Abu-Tair M, Brand M, Bulla-Hellwig M, et al. Immunoasorption therapy in autoimmune encephalitis. Neurol Neuroimmunol Neuroinflamm. 2016;3:e207.

6. Irani SR, Gelfand JM, Bettcher BM, Singhal NS, Geschwind MD. Effect of rituximab in patients with leucine-rich, glioma- inactivated 1 antibodyassociated encephalopathy. JAMA Neurol. 2014;71:896–900.

7. Wong SH, Saunders MD, Larner AJ, Das K, Hart IK. An effective immunotherapy regimen for VGKC antibody positive limbic encephalitis. J Neurol Neurosurg Psychiatry. 2010;81:1167–9.

8. Vincent A, Buckley C, Schott JM, Baker I, Dewar B-K, Detert N, et al. Potassium channel antibodyassociated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain. 2004;127:701–12.

9. Jaben EA, Winters JL. Plasma exchange as a therapeutic option in patients with neurologic symptoms due to antibodies to voltage-gated potassium channels: a report of five cases and review of the literature. J Clin Apher. 2012;27:267–73.

8.22 | Worksheet 22

Diseases: Arteriosclerosis obliterans

Procedure: LDL-A

Purpose: Improvement in numbness, coldness, intermittent claudication, and promotion of ulcer healing by improvement of microcirculation

Recommendation: 1C

Category: II

The number of references: RCT 0, CT 0, CS 8, CR 0

Description of the disease

It is an ischemic condition in the muscle and skin caused by chronic arteriosclerotic stenosis or occlusion of the main artery branching from the aorta. It occurs most often in the lower limb arteries. Mild cases may involve coldness and intermittent claudication. Severe cases may involve lower limb ulcers and necrosis, and could require lower limb amputation. Risk factors are old age, smoking, diabetes, hypertension, dyslipidemia, and renal failure.

Current management/treatment

In addition to dietary habits correction, lifestyle improvements (e.g., smoking cessation, exercise), regulating diabetes/dyslipidemia/hypertension, prescription of antiplatelet drugs and peripheral vasodilators are required. Severe cases often require endovascular treatment and vascular bypass surgery. LDL-A is also performed.

Rationale for apheresis

Case series have shown that LDL-A improves symptoms such as coldness and dullness of the lower limbs, improves intermittent claudication, and reduces ulcers (References 1–8).

The mechanism of action is improvement of blood viscosity and vascular endothelial function, vasodilation, anti-inflammatory effect (e.g., leukocyte adhesion factor expression, cytokine production suppression), vascular growth factor production (e.g., HGF, VEGF), increased collateral circulation, and oxidative stress control.

Technical notes

LDL-A is performed on the LDL adsorption column after plasma separation using liposorber LA15 fixed with dextran sulfate as a ligand. Angiotensin-converting enzyme inhibitors are contraindicated as they suppress metabolic degradation of bradykinin and might possibly induce hypotension and shock during LDL-A. LDL-A also removes fibrinogen to some extent, so there may be chances of bleeding. LDL-A may also be conducted with DFPP.

Duration and discontinuation/number of procedures

The number of times LDL-A is to be implemented for arteriosclerosis obliterans is covered by insurance (up to 10 times per series in a 3-month period) and can be calculated. Outpatient treatment is also possible. LDL-A is conducted once or twice a week.

LDL-A should be suspended in cases where significant hypotension is observed or when bleeding occurs.

References

1. Agishi T, Kitano Y, Suzuki T, Miura A, Murakami J, Minagawa H, et al: Improvement of peripheral circulation by low density lipoprotein adsorption. ASAIO Trans. 1989;35:349–51.

2. Mii S, Mori A, Sakata H, Nakayama M, Tsuruta H. LDL apheresis for arteriosclerosis obliterans with occluded bypass graft: change in prostacyclin and effect on ischemic symptoms. Angiology. 1998;49:175–80.

3. Kobayashi S, Moriya H, Negishi K, Maesato K, Ohtake T. LDL-aphereis up-regulates VEGF and IGF-1 in patients with ischemic limb. J Clin Apher. 2003;18:115–9.

4. Kobayashi S, Moriya H, Maesato K, Okamoto K, Ohtake T. LDL-apheresis improves peripheral arteial occlusive disease with an implication for anti-inflammatory effects. J Clin Apher. 2005;20:239–43.

5. Kobayashi S, Oka M, Moriya H, Maesato K, Okamoto K, Ohtake T. LDL-apheresis reduces p-selectin, CRP and fibrinogen - possible important implications for improving atherosclerosis. Ther Apher Dial. 2006;10:219–223.

6. Hara T, Kiyomoto H, Hitomi H, Moriwaki K, Ihara G, Kaifu K, et al. Low-density lipoprotein apheresis for haemodialyis patients with peripheral arteial disease reduces reactive oxygen species production via suppression of NADPH oxidase gene expression in leucocytes. Nephrol Dial Transplant. 2009;24:3818–25.

7. Tamura K, Tsurumi-Ikeya Y, Wakui H, Maeda A, Ohsawa M, Azushima K, et al. Therapeutic potential of low-density lipoprotein apheresis in the management of peripheral artery disease in patients with chronic kidney disease. Ther Apher Dial. 2013;17:185–192.

8. Ohtake T, Mochida Y, Matsumi J, Tobita K, Ishioka K, Oka M, et al. Beneficial effect of endovascular therapy and low-density lipoprotein apheresis combined treatment in hemodialysis patients with critical limb ischemia due to below-knee arteial lesions. Ther Apher Dial. 2016;20:661–7.

8.23 | Worksheet 23

Diseases: Ascites

Procedure: CART

Purpose: Improvement of fullness/symptoms, improvement of diuretic resistance

Recommendation: IC

Category: II

The number of references: RCT 0, CT 0, CS 19, CR 1

Description of the disease

There are various diseases resulting in ascites, of which cirrhosis is one of the main causes. Refractory ascites in particular has various complications such as diluted hyponatremia, hepatorenal syndrome, and spontaneous bacterial peritonitis. Prognosis is poor and the focus of treatment is essentially symptom relief. The first treatment to be developed was large volume paracentesis (LVP). However, it became evident that this was associated with risks of rapid ascites re-accumulation, hyponatremia, and renal damage due to paracentesis-induced circulatory dysfunction (PICD). It was considered that albumin administration might be effective as a volume expander, but it has been ineffectual thus far. Hence, cell-free and concentrated ascites reinfusion therapy has been developed.

Current management/treatment

Treatments for refractory ascites include LVP + albumin replenishment, peritoneovenous shunts (Denver shunt), transjugular intrahepatic portosystemic shunts (TIPS), and cell-free and concentrated ascites reinfusion therapy (CART).

Rationale for apheresis

Albumin replenishment is needed when protein is lost due to frequent ascites punctures. CART collects a large volume of ascites and passes it through two filters. First, cells and hemocytes are removed with a permeable filter. Next, the ascites is concentrated approximately 10 times by means of a concentration filter. Ascites with the patient's own albumin (molecular weight of 68 000) and globulin (molecular weight of 160 000) is then reinfused in order to prevent protein loss, and alleviate symptoms.

Technical notes

The upper and lower abdominal wall arteries and swelling blood vessels of the abdominal wall that run in the rectus abdominis muscle must be avoided when performing an abdominal puncture. For the puncture, prepare an 8Fr. Argyle Trocar Aspiration Kit, avoid blood vessels using ultrasound, puncture at a 45° angle using the Z-tracking method to avoid leakage, and collect as much ascites as possible. The ascites retrieval rate should be 1000–2000 ml/h. The concentrated ascites processing rate should be less than 3000 ml/h, and the reinfusion rate should be 100–150 ml/h. Attention should be paid to vital signs simultaneously. Slight decreases in blood pressure may occur during drainage, and increases in body temperature may occur during reinfusion. Infusions and antipyretic drugs should be administered as needed.

Duration and discontinuation/number of procedures

Insurance covers one session of CART every 2 weeks. Treatment should be completed if the general condition of the patient improves, and further ascites control can be accomplished with usual treatments such as drug therapy. Suspend treatment if the total bilirubin is over 5 mg/dl, bleeding tendencies are present, bacterial peritonitis emerges, or the ascites cannot be drained due to a deteriorating general condition.

References

1. Japanese CSG, Matsusaki K, Ohta K, et al. Novel cell-free and concentrated ascites reinfusion therapy (KM-CART) for refractory ascites associated with cancerous peritonitis: its effect and future perspectives. Int J Clin Oncol. 2011;16:395–400.

2. Orimi S, Mizuno K, Narahara M, et al. A study of appropriate flow rate settings for cell-free and concentrated ascites reinfusion therapy and change of cytokine concentrations in ascites. Ther Apher Dial. 2011;15:411–4.

3. Maeda A, Takeda K, Tsuruya K, et al. A case of cell-free and concentrated ascites reinfusion therapy effective for refractory ascites in spontaneous bacterial peritonitis in a renal transplant patient. Case Rep Nephrol Urol. 2012;2:138–44.

4. Ueda T, Maehara M, Takahashi Y, et al. Clinical significance of cell-free and concentrated ascites reinfusion therapy for advanced and recurrent gynecological cancer. Anticancer Res. 2012;32:2353–7.

5. Takahashi H, Sakai R, Fujita A, et al. Concentrated ascites reinfusion therapy for sinusoidal obstructive syndrome after hematopoietic stem cell transplantation. Artif Organs. 2013;37:932–6.

6. Ito T, Hanafusa N, Fukui M, et al. Single center experience of cell-free and concentrated ascites reinfusion therapy in malignancy related ascites. Ther Apher Dial. 2014;18:87–92.

7. Maeda O, Ando T, Ishiguro K, et al. Safety of repeated cell-free and concentrated ascites reinfusion therapy for malignant ascites from gastrointestinal cancer. Mol Clin Oncol. 2014;2:1103–6.

8. Togami S, Hori S, Kamio M, et al. Clinical usefulness of concentrated ascites reinfusion therapy (CART) for gynecological cancer patients with refractory massive ascites due to cancerous peritonitis. Eur J Gynaecol Oncol. 2014;35:301–3.

9. Ito T, Hanafusa N, Iwase S, et al. Effects of cell-free and concentrated ascites reinfusion therapy (CART) on symptom relief of malignancy-related ascites. Int J Clin Oncol. 2015;20:623–8.

10. Maeda S, Yabuuchi J, Nobuta H, et al. Characteristics of patients and their ascites who underwent repeated cell-free and concentrated ascites reinfusion therapy. Ther Apher Dial. 2015;19:342–8.

11. Wang L, Okubo T, Shinsaka M, et al. Efficacy and safety of cell-free and concentrated ascites reinfusion therapy (CART) in gynecologic cancer patients with a large volume of ascites. J Obstet Gynaecol Res. 2015;41:1614–20.

12. Yamaguchi H, Kitayama J, Emoto S, et al. Cell-free and concentrated ascites reinfusion therapy (CART) for management of massive malignant ascites in gastric cancer patients with peritoneal metastasis treated with intravenous and intraperitoneal paclitaxel with oral S-1. Eur J Surg Oncol. 2015;41:875–80.

13. Kozaki K, Illnuma M, Takagi T, et al. Cell-free and concentrated ascites reinfusion therapy for decompensated liver cirrhosis. Ther Apher Dial. 2016;20:376–82.

14. Matsusaki K. A new treatment strategy-novel cell-free and concentrated ascites reinfusion system (KM-CART) for massive malignant ascites. Gan To Kagaku Ryoho. 2016;43:2490–7.

15. Hanafusa N, Isoai A, Ishihara T, et al. Safety and efficacy of cell-free and concentrated ascites reinfusion therapy (CART) in refractory ascites: post-marketing surveillance results. PLoS One. 2017;12:e0177303.

16. Hisakane K, Ohmatsu H, Umemura S, et al. Efficacy of cell-free and concentrated ascites reinfusion therapy for palliative care in a patient with malignant pleural mesothelioma: a case report. J Nippon Med Sch. 2017;84:231–6.

17. Ito T, Hanafusa N. CART: cell-free and concentrated ascites reinfusion therapy against malignancy-related ascites. Transfus Apher Sci. 2017;56:703–7.

18. Ogasawara M, Miyashita M, Iida M, et al. Immunological analysis and generation of dendritic cells from lavage fluid obtained by cell-free and concentrated ascites reinfusion therapy. Ther Apher Dial. 2017;21:255–62.

19. Yamada Y, Yamaguchi A, Harada M, et al. Protein concentration of refractory ascites in cancer patients is reflected by the presence and severity of peritoneal and liver metastasis. Ther Apher Dial. 2017;21:263–9.

20. Hanada R, Yokomichi N, Kato C, et al. Efficacy and safety of reinfusion of concentrated ascitic fluid for malignant ascites: a concept-proof study. Support Care Cancer. 2018;26:1489–97.

8.24 | Worksheet 24

Diseases: Autoimmune antonomic ganglionopathy
Procedure: PE
Purpose: Removal of autoantibodies
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 0, CR 19

Description of the disease

Autoimmune autonomic ganglionopathy (AAG) is a primary autonomic neuropathy. The signs and symptoms of this condition include autonomic symptoms such as orthostatic hypotension, sweating disorders, dysuria, and constipation. Some cases of postural orthostatic tachycardia syndrome (POTS) are attributed to this syndrome. Its pathophysiology is presumed to involve an autoimmune mechanism that works through anti-ganglionic acetylcholine receptor (gAChR) antibodies against the gAChR in the autonomic ganglion.

Current management/treatment

There is no consensus on the course of treatment; however, intraveneous immunoglobluin therapy, apheresis therapy, and steroid pulse therapy are used as first-line treatments. Rituximab and mycophenolate mofetil have been reported to be effective as second-line treatments when first-line treatments are ineffective. Combined therapy may also be effective when first-line treatment is not effective.

Rationale for apheresis

Apheresis has been reported to be effective. More widespread and severe autonomic neuropathy tend to be exhibited in cases with higher antibody titers of the anti-gAChR antibody, and transitions in the antibody titer are correlated with clinical symptoms. Case reports have indicated that PE results in improved autonomic symptoms, such as improvement in the extent of orthostatic hypotension and abdominal pain, and significantly reduces the antibody titer. Therefore, apheresis is thought to be effective due to its ability to reduce the antibody titer.

Technical notes

Beaware of fluctuations in circulatory dynamics of blood pressure and heart rate due to autonomic neuropathy. Apheresis therapy for this disease is not covered by insurance.

Duration and discontinuation/number of procedures

Aim for 3–4 times a week while observing the clinical course of each individual case.

References

1. Vernino S, Adamski J, Kryzer TJ, et al. Neuronal nicotinic ACh receptor antibody in subacute autonomic neuropathy and cancer-related syndromes. Neurology 1998;50:1806–13.

2. Vernino S, Low PA, Fealey RD, et al. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med. 2000;343:847–55.

3. Iodice V, Kimpinski K, Vernino S, et al. Efficacy of immunotherapy in seropositive and seronegative putative autoimmune autonomic ganglionopathy. Neurology. 2009;72:2002–8.

4. Iodice V, Sandroni P. Autonomic neuropathies. Continuum. 2004;20:1373–97.

5. Schroeder C, Vernino S, Birkenfeld AL, et al. Plasma exchange for primary autoimmune autonomic failure. N Engl J Med. 2005;353:1585–90.

6. Imrich R, Vernino S, Eldadah BA, et al. Autoimmune autonomic ganglionopathy: treatment by plasma exchanges and rituximab. Clin Auton Res. 2009;19:259–62.

7. Gibbons CH, Vernino SA, Freeman R. Combined immunomodulatory therapy in autoimmune autonomic ganglionopathy. Arch Neurol. 2008;65:213–7.

8. Iodice V, Kimpinski K, Vernino S, et al. Immunotherapy for autoimmune autonomic ganglionopathy. Auton Neurosci. 2009;146:22–5.

9. Bouxin M, Schvartz B, Mestrallet S, et al. Rituximab treatment in seronegative autoimmune autonomic neuropathy and autoimmune autonomic ganglionopathy: case-report and literature review. J Neuroimmunol. 2019;326:28–32.

10. Gupta A, Harris S, Vernino S, et al. Rituximab-based therapy and long-term control of autoimmune autonomic ganglionopathy. Clin Auton Res. 2015;25:255–8.

11. Hollenbeck R, Black BK, Peltier AC, et al. Long-term treatment with rituximab of autoimmune autonomic ganglionopathy in a patient with lymphoma. Arch Neurol. 2011;68:372–5.

12. Benizri S, Agmon-Levin N, Kitrey ND, et al. Clinical problem solving: a tobacco merchant who can't spit. Isr Med Assoc J. 2017;19:786–91.

13. Dumitrascu OM, McKeon A, Zuniga L, et al. Opsoclonus-myoclonus syndrome during rituximab treatment for autoimmune autonomic ganglionopathy. Neurol Neuroimmunol Neuroinflamm. 2017;4:e376.

14. Gibbons CH, Vernino SA, Freeman R. Combined immunomodulatory therapy in autoimmune autonomic ganglionopathy. Arch Neurol. 2008;65:213–7.

15. Iodice V, Kimpinski K, Vernino S, et al. Immunotherapy for autoimmune autonomic ganglionopathy. Auton Neurosci. 2009;146:22–5.

16. Klein CM, Vernino S, Lennon VA, et al. The spectrum of autoimmune autonomic neuropathies. Ann Neurol. 2003;53:752–8.

17. Sandroni P, Vernino S, Klein CM, et al. Idiopathic autonomic neuropathy: comparison of cases seropositive and seronegative for ganglionic acetylcholine receptor antibody. Arch Neurol. 2004;61:44–8.

8.25 | Worksheet 25

Diseases: Autoimmune encephalitis/cerebellitis LGI1/Caspr2/GABAbR/AMPAR/GAD/GlyR/NAE

Procedure: PE, IAPP, and CAP

Purpose: Introduction and maintenance of remission

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 1, CR 6

Description of the disease

It is a type of encephalitis resulting from an autoimmune mechanism. Its characteristics differ with the target antigen. The anti-leucine-rich glioma-inactivated 1 (LGI1) antibody presents with limbic encephalitis, is commonly among the elderly, and causes complications of SIADH and thymoma. The anti-Caspr2 antibody is known as Isaacs' or Morvan's syndrome and causes the complication of thymoma. The anti-gamma aminobutyrate B receptor (GABAbR) antibody often exhibits limbic encephalitis with severe convulsions and causes the complication of small cell lung cancer. The anti-α-amino-3 -hydroxy-5-methylisoxazole-4-propionate receptor (AMPAR) antibody presents with limbic encephalitis with psychiatric symptoms and dementia and causes complications such as lung cancer, breast cancer, and thymoma. The anti-glycine receptor (GlyR) antibody causes Stiff-person syndrome and the complication of Hodgkin's disease. The anti-glutamic acid decarboxylase (GAD) antibody is common among women and manifests as cerebellar degeneration and Stiff-person syndrome. The antiNH2–terminal of alpha-enolase (NAE) antibody causes Hashimoto's encephalopathy associated with chronic thyroiditis.

Current management/treatment

The symptomatic treatment for psychiatric symptoms, convulsions, impaired consciousness, and involuntary movements, as well as treatment for causative autoantibodies are conducted. Antigens in this section are those associated with the nerve cell surface or intracellular synapses. They are rarely paraneoplastic, but tumors should be looked for. This is often responsive to immunotherapies, such as steroid pulse, IVIG, and apheresis; therefore, immunotherapy should be conducted if there are no tumors.

Rationale for apheresis

The literature includes only case reports, but it is thought that these autoantibodies (LGI1/Caspr2/GABAbR/AMPAR/GAD/GlyR/NAE) are involved in the pathophysiology of encephalitis; therefore, apheresis is expected to have therapeutic effects.

Technical notes

No case reports have shown the effectiveness of IAPP or CAP. However, PE, from which the greatest therapeutic effects can be expected, is ideal.

Duration and discontinuation/number of procedures

It is not covered by insurance. Previous reports involved four or six sessions of PE over 2 weeks.

References

1. Lancaster E. Paraneoplastic disorders. Continuum. 2015;21:452–75.

2. Dalmau J, Rosenfeld MR. Autoimmune encephalitis update. Neuro Oncol. 2014;16:771–8.

3. Dalmau J, Lancaster E, Martinez-Hernandez E, et al: Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10:63–74.

4. Vincent A, Bien CG, Irani SR, Waters P: Autoantibodies associated with diseases of the CNS:new developrnents and future challenges. Lancet Neurol. 2011;10:759–72.

5. Lancaster E, Huijbers MG, Bar V, et al: Investigations of Caspr2, an-autoantigen of encephalitis and neuromyotorlia. Ann Neurol. 2011;69:303–11.

6. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009;65:424–34.

7. Lai M, Huijbers MGM, Lancaster E, et al: Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010;9:776–85.

8. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008;71:1291–2.

9. Saiz A, Blanco Y, Sabater L, et al: Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain. 2008;131:2553–63.

8.26 | Worksheet 26

Diseases: Bickerstaff brainstem encephalitis
Procedure: PE, IAPP
Purpose: Removal of autoantibodies
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 0, CR 9

Description of the disease

Bickerstaff brainstem encephalitis (BBE) is an autoimmune disease characterized by the following three main symptoms: ocular motility disorder, ataxia, and impaired consciousness. A total of 75% of cases test positive for anti-GQ1b antibodies, and this is considered to be associated with Fisher syndrome.

Current management/treatment

There are no fixed guidelines for BBE treatment. Studies have indicated the effectiveness of apheresis therapy and immunotherapy. A study of the treatment in 62 cases of BBE conducted in Japan showed the following breakdown of acute treatment: combined corticosteroid and apheresis therapy, 26%; only apheresis therapy, 23%; only corticosteroids, 21%; combined corticosteroid and intravenous immunoglobulin (IVIG) therapy, 8%; combined therapy with IVIG after administration of corticosteroid + apheresis therapy, 5%; IVIG after apheresis therapy, 3%; only IVIG, 3%; and no immunotherapy, 11%.

Rationale for apheresis

There have been reports of BBE cases that were resistant to immunotherapy and corticosteroid therapy in which apheresis therapy was effective and neurological symptoms completely disappeared. It is presumed that the anti-GQ1b antibody, which is an anti-ganglioside antibody, is associated with the pathophysiology of BBE and removal of autoantibodies.

Technical notes

The disease presents with serious signs and symptoms such as impaired consciousness, pharyngeal muscle paralysis, limb weakness, and autonomic neuropathy. It requires systemic management (e.g., ventilator attachment and hemodynamics). Attention should be paid to changes in hemodynamics during apheresis therapy. Apheresis therapy for this disease is not covered by insurance.

Duration and discontinuation/number of procedures

This treatment is not covered by insurance. Aim for 3–4 times a week while observing the clinical course. Pay attention to decreases in the levels of coagulation factor (including fibrinogen).

References

1. Bickerstaff ER. Brain-stem encephalitis; further observations on a grave syndrome with benign prognosis. Br Med J. 1957;1(5032):1384–7.

2. Susuki K, Yuki N, Hirata K. Fine specificity of anti-GQ1b IgG and clinical features. J Neurol Sci. 2001;185:5–9.

3. Shimokawa M, Shinoda T, Takahashi M, Watabiki S. Successful plasmapheresis in the not-so-benign Bickerstaff's brain stem encephalitis associated with anti-GQ1b antibody. Ther Apher. 1998;2:240–2.

4. Koga M, Kusunoki S, Kaida K, et al. Nationwide survey of patients in Japan with Bickerstaff brainstem encephalitis: epidemiological and clinical characteristics. J Neurol Neurosurg Psychiatry. 2012;83:1210–5.

8.27 | Worksheet 27

Diseases: Blood type incompatible pregnancy
Procedure: PE, IAPP, DFPP
Purpose: Removal of anti-red blood cell antibodies
Recommendation: 2C
Category: II
The number of references: RCT 0, CT 0, CS 13, CR 27

Description of the disease

Blood type incompatible pregnancy is a pathological condition where IgG antibodies develop against the baby's red blood cells in the mother's blood for some reason when there is a blood type incompatibility between the mother and child, this causes hemolysis of the baby's red blood cells via placental exchange often resulting in heart failure due to fetal anemia and hydrops fetalis.

Current management/treatment

Hydrops fetalis due to fetal anemia is at the core of these poor outcomes making the improvement of the baby's anemia the most critical component in treatment. To this end this baby's can be treated with an intrauterine fetal transfusion after 18–20 weeks. Apheresis is used to remove the maternal antibodies, and high-dose immunoglobulin preparations can reduce antibody transfer in cases of 18–20 weeks or if there are procedural difficulties. The progress of the anemia is determined by monitoring the peak systolic velocity (PSV) of the middle cerebral artery (MCA) using ultrasonic Doppler.

Rationale for apheresis

Hemolytic anemia occurs when IgG antibodies against fetal erythrocytes flow from maternal blood through the placenta. This is treatment aimed at reducing the amount of antibodies flowing into the fetal side by removing IgG on the maternal side with various types of apheresis. There are some reports indicating that PE alone could manage pregnancies with a history of fetal death.

Technical notes

There is no issue with selecting albumin preparations as a replacement solution for PE. The volume per session is 1–1.5 times the circulating plasma volume and the time to start treatment is determined by referring to the previous medical history. However, removal efficiency is decreased when using DFPP, but this can be implemented while observing the antibody titer. There have been reports of immunoadsorption using erythrocytes as an adsorbent, but this is not currently part of the standard practice.

Duration and discontinuation/number of procedures

Usually conducted until 18–20 weeks of gestation, when intrauterine fetal transfusion is possible. Plasmapheresis is applied 2–3 times a week according to the maternal antibody titer. Once the antibody titer has been sufficiently decreased, high doses of immunoglobulin preparations can be combined with these treatments in order to control the transfer of antibodies to the fetus but these interventions are not covered by insurance in Japan.

References

1. Ruma MS, Moise KJ, Kim E, et al. Combined plasmapheresis and intravenous immune globulin for the treatment of severe maternal red cell alloimmunization. Am J Obstet Gynecol. 2007;196:138.e1–6.

2. Mari G, Deter RL, Carpenter RL, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative group for Doppler assessment of the blood velocity in anemic fetuses. N Engl J Med. 2000;342:9–14.

3. Angela E, RobinsonE, Tovey LA. Intensive plasma exchange in the management of severe Rh disease. Br J Haematol. 1980;45:621–31.

4. Graham-Pole J, Barr W, Willoughby ML. Continuous-flow plasmapheresis in management of severe rhesus disease. Br Med J. 1977;1:1185–8.

5. Fraser ID, Bothamley JE, Bennet MO, et al. Intensive antenatal plasmapheresis in severe rhesus isoimmunization. Lancet. 1976;1:6–8.

8.28 | Worksheet 28

Diseases: Buerger's disease
Procedure: LDL-A
Purpose: Improvements in peripheral circulation
Recommendation: Grade 1C
Category: II
The number of references: RCT 0, CT 1, CS 7, CR 1

Description of the disease

It is one of chronic obstructive arterial diseases that most often occurs in young male smokers. Unlike atherosclerosis, it segmentally generates transmural thromboangiitis obliterans in the peripheral arteries of the extremities, causing intermittent claudication, resting pain, and ulcers/gangrene of toe and finger as ischemic symptoms. Thrombophlebitis (migratory phlebitis) also occurs in superficial veins. Contributions by abnormal autoimmune response and periodontal disease bacteria have also been indicated, but the causes are still unknown. There is a strong association with smoking, and vascular spasms are considered to be a trigger for onset.

Current management/treatment

Strict adherence to the cessation of smoking (including avoidance of second-hand smoke), heat retention/protection of affected limbs, and walking training/exercise therapy are required. Drug therapies involve platelet drugs or anticoagulants and intravenous administration of prostaglandin E1 preparations. Revascularization may be considered in severely ill patients, and sympathectomies may be performed. Angiogenesis therapy through bone marrow and peripheral blood stem cell transplantation is effective, and LDL-A is also performed according to arteriosclerosis obliterans (ASO) (neither is covered by insurance).

Rationale for apheresis

The effectiveness of LDL-A in chronic obstructive arterial diseases (including this disease) has been confirmed, but there are no reports that have compared and evaluated usefulness in this disease alone. The confirmed mechanisms of action include improved blood viscosity and vascular endothelial function, vasodilatory action, anti-inflammatory actions (e.g., leukocyte adhesion factor expression and cytokine production suppression), vascular growth factor production (e.g., HGF and VEGF), increased collateral blood circulation, and oxidative stress control.

Technical notes

Implementation should be undertaken according to LDL-A for ASO. Administration of angiotensin-converting enzyme inhibitors when conducting LDL-A using liposorber LA15 may result in hypotension or shock. LDL-A also removes fibrinogen to some extent, so attention should be paid to bleeding. It may also be conducted with DFPP.

Duration and discontinuation/number of procedures

Implementation should be undertaken according to LDL-A for ASO and conducted at one to two times per week, aiming for 10 times in total.

Use must be suspended when significant hypotension is observed or bleeding tendencies appear.

References

1. Kim DI, Kim MJ, Joh JH, et al. Angiogenesis facilitated by autologous whole bone marrow stem cell transplantation for Buerger's disease. Stem Cells. 2006;24:1194–200.

2. Boda Z, Udvardy M, Rázsó K, et al. Stem cell therapy: a promising and prospective approach in the treatment of patients with severe Buerger's disease. Clin Appl Thromb Hemost. 2009;15;552–60.

3. Heo SH, Park YS, Kang ES, et al. Early results of clinical application of autologous whole bone marrow stem cell transplantation for critical limb ischemia with Buerger's disease. Sci Rep. 2016;6:19690.

4. Moriya J, Minamino T, Tateno K, et al. Long-term outcome of therapeutic neovascularization using peripheral blood mononuclear cells for limb ischemia. Circ Cardiovasc Interv. 2009;2:245–54.

8.29 | Worksheet 29

Diseases: Calciphylaxis

Procedure: LDL-A, PE, cryofiltration

Purpose: Improvement of skin ulcers/pain associated with calciphylaxis

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 0, CR 4

Description of the disease

This intractable disease occurs mainly in chronic dialysis patients who, as a consequence, present with multiple painful skin ulcers. It is thought to be caused by the calcification of cutaneous arterioles and is often accompanied by painful purpura around the ulcer.

Current management/treatment

Surgical resection of necrotic tissue, calcium and phosphorus control, treatment of secondary hyperparathyroidism, sodium thiosulfate administration, and hyperbaric oxygen therapy have been conducted. However, there is currently no established effective treatment.

Rationale for apheresis

There are only a few case reports on apheresis treatment for calciphylaxis. There has been one case each of effective and noneffective use of LDL-A, one case of effective use of PE, and one case of effective use of cryofiltration.

Technical notes

Angiotensin-converting enzyme inhibitors are contraindicated when using LDL-A with liposorbers since they suppress metabolic degradation of bradykinin and may possibly induce hypotension and shock during apheresis treatment. It has also been reported that cryofiltration is effective for 7 consecutive days, with a total of 18 sessions in a single month.

Duration and discontinuation/number of procedures

There is currently no insured coverage. LDL-A is used with liposorber LA15 once or twice a week, with a total of 10–12 courses. The amount of plasma processed per course is 50–60 ml/kg of body weight.

References

1. Iwagami M, Mochida Y, Ishioka K, et al. LDL-apheresis dramatically improves generalized calciphylaxis in a patient undergoing hemodialysis. Clin Nephrol. 2014;8(3):198–202.

2. Shinozaki Y, Furuichi K, Sagara A, et al. Calciphylaxis induced by warfarin therapy in a patient with anti-phospholipid antibody syndrome associated with systemic lupus erythematosus. CEN Case Rep. 2015;4(2):169–73.

3. Cai MM, Smith ER, Brumby C, et al. Fetuin-A-containing calciprotein particle levels can be reduced by dialysis, sodium thiosulphate and plasma exchange. Potential therapeutic implications for calciphylaxis? Nephrology. 2013;18(11):724–7.

4. Siami GA, Siami FS. Intensive tandem cryofiltration apheresis and hemodialysis to treat a patient with severe calciphylaxis, cryoglobulinemia, and end-stage renal disease. ASAIO J. 1999;45(3):229–33.

8.30 | Worksheet 30

Diseases: Cholesterol crystal embolism
Procedure: LDL-A
Purpose: To improve renal function
Recommendation: 2C
Category: II or III
The number of references: RCT 0, CT 0, CS 3, CR 0

Description of the disease

This disease is caused by the obstruction of small blood vessels throughout the body due to the cholesterin crystals sprinkled from plaques on the walls of the large blood vessels. One type presents with relatively localized organ damage (e.g., on the skin, kidneys, or fundus) and the other presents with extensive organ damage (e.g., brain, abdominal organs such as the gastrointesitinal tract, lungs, and limbs). It often occurs after invasive intravascular procedures, but it can be idiopathic without any prior factors. The mode of onset ranges from acute to subacute to chronic, which can affect patient survival depending on the extent of organ damage.

Current management/treatment

A small dose of oral steroids (<0.3–0.4 mg/kg) is used for its anti-inflammatory effects. Statins are also used for plaque stabilization.

Rationale for apheresis

Results of a retrospective study conducted in Japan reported that the monthly rate of estimated glomerular filtration rate (eGFR) decline by low-density lipoprotein apheresis (LDL-A) dropped from 7.2 ± 2.5 ml/min/1.73 m^2 to 0.3 ± 0.7 ml/min/1.73 m^2, and renal function impairment was stabilized. Additionally, a study demonstrated that the dialysis incidence was significantly lower in the LDL-A group than the control group (8% vs. 33%, $p = 0.037$), and that the 24-week mortality rate tended to be lower in the LDL-A group than the control group (8% vs. 29%, $p = 0.074$).

A study that investigated the difference of change in eGFR between the steroid monotherapy group and the group combined with the LDL-A showed that changes in eGFR after 1 year were 7.5 ml/min/1.73 m^2 (5.4–8.7) and 2.2 ml/min/1.73 m^2 (−3.8 to −5.1) in the LDL group and the steroid monotherapy group, respectively ($p = 0.019$). The combination of LDL-A and corticosteroid was more effective in preserving renal function compared to the steroid monotherapy group.

Technical notes

LDL-A for cholesterol crystal embolism is currently not covered by the insurance. In addition to written informed consent, the ongoing Advanced Medical Care plan study by the Ministry of Health, Labour and Welfare currently requires the following for inclusion: (i) history of vascular procedures or intravascular surgery within 24 weeks before the time of the informed consent acquisition; (ii) diagnosed by the presence of rapid progression of renal dysfunction, skin lesions, eosinophilia, or by biopsy (skin biopsy, renal biopsy); and (iii) 20–85 years old. Drug therapy (i.e., those that use corticosteroids or HMG-CoA reductase inhibitors) should be administered concurrently with the blood purification therapy. The production of bradykinin during LDL-A is enhanced. The administration of angiotensin-converting enzyme inhibitors is contraindicated because it induces severe hypotension during apheresis by suppressing the degradation of bradykinin.

Duration and discontinuation/number of procedures

LDL-A is conducted using liposorber LA15, a dextran sulfate conjugated column, on the plasma separated by a membrane plasma separator. The number of sessions to be implemented is not fixed in previous reports. The ongoing Advanced Medical Care study currently consists of six sessions within 4 weeks of starting treatment as the number of therapy sessions. The plasma processing volume is approximately 3000 L, and the nafamostat mesylate is used as the anticoagulant.

References

1. Ishiyama K, Sato T, Yamaguchi T, et al. Efficacy of low-density-lipoprotein apheresis combined with corticosteroids for cholesterol crystal embolism. Clin Exp Nephrol. 2017;21:228–35.

2. Ishiyama K, Sato T, Taguma Y, et al. Low-density lipoprotein apheresis ameriolates renal prognosis of cholesterol crystal embolism. Ther Apher Dial. 2015;19:355–60.

3. Hirai K, Okawara S, Miyazawa H, et al. Low-density lipoprotein apheresis ameriolates monthly estimated glomerular filtration rate decline in patients with renal cholesterol crystal embolism. J Artif Organs. 2015;18:72–8.

8.31 | Worksheet 31

Diseases: Chronic focal encephalitis (Rasmussen encephalitis)

Procedure: PE, IAPP

Purpose: Removal of autoantibodies

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 2, CR 8

Description of the disease

The disease is a unilaterally occurring localized autoimmune inflammation caused by previous infection with some virus or vaccination that involves refractory epileptic seizures accompanied by hemiplegia and intellectual disability, which progresses chronically and involves atrophy of the cerebral hemisphere. It is common during childhood. Humoral immunity such as autoantibodies and cell-mediated immunity such as cytotoxic T-cells and glial cells are presumed to be involved.

Current management/treatment

Antiepileptic drugs have been used for symptomatic therapy. Epilepsy surgery (functional hemisphere resection), steroid pulse therapy, immunoglobulin therapy, oral steroids, azathioprine, tacrolimus, and blood purification therapy are used alone or in combination to control disease activity, but rituximab and natalizumab have also been recently reported.

Rationale for apheresis

Removal of autoantibodies such as GluR3 antibodies (6) and complements have been shown to be effective (2, 7, 8). Apharesis was used for control when existing immunotherapies (e.g., functional hemispherectomy, steroid pulse therapy, immunoglobulin therapy) were ineffective against refractory epilepsy with severe status epilepticus and frequent seizures (9–12). Recovery of consciousness disorders and speech disorders can be done relatively quickly, and the control of epileptic seizures and reduction of brain atrophy are possible.

Technical notes

Be aware of securing and fixing blood access since there are many pediatric patients. Pay attention to the presence of infection or coagulation/bleeding at the puncture site, and route fixation (in cases of consciousness disorder and involuntary movements).

Duration and discontinuation/number of procedures

This is not covered by insurance. It is implemented 2–3 times a week depending on the pathological conditions (e.g., refractory epilepsy), but this often only has transient effects, and the implementation of 3–6 times on consecutive days or every other day is repeated for 2–8 weeks. Treatment is maintained for five times a week per month for the first 3 months, and then once a week per month for the next 3 months, with some cases reporting an additional treatment of three times a week per month over half a year.

References

1. Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. Brain. 2005;128:454–71.

2. Bien CG, Elger CE, Wiendl H. Advances in pathogenic concepts and therapeutic agents in Rasmussen's encephalitis. Expert Opin Investig Drugs. 2001; 11(7):981–9.

3. Varadkar S, Bien CG, Kruse CA, Jensen FE, Bauer J, Pardo CA, et al. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. Lancet Neurol. 2014 Feb;13(2):195–205.

4. Counce D, Limdi N, Kuzniecky R. Rasmussen's encephalitis. Curr Treat Options Neurol. 2001; 3(6):555–63.

5. Rogers SW, Andrews PI, Gahring LC, Whisenand T, Cauley K, Crain B, et al. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. Science. 1994;265:648–51.

6. Andrews PI, McNamara JO, Lewis DV. Clinical and electroencephalographic correlates in Rasmussen's encephalitis. Epilepsia. 1997;38(2):189–94.

7. Antozzi C, Granata T, Aurisano N, Zardini G, Confalonieri P, Airaghi G, et al. Long-term selective IgG immuno-adsorption improves Rasmussen's encephalitis. Neurology. 1998;51(1):302–5.

8. Palcoux JB, Carla H, Tardieu M, Carpentier C, Sebire G, Garcier JM, et al. Plasma exchange in Rasmussen's encephalitis. Ther Apher. 1997;1(1):79–82.

9. Bernasconi P, Antozzi C, Granata T, Spreafico R, Mantegazza R. Rasmussen's encephalitis: update on pathogenesis and treatment. Expert Rev Neurother. 2003;3(6): 835–43.

10. Kes P, Basić-Kes V, Basić-Jukić N, Demarin V. Therapeutic plasma exchange in the neurologic intensive care setting recommendation for clinical practice. Acta Clin Croat. 2012;51(1):137–53.

11. Granata T, Fusco L, Gobbi G, Freri E, Ragona F, Broggi G, et al. Experience with immunomodulatory treatments in Rasmussen's encephalitis. Neurology. 2003 Dec 23;61(12):1807–10.

12. Andrews PI, Dichter MA, Berkovic SF, Newton MR, McNamara JO. Plasmapheresis in Rasmussen's encephalitis. Neurology. 1996;46(1):242–6.

13. Andrews PI, Dichter MA, Berkovic SF, Newton MR, McNamara JO. Plasmapheresis in Rasmussen's encephalitis. 1996. Neurology. 2001;57(11 Suppl 4): S37–41.

14. Guimarães CA, Souza EA, Montenegro MA, Marques Jr JFC, Cendes F, Guerreiro MM. Rasmussen's encephalitis: the relevance of neuropsychological assessment in patient's treatment and follow up. Arq Neuropsiquiatr. 2002;60(2-B):378–81.

15. Sanfilippo C, Giuliano L, Fatuzzo D, Sortino G, Le Pira F, Sofia V, et al. Late onset Rasmussen encephalitis: complete remission after one session of plasmapheresis. Eur J Neurol. 2016;23(3):e15–6.

8.32 | Worksheet 32

Diseases: Chronic hepatitis C
Procedure: DFPP
Purpose: Removal of hepatitis C virus
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 8, CR 2

Description of the disease

An individual exposed to the hepatitis C virus has a high probability of developing hepatitis. There are no symptoms associated with a hepatitis C virus infection, and it often progresses to chronic hepatitis and cirrhosis, and ultimately,in some cases, to liver cancer. It is currently the fourth leading cause of death, associated with cancer, in Japan. Removal of the hepatitis C virus is the most effective treatment method for infection, and is heavily encouraged.

Current management/treatment

Interferon treatment has been performed for hepatitis C from 1992. By 2004, the virus could be removed by up to 50% and, since 2011, continuing progress has been made in treatment methods. Direct-acting antivirals (DAAs) have been used, so that the virus removal rate using DAAs, to date, is approximately 95%–98%.

Rationale for apheresis

From April 2008, DFPP for hepatitis C interferon treatment in intractable cases has been covered by insurance. This treatment method was developed with the objectives of reducing the viral load with DFPP and increasing the effectiveness of interferon treatment. Some have reported improved virus removal rates, and a number of possibilites of improving removal rates have been suggested, but none have exhibited clear evidence of effectiveness to date.

Technical notes

Adverse events caused by DFPP include dysphoria, hypotension, fever/chills, and nausea/vomiting, but previous reports have not focused attention on these side-effects. Studies, to date, have all had small sample sizes, and no clinical trials have been conducted to clarify these issues.

Duration and discontinuation/number of procedures

The maximum number of DFPP implementations is considered to be five times. However, there is insufficient evidence regarding the number of times of implementation, the amount of plasma to be processed, time intervals between implementations, and criteria for completion.

References

1. Ishikawa T, Abe S, Kojima Y, Sano T, Iwanaga A, Seki KI, et al. Prediction of a sustained viral response in chronic hepatitis C patients who undergo induction therapy with double filtration plasmapheresis plus interferon-β/ribavirin. Exp Ther Med. 2015;9:1646–50.

2. Morisue A, Fukuoka K, Goto R, Ota K, Yamashita H, Shinno Y, et al. Hepatitis C virus-related glomerulonephritis with acute kidney injury requiring hemodialysis that improved with virus removal and eradication using double-filtration plasmapheresis without interferon. CEN Case Rep. 2015;4:38–42.

3. Zeniya M, Nakano M, Saeki C, Yokoyama K, Ishikawa T, Takaguchi K, et al. Usefulness of combined application of double-filtration plasmapheresis and twice-daily injections of interferon-β in hemodialysis patients with hepatitis C virus genotype 1b infection and a high viral load. Hepatol Res. 2014;44:E257–60. https://doi.org/10.1111/hepr.12207

4. Cao H, Wen P, Ye H, Sun Z, Shen X, Wu X, et al. A study of the immunoloregulation of double filtration plasmapheresis in maintenance hemodialysis patients with chronic hepatitis C. PLoS One. 2013;8:e82524. https://doi.org/10.1371/journal.pone.0082524

5. Ohara T, Oteki T, Suzuki T, Suzuki M, Matsuzaki Y. Efficacy of double filtration plasmapheresis with pegylated interferon/ribavirin therapy for intractable chronic hepatitis C patients and hepatitis C patients with combined liver cirrhosis by HBV, leading to early viral elimination. Hepatogastroenterology. 2011;58:133–6.

6. Ishikawa T, Higuchi K, Kubota T, Seki K, Honma T, Yoshida T, et al. Complete early virological response was highly achieved by double filtration plasmapheresis plus IFN-beta induction therapy for HCV-1b patients with relapse or no response after previous IFN therapy. Ther Apher Dial. 2011;15:400–5.

7. Kim SR, Saito J, Imoto S, Komaki T, Nagata Y, Kim KI, et al. Double-filtration plasmapheresis plus interferon-β for HCV-1b patients with non-sustained virological response to previous combination therapy. Digestion. 2011;84(Suppl 1):10–6.

8. Kim SR, Imoto S, Kudo M, Mita K, Taniguchi M, Kim KI, et al. Double-filtration plasmapheresis plus IFN for HCV-1b patients with non-sustained virological response to previous combination therapy: early viral dynamics. Intervirology. 2010;53:44–8.

9. Fujiwara K, Kaneko S, Kakumu S, Sata M, Hige S, Tomita E, et al. Double filtration plasmapheresis and interferon combination therapy for chronic hepatitis C patients with genotype 1 and high viral load. Hepatol Res. 2007;37:701–10.

10. Yamashita T, Arai K, Sakai A, Mizukoshi E, Sakai Y, Kagaya T, et al. Virological effects and safety of combined double filtration plasmapheresis (DFPP) and interferon therapy in patients with chronic hepatitis C: a preliminary study. Hepatol Res. 2006;36:167–75.

8.33 | Worksheet 33

Diseases: Chronic inflammatory demyelinating polyneuropathy

Procedure: PE, IAPP

Purpose: Control of CIDP disease activity

Recommendation: 1A

Category: I

The number of references: RCT 5, CT 0, CS 38, CR NA

Description of the disease

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a peripheral neurological disorder of unknown cause that is characterized by chronic progressive or bilaterally symmetric distal and proximal muscle weakness and sensory impairment for two or more months. Its clinical symptoms include movement/sensory disorders of the limbs and, occasionally, cranial nerve and autonomic nerve impairment. Tendon reflexes in the limbs may be decreased or lost. Cerebrospinal fluid examinations show protein cell dissociation; electrophysiological examinations/nerve biopsies show demyelination; and imaging examinations show Gd contrast effects and nerve thickening in the cervical cord and lumbar spinal cord. Clinical symptoms improve after immunotherapy (e.g., corticosteroid therapy, blood purification therapy, IVIG). The cause of CIDP is unknown, but it is thought to be an autoimmune disease caused by abnormalities of the immune system in the peripheral nerve myelin component (e.g., neurofascin 155, contactin-1).

Current management/treatment

The basic treatments for CIDP include (1) apheresis therapy, (2) IVIG, and (3) corticosteroid treatment. RCTs have shown that all of these have similar therapeutic effects. The therapeutic effects in the early stages were 60%–80% for all these treatments, but there were no long-term therapeutic effects. Replenishment therapy is required because of frequent occurrence, with oral corticosteroids, immunosuppressants, and sometimes IVIG and apheresis therapy used. Combined use with immunosuppressants (e.g., cyclosporine, azathioprine, cyclophosphamide, rituximab) is conducted in refractory cases.

Rationale for apheresis

Apheresis is conducted to remove humoral factors (e.g., autoantibodies, complements, inflammatory cytokines) associated with the pathogenesis of CIDP. A 2004 Cochrane review (2010 revision) included a meta-analysis of two placebo (sham) and randomized controlled trials (RCTs), where it was concluded that PE resulted in short-term improvements of clinical symptoms and nerve conduction tests in 33%–66% of CIDP cases. Dyck et al. conducted comparative studies of CIDP with a 3 week/twice per week PE group (six sessions) and a sham group, and they reported improvements in clinical symptoms and electrophysiological findings in the PE group. Hahn et al. conducted comparative cross-over studies of CIDP involving PE (10 sessions) and sham groups, and they reported significant improvements in the clinical symptoms and electrophysiological findings in the PE group. Dyck et al. conducted a comparative study for CIDP involving PE and IVIG groups and showed no statistically significant differences between them, concluding that both were effective treatment methods.

Technical notes

PE is the only plasmapheresis with strong evidence of efficacy. PE is effective as the first-line treatment for CIDP. It has recently been reported that PE and IAPP have similar therapeutic effects. PE was effective in cases where rapid improvements in neurological symptoms were required, but it was associated with a high recurrence rate. The combined use of oral corticosteroids and immunosuppressants should be considered in these cases. Blood purification therapy is inferior to IVIG and corticosteroid treatment based on side effects and tolerability.

Duration and discontinuation/number of procedures

Insurance for CIDP covers PE or IAPP for up to seven times a month in a single series for cases of acute exacerbation. PE is generally administered twice a week, with a gradual decrease when neurological improvements are observed. The duration of therapeutic effects of PE and IAPP is short, and maintenance therapy, repeated plasma purification therapy, and other immunotherapies are needed.

References

1. Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology. 1997;48(2):321–8.

2. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. J Peripher Nerv Syst. 2005; 10(3):220–8.

3. Koski CL. Therapy of CIDP and related immune-mediated neuropathies. Neurology. 2002;59(Suppl 6): S22–7.

4. Toyka KV, Gold R. The pathogenesis of CIDP: rationale for treatment with immunomodulatory agents. Neurology. 2003;60(Suppl 3):S2–7.

5. Dyck PJ, Daube J, O'Brien P, et al: Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. N Engl J Med. 1986;314(8):461–5.

6. Hahn AF, Bolton CF, Pillay N, et al: Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy. A double-blind, sham-controlled, cross-over study. Brain. 1996;119:1055–66.

7. Dyck PJ, Litchy WJ, Kratz KM, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol. 1994;36(6):838–45.

8. Lieker I, Slowinski T, Harms L, et. al. A prospective study comparing tryptophan immunoadsorption with therapeutic plasma exchange for the treatment of chronic inflammatory demyelinating polyneuropathy. J Clin Apher. 2017;32(6):486–93.

8.34 | Worksheet 34

Diseases: Combined central and peripheral demyelination

Procedure: PE

Purpose: Introduction of remission

Recommendation: 1D

Category: III

The number of references: RCT 0, CT 0, CS 0, CR 0

Description of the disease

Combined central and peripheral demyelination (CCPD) is a disease that simultaneously causes demyelinating lesions in the central and peripheral nerves and has been reported under various disease names. Antigens common to both nervous systems, such as myelin-associated glycoprotein (MAG) and neurofascin, are assumed to be associated with this pathological condition. Neurofascin is an adhesion molecule present in and near the Ranvier node of both nervous systems. Kawamura et al. have reported that six of seven (86%) cases diagnosed as CCPD were positive for serum anti-neurofascin 155 (N155) antibodies. However, subsequent accumulation of cases have suggested that the anti-NF155 antibodies are more strongly associated with peripheral nerve demyelination.

Current management/treatment

Cases that were positive for anti-NF155 antibodies exhibited poor therapeutic effects with steroids and were responsive to intravenous immunoglobulin (IVIG) and PE. A national clinical survey reported 38 cases of CCPD, with treatment primarily consisting of corticosteroids and IVIG; however, effects were seen only in a few cases. PE was performed in eight cases, with efficacy confirmed in seven (88%) of these cases. Some case reports have reported that PE was effective against CCPD in some cases.

Rationale for apheresis

The fact that steroid pulse therapy was ineffective and PE was considerably effective for cases that were positive for anti-NF155 antibodies suggests the involvement of humoral factors such as autoantibodies against molecules present in both the central and peripheral nerves. Removal of autoantibodies is considered important for improvement; however, since the therapeutic response to IVIG is poor, apheresis is prioritized.

Technical notes

Since the anti-NF155 antibody is an IgG4 fraction, IAPP may less effective. PE should be selected for cases positive for anti-NF155 antibodies.

Duration and discontinuation/number of procedures

Treatment similar to that for multiple sclerosis and chronic inflammatory demyelinating polyradiculoneuropathy should be administered. In reported cases, PE was performed 4–6 times/2 weeks.

References

1. Kamm C, Zettl UK. Autoimmune disorders affecting both the central and peripheral nervous system. Autoimmun Rev. 2012;11:196–202.

2. Zéphir H, Stojkovic T, Lacour A, et al. Relapsing demyelinating disease affecting both the central and peripheral nervous systems. J Neurol Neurosurg Psychiatry. 2008;79:1032–9.

3. Rubin M, Karpati G, Carpenter S. Combined central and peripheral myelinopathy. Neurology. 1987;37:1287–90.

4. Pareyson D, Ciano C, Flacchino F, et al. Combined central and peripheral acute demyelination. Ital J Neurol Sci. 1993;14:83–6.

5. Butzkueven H, O'Brien TJ, Sedal L. Combined peripheral nerve and central nervous system demyelination in a patient with chronic inflammatory demyelinating polyneuropathy. J Clin Neurosci. 1999;6:358–60.

6. Waxman SG. Peripheral nerve abnormalities in multiple sclerosis. Muscle Nerve. 1993;16:1–5.

7. Kriebel M, Wuchter J, Trinks S, et al. Neurofascin: a switch between neuronal plasticity and stability. Int J Biochem Cell Biol. 2012;44:694–7.

8. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology. 2014;82:879–86.

9. Kawamura N, Yamasaki R, Yonekawa T, et al. Anti-neurofascin antibody in patients with combined central and peripheral demyelination. Neurology. 2013;81(8):1714–22.

10. Ogata H, Yamasaki R, Hiwatashi A, et al. Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. Ann Clin Transl Neurol. 2015;2(10):960–71.

11. Ogata H, Matsuse D, Yamasaki R, Kawamura N, Matsushita T, Yonekawa T, et al. A nationwide survey of combined central and peripheral demyelination in Japan. J Neurol Neurosurg Psychiatry. 2016 Jan;87(1):29–36.

12. Kuwahara M, Suzuki H, Oka N, et al. Electron microscopic abnormality and therapeutic efficacy in chronic inflammatory demyelinating polyneuropathy with anti-neurofascin155 immunoglobulin G4 antibody. Muscle Nerve. 2018;57(3):498–502.

8.35 | Worksheet 35

Diseases: Complex regional pain syndrome (CRPS)
Procedure: PE
Purpose: CRPS pain control
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 2, CR 2

Description of the disease

Complex regional pain syndrome (CRPS) is a disease characterized by autonomic symptoms (e.g., sweat, vasomotor abnormalities), motor symptoms (e.g., muscle weakness, dystonia), and atrophic symptoms (skin/bone atrophy, hair loss, joint contraction), where the main complaint is chronic neuropathic pain that is more severe and lasts longer than expected after soft tissue/bone damage (Type I) and nerve damage (Type II). The onset mechanisms of CRPS includes neuropeptide-related neuroinflammation (substan P, CGRP), sympathetic neuropathy in the peripheral and central nervous systems, and a cortical reorganization process. There has recently been speculation regarding the immunological mechanisms involved in the production of autoantibodies.

Current management/treatment

Oral administration of vitamin C is useful for prophylaxis. Treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, anticonvulsants, antidepressants, opioids, intravenous ketamine, calcitonin, free radical scavengers, electrical stimulation of the spinal cord, and intrathecal baclofen. Immunotherapy includes corticosteroids, IVIG, and rituximab. With regard to apheresis therapy, it has been reported that a combination of PE and immunosuppressants or other adjuvant therapies, and the periodical continuation of PE, maintained improvements in symptoms.

Rationale for apheresis

There have been some reports of effective apheresis implementations, and some retrospective studies have been identified, but there have not been any RCTs. It has been reported that 90% of CRPS patients who underwent PE showed improvements in pain and other symptoms. It is considered that the removal of autoantibodies for β2 adrenaline, α1 adrenaline, and muscarinic M2 receptors by PE alleviates symptoms.

Technical notes

Apheresis therapy for CRPS should be combined with other immunotherapies (including IVIG). Regular apheresis therapy should be used as a maintenance therapy, since initial treatment alone is likely to result in a symptom relapse.

Duration and discontinuation/number of procedures

The plasma treatment volume for one session of PE is set as 1.5 times that of the patient's plasma volume (PV), and a 5% albumin solution should be used as replenishment. Seven sessions of PE are set as one course, conducted over 2–3 weeks. It has been reported that pain is alleviated for an average of 5.4 months by combining PE with other immunotherapies, and conducting PE twice a week for over 4 weeks as a maintenance therapy after the completion of a course.

References

1. Aradillas E, Schwartzman RJ, Grothusen JR, et al. Plasma exchange therapy in patients with complex regional pain syndrome. Pain Physician. 2015;18:383–94.

2. Blaes F, Dharmalingam B, Tschernatsch M, et al. Improvement of complex regional pain syndrome after plasmapheresis. Eur J Pain. 2015;19:503–7.

3. Bruehl S. Complex regional pain syndrome. BMJ. 2015;351:h2730.

4. Dawes JM, Vincent A. Autoantibodies and pain. Curr Opin Support Palliat Care. 2016 Jun;10:137–42.

5. Dubuis E, Thompson V, Leite MI, et al. Longstanding complex regional pain syndrome is associated with activating autoantibodies against alpha-1a adrenoceptors. Pain. 2014;155:2408–17.

6. Hendrickson JE, Hendrickson ET, Gehrie EA, et al. Complex regional pain syndrome and dysautonomia in a 14-year-old girl responsive to therapeutic plasma exchange. J Clin Apher. 2016;31(4):368–74.

8.36 | Worksheet 36

Diseases: Crohn's disease

Procedure: GMA

Purpose: Adsorption and removal of abnormally activated granulocytes and monocytes

Recommendation: 2B

Category: II

The number of references: RCT 4, CT 9, CS 20, CR 12

Description of the disease

Crohn's disease is an inflammatory disease that develops in young patients and is considered to be caused by excessive immune activity in the intestinal mucosa caused by a genetic predisposition, environmental factors, and the stimulation of intestinal bacteria. However, the exact cause remains unknown. Inflammation may occur anywhere along the gastrointestinal tract, from the oral cavity to the anus; however, the most common site is the ileocecal region. Unlike ulcerative colitis, this disease causes transmural inflammation, and is characterized by gastrointestinal complications such as stenosis, fistulas, and intra-abdominal abscesses. The most common symptoms are abdominal pain, diarrhea, weight loss, fever, and anal lesions. It may, however, also be accompanied by appendicitis, intestinal obstruction, intestinal perforation, and major bleeding, at times.

Current management/treatment

Remission induction therapies include enteral nutrition therapy and drug therapy. Drug therapy includes the use of 5-ASA preparations, corticosteroids, or anti-TNFα receptor antagonists. Budesonide, a steroid that is rapidly metabolized in the body, has recently become available for use mainly in the ileocecal region, for mildly to moderately ill patients. Ustekinumab, an IL-12/23 receptor antagonist, may be administered in cases with anti-TNFα receptor antagonist resistance. Cytapheresis is covered under insurance for patients with a predominant inflammation of the large intestine, who are resistant to drug treatment.

Rationale for apheresis

The effectiveness of GMA has been proven in active patients with colorectal lesions that did not improve with existing drug and nutrition therapies. In 2010, it became covered by insurance in Japan. Yoshimura et al. reported that early stage remission induction by the twice-a-week method was an effective implementation method. However, Sands et al. reported that there were no differences in effectiveness between the GMA group and a sham-control group. There are presently almost no studies showing evidence for the efficacy of apheresis in Crohn's disease, and there are only a few case reports showing its effectiveness in remission maintenance.

Technical notes

To be implemented with the objective of introducing remission for patients with moderate to severe active Crohn's disease who have obvious clinical symptoms due to colorectal lesions for which nutrition therapy and existing drug therapy are ineffective or inapplicable.

Be aware that the usefulness of this therapy alone against Crohn's disease, for cases with fistulas or stenotic lesions, and as a reintroduction therapy during recurrence have not been established. This should also be carefully used as cases may rapidly worsen when therapeutic effects are not seen.

Consider changing treatment to steroids, infliximab, adalimumab, ustekinumab, or surgery for ineffective cases. Maintain remission after the introduction of remission using 5-ASA preparations, immunomodulators, and nutritional therapy.

Duration and discontinuation/number of procedures

GMA mainly removes granulocytes and monocytes using a column filled with immunoadsorbing beads. As a general rule, GMA should conduct circulation with a flow rate of 30 ml/min, with apheresis conducted over a 60-min treatment period. The number of implementations should be limited to 10 times per series, but there is no limit on the interval between each treatment.

References

1. Fukuda Y, et al. Adsorptive granulocyte and monocyte apheresis for refractory Crohn's disease: an open multicenter prospective study. J Gastroenterol. 2004 Dec;39(12):1158–64.

2. Yoshimura N, et al. An open-label prospective randomized multicenter study of intensive versus weekly granulocyte and monocyte apheresis in active crohn's disease. BMC Gastroenterol. 2015 Nov 19;15:163.

3. Sands BE, et al. A randomised, double-blind, sham-controlled study of granulocyte/monocyte apheresis for moderate to severe Crohn's disease. Gut. 2013 Sep; 62(9):1288–94.

8.37 | Worksheet 37

Diseases: Cryoglobulinemia
Procedure: PE
Purpose: Removal of cryoglobulin
Recommendation: Grade 2A
Category: II
The number of references: RCT 1, CT 0, CS 24, CR NA

Description of the disease

Cryoglobulinemia is a condition characterized by the presence of cryoglobulin in the blood. Cryoglobulin is an immunoglobulin that precipitates at temperatures lower than 37°C and dissolves when heated to 37°C or higher. Cryoglobulinemia is classified into three according to immunoglobulin composition: Type I involves the monoclonal immunoglobulin and is mainly observed in multiple myeloma and Waldenström's macroglobulinemia. Type II and Type III are also called mixed types since they involve IgG and IgM. Type II involves multiclonal IgG and monoclonal IgM, which are observed in patients with hepatitis C virus (HCV). Type III involves multiclonal IgG and multiclonal IgM, which are observed in patients with inflammatory diseases, immune diseases, and infectious diseases (including HCV). The mixed types account for approximately 80%–90% of all cryoglobulinemia cases, most of which have complications of HCV infection. The basic pathophysiology of cryoglobulinemia is systemic vasculitis caused by the deposition of immune complexes formed by immunoglobulins on the walls of microvessels throughout the body that activate complements and induce an immune response. This mainly affects the skin (purpura, necrotic ulcer), joints, peripheral nerves, and kidneys. Diagnosis is based on medical history, physical findings, decreased serum complement levels, and detection of cryoglobulin.

Current management/treatment

Treatment is based on the severity and underlying disorder. Screening for infectious diseases is especially important for the mixed type. Treatment is not required for asymptomatic cases, and preventing cold sensations and heat retention are effective in alleviating symptoms for mild cases. Analgesics can also be used. Immunosuppressant therapy (steroids, cyclophosphamide, rituximab) is used for severe cases. Rituximab is an anti-CD20 monoclonal antibody preparation that controls the monoclonal proliferation of B cells and cryoglobulin production. Multicenter RCTs and large-scale studies have shown better outcomes of rituximab when compared with conventional therapies (steroid pulse therapy, azathioprine, cyclophosphamide, PE). Antiviral therapy for HCV is administered for HCV-related cryoglobulinemia. The sustained virological response rate was low at approximately 60% in conventional treatments with interferons. However, the therapeutic outcomes of recent direct-acting antivirals (DAAs) were favourable; these DAAs have been reported to have a sustained virological response rate of more than 95%, and it is expected to be a treatment method for cryoglobulin vasculitis. The symptoms of PE can be improved by promptly removing cryoglobulin in response to the exacerbation of pathological conditions. However, the effects are temporary, and this is positioned as adjunct immunotherapy and treatment for the underlying disease.

Rationale for apheresis

PE efficiently removes cryoglobulin, with CRs and large-scale studies showing improvements in 70%–80% of treated patients. PE has been used mainly for patients with moderate to severe active cryoglobulinemia and renal impairment, neuropathy, arthritis, and ulcerative purpura. PE is administered for short-term or long-term management alone or in combination with immunosuppressive therapy. Both double and cascade filtrations are used to treat cryoglobulinemia because the first filter separates plasma from the whole blood, and the second filter removes high-molecular-weight proteins (e.g., IgM). Other apheresis modalities include cryofiltration and cryoglobulin apheresis. These remove plasma globulin by cooling the plasma in a continuous or two-step procedure with extracorporeal circulation. The remaining plasma is warmed to body temperature before being returned into the patient. The cryoglobulin removal efficiency is lower for cryofiltration than DFPP. Only one RCT has shown that PE was effective in reducing cryoglobulin.

Technical notes

PE is used to prevent cryoglobulin precipitation in blood vessels. It is important to warm the room, drip line, and replenishment solution. It has also been reported that cryoglobulin precipitated in the extracorporeal circulation circuit. Meanwhile, cryofiltration, which is a modified method of DFPP, involves the efficient removal of cryoglobulin, and plasma is intentionally cooled to form cryoglobulin to efficiently remove cryoglobulin.

Duration and discontinuation/number of procedures

Consider 3–8 treatment sessions over a period of approximately 2–3 weeks and clinically determining its therapeutic effects for acute treatment.

References

1. Terri B, Krastinova E, Marie I, et al. Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. Blood. 2012;119:5996–6004.

2. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis

C in chronic kidney disease. Kidney Int Suppl. 2008;109: S1–S99.

3. Terri B, Marie I, Lacraz A, et al. Non HCV-related infection cryoglobulinemia vasculitis: results from the French nationwide CryoVas survey and systematic review of the literature. J Autoimmun. 2015;65:74–81.

4. Stefanutti C, Vivensio A, DiGiamcomo S, et al. Immunoadsorption apheresis and immunosuppressive drug therapy in the treatment of complicated HCV-related cryoglobulinemia. J Clin Apher. 2009;24:241–6.

5. Montero N, Fava A, Rodriguez, et al. Treatment for hepatitis C virus associated mixed cryoglobulinaemia. Cochrane Database Syst Rev. 2018;5:CD011403.

6. Roccatello D, Saadoun D, Ramos-Casals M, et al. Cryoglobulinaemia. Nat Rev Dis Primers. 2018.

7. Desbois AC, Cacoub P, Saadoun D. Cryoglobulinemia: an update in 2019. Joint Bone Spine. 2019;86:707–13.

8. Bhattarai M, Woytowitz DV, Kaldash H, et al. Recurrent mixed cryoglobulinemia(MCS): a case report and literature review. R I Med J. 2015;98:33–7.

9. Dammacco F, Sansonno D. Therapy for hepatitis C virus-related cryoglobulinemic vasculitis. N Engl J Med. 2013;369:1035–45.

10. De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum. 2012;64:843–53.

11. Auzerie V, Chiali A, Bussel A, et al. Leg ulcers associated with cryoglobulinemia: clinical study of 15 patients and response to treatment. Arch Drematol. 2003;13:391–3.

8.38 | Worksheet 38

Diseases: Cutaneous T-cell lymphoma

Procedure: ECP

Purpose: Decrease tumor cells

Recommendation: 1B (erythroderma-type mycosis fungoides, Sezary syndrome)

1C (types other than erythroderma)

Category: I (erythroderma-type mycosis fungoides, Sezary syndrome)

II (types other than erythroderma)

The number of references: RCT 2, CT 13, CS 18, CR 60

Description of the disease

Primary cutaneous lymphomas are malignant tumors derived from lymphoid cells with no tumors in organs other than the skin. Ninety percent of primary cutaneous lymphomas are cutaneous T-cell lymphomas (CTCL). Mycosis fungoides (MF) and Sezary syndrome are representative CTCL diseases. MF is divided into three stages: erythematous, plaque, and tumor stages depending on the disease course. Sezary syndrome is characterized by the three main features of erythroderma: severe pruritus, superficial lymphadenopathy, and presence of abnormal lymphocytes in the peripheral blood.

Current management/treatment

The same treatments are used for both MF and Sezary syndrome. This includes (1) topical steroids, (2) phototherapy (e.g., PUVA and narrow-band UVB), (3) interferons, and (4) multidrug chemotherapy.

Rationale for apheresis

It induces apoptosis of the tumor cells (T-cells) in the blood to reduce the tumor burden. In addition, attempts to activate cytotoxic CD8+ T-cells by increasing MCH class I molecule expression were made. The overall response (OR) rates for erythroderma-type MF and Sezary syndrome treated with ECP alone are 36% and 25%, respectively, with a safe remission of 10%.

Technical notes

This treatment is contraindicated in patients who are allergic to methoxsalen (8-MOP) or who have photosensitivity. Use with caution in patients with decreased platelet count. Protective sunglasses should be worn during treatment to protect eyes from long-wavelength UV rays. A dedicated device that combines a centrifuge and ultraviolet irradiation device (UVAR system, CELLEX system, both from THERAKOS; COBE Spectra, Terumo BCT) is needed when conducting ECP. For treatment using the UVAR system, 300 ml of isolated plasma mixed with 240 ml of buffy coat (40 ml × 6 blood collection cycles) and 200 ml of saline (a total of 740 ml) is exposed to long-wavelength UV rays.

Duration and discontinuation/number of procedures

A single course is set once every 4 weeks for two consecutive days, with a total of seven or more courses. ECP is not covered under insurance in Japan, and it is currently conducted on a research basis in very limited facilities. However, this treatment technology is widely used in Western countries and is likely to be introduced in Japan in the future. Therefore, it is described here.

References

1. Schwarz J, Winter JL, Padmanabhan A, et al. Guidlines on the use of therapeutic apheresis in clinicalpractice-evidence-based approch from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apher. 2013;28:145–284.

2. McKenna KE, Whittaker S, Rhodes LE, et al. Evidence-based practice of photopheresis 1987–2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin lymphoma Group. Br J Dermatol. 2006;154:7–20.

3. Scarisbirk JJ, Taylor P, Holtick U, et al. U.K.consensus statement on the use of extracorporeal phtopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. Br J Dermatol. 2008;158:659–78.

4. Child FJ, Mitchell TJ, Whittaker SJ, et al. A randomized cross-over study to compare PUVA and extracorporeal photophereis in the treatment of plaque stage(T2) mycosis fungoides. Clin Exp Dermatol. 2004;29:231–6.

5. Knobler R, Duvic M, Querfeld C, et al: Long-term follow-up and survival of cutaneous T-cell lymphoma patients treated with extracorporeal photopheresis. Photodermatol Photoimmunol Photomed. 2012;28:250–7.

6. Szczepiorkowski ZM, Burnett CA, Dumont LJ, et al. Apheresis buffy coat collection without photoactivation has no effect on apotosis, cell proliferation, and total viability of mononuclear cells collected using photopheresis systems. Transfusion. 2018;58:947–50.

7. Dippel E, Schrag H, Goerdt S, et al: Extracorporeal photopheresis and interferon-alpha in advanced cutaneous T-cell lymphoma. Lancet. 1997;350:32–33.

8. Zouboulis CC, Schmuth M, Doepfmer S, et al. Extracorporeal photopheresis of cutaneous T-cell lymphoma is associated with reduction of peripheral CD4+ T lymphocytes. Dermatology. 1998;196:305–8.

9. Demierre MF, Ferzli P, Miller D, et al. Measuring HRQOL in patients with cutaneous T-cell lymphoma

undergoing therapy with oral bexarotene and extracorporeal photopheresis. Arch Dermatol. 2007;143:659–61.

10. Booken N, Weiss C, Utikal J, et al. Combination therapy with extracorporeal photopheresis, interferon-alph PUVA and topical corticosteroids in the management of Sezary syndrome. J Dtsch Dermatol Ges. 2010;8:428–38.

11. Talpur R, Demierre MF, Geskin L, et al. Multicenter photopheresis intervention trail in early-stage mycosis fungoides. Clin Lymphoma Myeloma Leuk. 2011;11:219–27.

8.39 | Worksheet 39

Diseases: Dermatomyositis (DM) and polymyositis (PM)

Procedure: PE, IAPP, and CAP

Purpose: Introduction and maintenance of remission

Recommendation: 2B/2C

Category: IV

The number of references: RCT 1, CT 2, CS 4, CR 18

Description of the disease

It is an inflammatory myopathy with symmetric proximal limb myalgia, muscle weakness, and elevated muscle enzymes that progresses from acute to subacute. Polymyositis (PM) is associated with only myopathy, while dermatomyositis (DM) is associated with cutaneous symptoms. Specific skin symptoms include edematous erythema (heliotrope rashes) and papules with strong keratinization on the back of the small joints in the hand (Gottron sign). Complications include interstitial pneumonia, myocardial damage, malignant tumors, and interstitial pneumonia, which is common in anti-ARS-antibody-positive cases. The prevalence is 2–5 per 100 000 people, and a female predilection is seen. The definitive diagnosis is based on muscle biopsy findings of inflammatory cell infiltration and muscle fiber necrosis.

Current management/treatment

The treatment is commonly performed with corticosteroids but with immunosuppressants (e.g., cyclophosphamide, azathioprine, methotrexate, and cyclosporine) and high-dose immunoglobulin therapy in refractory cases with corticosteroid resistivity. Apheresis may be provided in combination with these treatments, but its frequency has decreased.

Rationale for apheresis

The immune response is involved in pathological conditions, and therapeutic effects can be expected from apheresis. Common pathological findings of PM and DM are the abundant distribution of B and CD4+ T cells around blood vessels and the perimysium and of CD8+ T cells in the endomysium and muscle fibers. CD8+ T cell infiltration and upregulation of MHC Class 1 are observed around muscle fibers in PM, with cytotoxic T cells involved. CD4+ T cell infiltration is observed around the blood vessels around the muscle fiber bundle in DM, and vasculitis due to humoral factors, such as immune complexes, is involved.

Technical notes

Treatment-resistant cases are often reported. An international open trial that used PE and cyclophosphamide for 35 patients resistant to corticosteroids and immunosuppressants showed improved muscle strength in 32 patients. However, a double-blind trial in which 39 patients were divided into PE, leukapheresis, and sham treatment groups and 12 treatment sessions were conducted over 1 month showed no significant differences in muscle strength recovery. Studies with small sample sizes and case reports have shown apheresis to be useful. However, no clear therapeutic effects have been proven in comparative trials with other treatment methods using a large sample size; therefore, this treatment should be considered only for refractory cases with resistivity against various other treatments.

Duration and discontinuation/number of procedures

It is not covered by insurance. No report has shown clear efficacy, and indications are limited.

References

1. Choy EHS, Isenberg DA. Treatment of dermatomyositis and polymyositis. Rheumatology. 2002;41:7–13.

2. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies. Quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibers invated by T cells. Ann Neurol. 1984;16:193–208.

3. Kissel JT, et al. Microvascular deposition of complement membrane attack complex in dermatomyositis. N Engl J Med. 1986;314:329–34.

4. Dau PC. Plasmapheresis in idiopathic inflammatory myopathy. Experience with 35 patients. Arch Neurol. 1981;38:544.

5. Bennington JL, Dau PC. Patients with polymyositis and dermatomyositis who undergo plasmapheresis therapy. Pathologic findings. Arch Neurol. 1981;38:553.

6. Brewer EJ, et al. Plasma exchange therapy of a childhood onset dermatomyositis patient. Arthritis Rheum. 1980;23:509.

7. Koh C-S, et al. Successful treatment of polymyositis with immunoadsorption. In: Oda T, editor. Therapeutic plasmapheresis. Vol. 9. Cleaveland: ISAO Press;1991.

8. Miller FW, et al. Controlled trial of plasma exchange and leukapheresis in polymyositis and dermatomyositis. N Engl J Med. 1992;326:1380–4.

8.40 | Worksheet 40

Diseases: Diabetic nephropathy

Procedure: LDL-A

Purpose: Reduction of urinary protein and inhibition of renal function deterioration

Recommendation: 1C

Category: III

The number of references: RCT 0, CT 2, CS 1, CR 1

Description of the disease

This disease presents with renal disorders mainly due to microangiopathy of the renal glomerulus due to metabolic disorders and circulatory disorders by diabetes as the underlying disease. A typical example involves progressive renal dysfunction accompanied by a massive proteinuria, resulting in end-stage renal failure. Currently, diabeic nephropathy is the most prevalent primary disease among incident dialysis population in Japan.

Current management/treatment

A comprehensive management is peformed including blood glucose control, salt and calorie reduction, medications such as renin-angiotensin system inhibitors and SGLT2 inhibitors.

Rationale for apheresis

There are four reports ever since a case report of LDL apheresis (LDL-A) against drug-resistant diabetic nephropathy presenting with a large degree of urinary protein was published in 1998. These reports were observational studies; however, they suggested the effectiveness of LDL-A in reducing the amount of urinary protein, preserving renal function (reducing or improving deterioration rate), and preventing renal events (serum creatinine doubling, dialysis induction, and renal transplantation) in patients with diabetic nephropathy. A multi-center prospective intervention study (LICENSE study) in 40 diabetic nephropathy patients with a massive urinary protein demonstrated that LDL-A could reduce all-cause mortality, and a composite endpoint of renal events and mortality.

Technical notes

LDL-A is conducted using liposorber LA15, a dextran sulfate conjugated column, on the plasma separated by a plasma separator. Angiotensin-converting enzyme inhibitors are contraindicated because they can inhibit the degradation of bradykinin and induce hypotension/shock during this apheresis therapy.

Duration and discontinuation/number of procedures

The condition is not covered by the insurance. The apheresis is performed 1–2 times a week, for a total of 10–12 times per course, with the plasma processing volume per session as 50–60 ml/kg of body weight.

References

1. Kobayashi S. LDL-apheresis for diabetic nephropathy: a possible new tool. Nephron. 1998:79:505–6.

2. Nakao T, Yoshino M, Matsumoto H, et al. Low-density lipoprotein apheresis retards the progression of hyperlipidemic overt diabetic nephropathy. Kidney Int Suppl. 1999:71:S206–9.

3. Nakamura T, Kawagoe Y, Ogawa H, et al. Effect of low-density lipoprotein apheresis on urinary protein and podocyte excretion in patients with nephrotic syndrome due to diabetic nephropathy. Am J Kidney Disease. 2005;45:48–53.

4. Sato E, Amaha M, Nomura M, et al. LDL-apheresis contributes to survival extension and renal function maintenance of severe diabetic nephropathy patients: a retrospective analysis.Diabetes Res Clin Pract. 2014;106:241–6.

5. Wada T, Muso E, Maruyama S, et al. Effects of LDL apheresis on proteinuria in patients with diabetes mellitus, severe proteinuria, and dyslipidemia. Clin Exp Nephrol. 2020 Aug 28. https://doi.org/10.1007/s10157-020-01959-9

8.41 | Worksheet 41

Diseases: Dialysis-associated amyloidosis
Procedure: DHP
Purpose: Removal of β2 microglobulin
Recommendation: 2B
Category: 2
The number of references: RCT 1, CT 3, CS 10, CR 10

Description of the disease

The removal efficiency of β2 microglobulin (β2MG) by dialysis is low, and long-term dialysis causes deposits in various organs in the body, resulting in various signs and symptoms. Deposits in the carpal tunnel cause carpal tunnel syndrome through the compression of the median nerve, deposits in the vertebrae cause destructive spondyloarthropathy, and deposits in the bone cause bone cyst formation. The amlyroid protein can deposit also in the soft tissue.

Current management/treatment

Hemodialysis with a high-flux dialyzer, purification of the dialysate, and online hemodiafiltration (HDF) with a large volume of replacement fluid are performed to remove β2MG.

Rationale for apheresis

β2MG has been seen in the affected tissues. β2MG adsorption with Lixelle can alleviate symptoms. The column also adsorbs peptides and small-molecular-weight proteins of 4–20 kDa including inflammatory cytokines. The removal of such cytokines can also contribute to symptom improvement. Many reports, including randomized controlled trials, demonstrated that the combination use of Lixelle with hemodialysis (HD) or online HDF favorable effects on joint pain, pinch force, quality of life, activities of daily living, and bone cyst progression, while some reportes did not show an additional effect of Lixelle on symptoms in patients already receiving online HDF.

Technical notes

Insurance coverage requires that the followings should be satisfied: (1) amyloid deposition due to β2MG confirmed by surgery or biopsy, (2) dialysis vintage longer than 10 years and the patient has undergone open surgery for carpal tunnel in the past, and (3) bone cysts have been confirmed through radiological imaging.

The adsorption column is connected before the dialyzer serially. Simultaneous implementation with online HDF is not covered by the insurance. Hemolytic anemia is reported as an adverse effect.

Duration and discontinuation/number of procedures

Implement three times a week at the same time as HD. A course can last a year. When symptoms such as pain recur after completion of a course, another course can be resumed for a year so long as the above-mentioned conditions (2) and (3) are met. More courses can be performed as long as the indications are satisfied.

References

1. Gejyo F, Amano I, Ando T, et al. Survey of the effects of a column for adsorption of b2-microglobulin in patients with dialysis-related amyloidosis in Japan. Ther Apher Dial. 2013 Feb;17(1):40–7.

2. Yamamoto Y, Hirawa N, Yamaguchi S, et al. Long-term efficacy and safety of the small-sized b2-microglobulin adsorption column for dialysis-related amyloidosis. Ther Apher Dial. 2011 Oct;15(5):466–74.

3. Kuragano T, Inoue T, Yoh K, et al. Effectiveness of b(2)-microglobulin adsorption column in treating dialysis-related amyloidosis: a multicenter study. Blood Purif. 2011;32(4):317–22.

4. Gejyo F, Kawaguchi Y, Hara S, et al. Arresting dialysis-related amyloidosis: a prospective multicenter controlled trial of direct hemoperfusion with a beta2-microglobulin adsorption column. Artif Organs. 2004 Apr;28(4):371–80.

5. Abe T, Uchita K, Orita H, et al. Effect of beta(2)-microglobulin adsorption column on dialysis-related amyloidosis. Kidney Int. 2003 Oct;64(4):1522–8.

8.42 | Worksheet 42

Diseases: Dilated cardiomyopathy

Procedure: ① IAPP, ② DFPP, ③ PE

Purpose: Complete removal of cardiac inhibitory anti-myocardial autoantibodies

Recommendation: ① 1B, ② 1C, ③ 2B

Category: ① II, ② II, ③ III

The number of references: RCT ① 4 ② 0 ③ 0, CT ① 11 ② 0 ③ 0, CS ① 17 ② 2 ③ 2, CR ① 0 ② 2 ③ 2

Description of the disease

This is an intractable myocardial disease that causes severe heart failure. The assumed cause is an autoimmune disorder instigated by a viral infection, with underlying genetic factors. Autoantibodies (IgG) acting against some form of autoantigen (e.g., myosin, β1 receptor, M2 receptor, Na-K-ATPase, and troponin I) have been detected in over 90% of cases.

Current management/treatment

Diuretics (including tolvaptan), ACE inhibitors (or ARB), β-blockers, anti-aldosterone drugs or digitalis, anticoagulants (direct oral anticoagulants and warfarin), and antiarrhythmic drugs (e.g., amiodarone) are used. Nondrug therapies include CRT-D implantation for patients with left ventricular dyssynchrony or ventricular tachycardia, as well as VAD to enhance circulation. Heart transplantation is, however, the ultimate treatment.

Rationale for apheresis

A multicenter, randomized, double-blind trial is currently underway in the West. The autoantibody IgG exerts a negative inotropic effect by simultaneously adhering the autoantigen on the myocardial cell membrane and Fcγ receptor IIa. The complete removal of this "cardiac inhibitory anti-myocardial autoantibody" is assumed to be the therapeutic mechanism. Approximately 60% of cases in both the West and Japan have been responsive to treatment (i.e., patients were positive for the autoantibody). These have included improvements in subjective symptoms (NYHA classification, maximal oxygen uptake, and exercise tolerance), improvements in hemodynamics before and after treatment, and decreases in plasma BNP levels after one course. Left ventricle ejection fraction improves 3 months after surgery, and improved effects on long-term prognosis have also been reported. IAPP is the most commonly used apheresis method, but DFPP and PE (pediatric cases) have also been reported from Japan.

Technical notes

Therapeutic effects are expected in patients who are positive for myocardial autoantibodies (especially "cardiac inhibitory antimyocardial autoantibodies"). ACE inhibitors are essential for the treatment of heart failure, but they are contraindicated during immunoadsorption therapy using Immusorba TR columns. ACE inhibitors must be switched to ARB prior to treatment. Clinical trials and advanced medical treatments B have been conducted in Japan, but the treatment has not yet been approved for coverage by insurance.

Duration and discontinuation/number of procedures

Implementation should be undertaken according to normal apheresis procedures. The amount of processed plasma per session should be 1.5 L in the case of IAPP by Immusorba TR, with three to five sessions per course. The same course should be repeated every 3 months until the myocardial autoantibodies disappear. Treatment can also be resumed in cases of recurrence.

References

1. Moriguchi T, Koizumi K, Matsuda K, Harii N, Goto J, Harada D, et al. Plasma exchange for the patients with dilated cardiomyopathy in children is safe and effective in improving both cardiac function and daily activities. J Artif Organs. 2017;20:236–43.

2. Yoshikawa T, Baba A, Akaishi M, Wakabayashi Y, Monkawa T, Kitakaze M, et al. Immunoadsorption therapy for dilated cardiomyopathy using tryptophan column-A prospective, multicenter, randomized, within-patient and parallel-group comparative study to evaluate efficacy and safety. J Clin Apher. 2016;31:141–50.

8.43 | Worksheet 43

Diseases: Drug-induced lung damage
Procedure: PMX–DHP
Purpose: Oxygenation/vital prognosis improvement
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 1, CR 2

Description of the disease

Respiratory disorders that occur during drug administration, that are associated with the drug.

Diagnosis of drug-induced lung damage is done when a new abnormal chest shadow appears during drug administration, and when other diseases (e.g., infection, heart failure) can be ruled out.

Various pathological conditions are shown, but prognosis is poor, especially for cases presenting with diffuse alveolar damage (DAD).

Current management/treatment

For mild cases, improvement in conditions is seen solely by suspending the causative drug. However, cases with poor respiratory condition may require steroid therapy (i.e., steroid pulse therapy).

Rationale for apheresis

There have been reports where respiratory status improved due to PMX-DHP.

Technical notes

Effects cannot be seen unless used for at least 2 h. However, caution is required as blood flow tends to become clogged in the column when coagulation is hyperactive.

Duration and discontinuation/number of procedures

There are no established guidelines. Comprehensive decisions based on factors such as respiratory status (e.g., improved oxygenation) are necessary.

References

1. Izumikawa K, Nakano K, Kurihara S, Imamura Y, Yamamoto K, Miyazaki T, et al. Diffuse alveolar hemorrhage following itraconazole injection. Intern Med. 2010;49(5):497–500.

2. Yokoyama T, Tsushima K, Yamamoto H, Ito M, Agatsuma T, Kozumi T, et al. Polymyxin B-immobilized fiber column hemoperfusion treatment for drug-induced severe respiratory failure: report of three cases. Intern Med. 2010;49(1):59–64.

3. Sato N, Kojima K, Horio Y, Goto E, Masunaga A, Ichiyasu H, et al. Successful treatment of severe amiodarone pulmonary toxicity with polymyxin B-immobilized fiber column direct hemoperfusion. Chest. 2013;143(4):1146–50.

8.44 | Worksheet 44

Diseases: DSA-positive kidney transplant
Procedure: PE-DFPP
Purpose: Removal of DSA
Recommendation: 1C
Category: I
The number of references: RCT 0, CT 2, CS 18, CR 0

Description of the disease

An anti-donor specific antibody (DSA) is an anti-human leukocyte antigen (HLA) antibody that is sensitized by pregnancy, blood transfusion, and past transplantation. This induces antibody-mediated rejection at a high rate after renal transplantation when the DSA found in the recipient serum is an antibody against the donor HLA. The DSA has a large influence on the prognosis of the graft function. For this reason, a DSA-positive kidney transplantation is still an urgent issue in Japan, where the number of kidney donations is low. Additionally, the donor source depends on living-donor kidney transplantation, even in the present day with the developments in transplantation medicine. Desensitization therapy is performed prior to transplantation; however, there is no consensus on its effects.

Current management/treatment

Prior to transplantation, desensitization therapy often involves the combination of immunosuppressants, PE or DFPP as an apheresis therapy for DSA removal, high-dose intravenous immunoglobulin (IVIG) for antibody neutralization, and rituximab (RIT) for suppressing antibody production according to the DSA titer; however, the protocol varies for each facility. It is important to ensure that the lymphocyte cross-match is negative at the time of transplantation. Splenectomy was previously performed to suppress antibody production; however, RIT administration is currently the main form of treatment. The immunosuppressants used in Japan include methylprednisolone, calcineurin inhibitors, mycophenolate mofetil, and basiliximab. However, antithymocyte globulin (ATG) and bortezomib are used overseas.

Rationale for apheresis

There are no reports on the effectiveness of apheresis by itself as desensitization therapy in DSA-positive kidney transplantation. There are no RCTs for desensitization therapy that involved apheresis conducted along with IVIG and RIT according to the DSA titer. However, there are several reports that showed that the desensitization protocol prior to the operation attained the lymphocyte cross-match negativity during transplantation and reduced antibody-associated rejection after transplantation. The protocol also improved the graft survival compared to those which did not undergo desensitization therapy. Some studies reported that lymphocyte cross-match did not become negative only with RIT and IVIG without apheresis, which reinforces the effectiveness of apheresis therapy.

Technical notes

A volume of 1–1.5 times the circulating plasma volume is processed in PE or DFPP and is supplemented with either albumin solution or FFP. It is desirable to monitor the blood coagulation time and to replace coagulation factors with FFP immediately before surgery to avoid bleeding complications during the kidney transplantation procedure; however, attention should be given to allergic reactions. Attention should be paid regarding post-transplantation infections, such as the BK virus when a combined desensitization therapy is performed.

Duration and discontinuation/number of procedures

PE and DFPP are both covered by insurance for up to four times before surgery and up to two times after surgery in Japan. However, apheresis is required until the lymphocyte cross-match turns negative at the time of kidney transplantation. The procedure is usually carried out every day or every other day.

References

1. Akalin E, Dinavahi R, Friedlander R, et al. Addition of plasmapheresis decreases the incidence of acute antibody-mediated rejection in sensitized patients with strong donor-specific antibodies. Clin J Am Soc Nephrol. 2008 Jul;3(4):1160–7. https://doi.org/10.2215/CJN.05321107

2. Gabardi S, Townsend K, Martin ST, et al. Evaluating the impact of pre-transplant desensitization utilizing a plasmapheresis and low-dose intravenous immunoglobulin protocol on BK viremia in renal transplant recipients. Transpl Infect Dis. 2013 Aug;15(4):361–8. https://doi.org/10.1111/tid.12087

3. Haas M, Montgomery RA, Segev DL, et al. Subclinical acute antibody-mediated rejection in positive crossmatch renal allografts. Am J Transplant. 2007 Mar;7(3):576–85.

4. Hirai T, Ishida H, Toki D, et al. Comparison of the acute rejection incidence rate in spousal donor transplantation before and after anti-CD20 antibody (rituximab) protocol as desensitization therapy. Ther Apher Dial. 2011 Feb;15(1):89–97. https://doi.org/10.1111/j.1744-9987.2010.00856.x

5. Hirai T, Kohei N, Omoto K, et al. Significance of low-level DSA detected by solid-phase assay in association with acute and chronic antibody-mediated rejection. Transpl Int. 2012 Sep;25(9):925–34. https://doi.org/10.1111/j.1432–2277.2012.01518.x

6. Kauke T, Klimaschewski S, Schoenermarck U, et al. Outcome after desensitization in HLA or

ABO-incompatible kidney transplant recipients: a single center experience. PLoS One. 2016 Jan 5;11(1):e0146075. https://doi.org/10.1371/journal.pone.0146075

7. Kozlowski T, Andreoni K. Limitations of rituximab/IVIg desensitization protocol in kidney transplantation; is this better than a tincture of time? Ann Transplant. 2011 Apr-Jun;16(2):19–25.

8. Lee KW, Park JB, Cho CW, et al. The impact of donor-specific anti-human leukocyte antigen (HLA) antibody rebound on the risk of antibody mediated rejection in sensitized kidney transplant recipients. Ann Transplant. 2017 Mar 28;22:166–76.

9. Magee CC, Felgueiras J, Tinckam K, et al. Renal transplantation in patients with positive lymphocytotoxicity crossmatches: one center's experience. Transplantation. 2008 Jul 15;86(1):96–103. https://doi.org/10.1097/TP.0b013e318176ae2c

10. Maillard N, Absi L, Claisse G, et al. Protein A-based immunoadsorption is more efficient than conventional plasma exchange to remove circulating anti-HLA antibodies. Blood Purif. 2015;40(2):167–72.

11. Montgomery RA, Lonze BE, King KE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med. 2011 Jul 28;365(4):318–26. https://doi.org/10.1056/NEJMoa1012376

12. Higgins R, Lowe D, Hathaway M, et al. Human leukocyte antigen antibody-incompatible renal transplantation: excellent medium-term outcomes with negative cytotoxic crossmatch. Transplantation. 2011 Oct 27;92(8):900–6. https://doi.org/10.1097/TP.0b013e31822dc38d

13. Riella LV, Safa K, Yagan J, et al. Long-term outcomes of kidney transplantation across a positive complement-dependent cytotoxicity crossmatch. Transplantation. 2014 Jun 27;97(12):1247–52. https://doi.org/10.1097/01.TP.0000442782.98131.7c

14. Santos C, Costa R, Malheiro J, et al. Kidney transplantation across a positive crossmatch: a single-center experience. Transplant Proc. 2014 Jul–Aug;46(6):1705–9. https://doi.org/10.1016/j.transproceed.2014.05.012

15. Sharma A, King A, Kumar D, et al. Perioperative desensitization improves outcomes among crossmatch positive recipients of deceased donor renal transplants. Prog Transplant. 2016 Jun;26(2):157–61. https://doi.org/10.1177/1526924816640678

16. Stegall MD, Gloor J, Winters JL, et al. A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific alloantibody. Am J Transplant. 2006 Feb;6(2):346–51.

17. Terasaka S, Kitada H, Okabe Y, et al. Living-donor kidney transplant in T-cell and B-cell flow cytometry crossmatch-positive patients. Exp Clin Transplant. 2014 Jun;12(3):227–32.

18. Thielke JJ, West-Thielke PM, Herren HL, et al. Living donor kidney transplantation across positive crossmatch: the University of Illinois at Chicago experience. Transplantation. 2009 Jan 27;87(2):268–73. https://doi.org/10.1097/TP.0b013e3181919a16

19. Tipjaiaue P, Ingsathit A, Kantachuvesiri P, et al. Outcome of pretransplantation therapeutic plasma exchange in highly sensitized deceased-donor kidney transplant recipients. Transplant Proc. 2017 Jul–Aug;49(6):1249–1255. https://doi.org/10.1016/j.transproceed.2017.02.059

20. Turza KC, Shafique M, Lobo PI, et al. Infectious complications in living-donor kidney transplant recipients undergoing multi-modal desensitization. Surg Infect. 2014 Jun;15(3):182–6. https://doi.org/10.1089/sur.2012.231

8.45 | Worksheet 45

Diseases: Fisher syndrome
Procedure: PE, DFPP, IAPP
Purpose: Removal of autoantibodies
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 0, CR 58

Description of the disease

Fisher syndrome (FS), a syndrome characterized by symptoms of extraocular muscle paralysis, ataxia, and decreased/lost tendon reflexes, develops acutely after a previous infection. The pathology is associated with the anti-GQ1b antibody, which is an anti-ganglioside antibody that is considered a subtype of Guillain-Barré syndrome (GBS). Typical FS exhibits favorable recovery over a natural course, with symptoms almost disappearing entirely within 6 months.

Current management/treatment

Although some case reports have shown the effectiveness of immunoglobulin therapy and apheresis therapy, there is no evidence that these treatments promote recovery. Neurological symptoms often show spontaneous recovery in typical FS; therefore, the evidence on the necessity of intraveneous immunoglobulin (IVIG) and apheresis therapy for mild and moderate cases is poor. However, they may be considered when there is a possibility of poor recovery (such as in cases involving older patients, sudden onset, and complete extraocular muscle paralysis).

Rationale for apheresis

A comparative study of the effects of PE, IAPP, and IVIG on the three characteristic symptoms of FS among 15 patients with FS showed short-term effects such as the shortening of the period of intense symptoms compared with other therapies and nontreatment; PE and IAPP are expected to have short-term effects. Since neurological symptoms of FS improve spontaneously, treatment is considered in severe cases. The pathology of FS is associated with the anti-GQ1b antibody, which is an anti-ganglioside antibody, and removal of autoantibodies. The GQ1b antibody belongs to the IgG1 and IgG3 classes; therefore, it is thought that it can be removed with PE.

Technical notes

Attention should be paid to hypotension and deep vein thrombosis when performing apheresis. Coagulation factors such as serum immunoglobulins and fibrinogen non-specifically decrease with plasmapheresis; therefore, adjustments of the implementation interval may be required. Apheresis therapy for this disease is not covered by insurance.

Duration and discontinuation/number of procedures

Some FS cases may include weakness of the limbs and present with the symptoms of GBS. In these cases, immunotherapy similar to that for GBS should be administered. Immunotherapy should actively be performed in cases that progress to bickerstaff brainstem encephalitis with impaired consciousness. Therapy should be implemented 3–4 times a week while observing the clinical course of each case according to GBS therapy (GBS insurance coverage: limited to patients with a Hughes severity classification of ≥4. The number of implementations is limited to seven a month per series and calculated only over 3 months).

References

1. Chiba A, Kusunoki S, Obata H, et al. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. Neurology. 1993;43:1911–7.

2. Mori M, Kuwabara S, Fukutake T, et al. Clinical features and prognosis of Miller Fisher syndrome. Neurology. 2001;56:1104–6.

3. Ejma M, Waliszewska-Prosół M, Hofman A, et al. Progressive subacute Miller-Fisher syndrome successfully treated with plasmapheresis. Neurol Neurochir Pol. 2015;49:137–8.

4. Mori M, Kuwabara S, Fukutake T, et al. Intravenous immunoglobulin therapy for Miller Fisher syndrome. Neurology. 2007;68:1144–6.

5. Mori M, Kuwabara S. Fisher syndrome. Curr Treat Options Neurol. 2011;13:71–8.

8.46 | Worksheet 46

Diseases: Guillain-Barré syndrome

Procedure: PE, IAPP

Purpose: Control of GBS disease activity Removal of autoantibodies

Recommendation: 1A

Category: I

The number of references: RCT 21, CT 1, CS NA, CR NA

Description of the disease

Guillain-Barré syndrome (GBS) is an acute-onset peripheral neurological disorder with an underlying autoimmune mechanism. The main symptom is motor paralysis of the limbs 1–2 weeks after infections (e.g., diarrhea, sore throat) accompanied by sensory disorders, cranial neuropathy, and autonomic neuropathy. The demyelinating type is most common, which is characterized by the impairment of the peripheral nerve myelin; some cases are of the axon type, which is characterized by impairment of the axons. It is thought that peripheral neuropathy is caused by the specific binding of autoantibodies (e.g., anti-ganglioside antibodies) to the peripheral nerve myelin components at the target antigen site.

Current management/treatment

Immunomodulatory therapy is administered during the active phase of the disease. Immunomodulatory therapies include (1) blood purification therapy (PE, DFPP, IAPP) and (2) IVIG. Both have been shown to be effective by randomized controlled trials (RCTs). There is no evidence that adrenocortical steroid treatment alone is effective. Cases with dysphagia, respiratory muscle paralysis, and severe autonomic neuropathy (e.g., arrhythmia, blood pressure fluctuations) during the acute phase of severe GBS require systemic management in the intensive care unit. Rehabilitation should be initiated early to prevent joint contracture, disuse muscular atrophy, deep vein thrombosis, and pulmonary infarction.

Rationale for apheresis

Apheresis is conducted to remove humoral factors (e.g., autoantibodies, complements, inflammatory cytokines) associated with pathogenesis during GBS activity. Large-scale RCTs on the efficacy of PE against GBS have been conducted in North America and France, with both trials reporting that the PE group showed significant clinical improvements relative to the control treatment group. There are no large-scale RCTs for the efficacy of IAPP relative to a control treatment. Only a few RCTs and comparative trials have compared PE and IVIG groups, and they have reported no significant differences between them. The efficacy of DFPP was demonstrated through comparative trials of small samples.

Technical notes

PE, IAPP, and DFPP are all covered by insurance for GBS in Japan, and no reports have compared the efficacies of the treatments. Treatment selection varies the available equipment at each facility and the proficiency level of each treatment method, and the implementers need to choose the treatment method for which they have the highest proficiency. GBS also impairs the autonomic nerves, and blood purification therapy should be carefully selected. IVIG should be the first choice for patients with orthostatic hypotension, arrhythmia, hypertension, and others.

Duration and discontinuation/number of procedures

Insured medical treatment in Japan includes the administration of PE, IAPP, or DFPP for up to seven times a month for a single series for cases of acute exacerbation. For PE, the blood processing volume per session should be 40–50 ml/kg for 4–5 times over 2 weeks, and 5% albumin solution for replenishment. Optimally, PE should be administered twice for mild cases (i.e., capable of walking 5 m) and four times for moderate (i.e., cannot stand without assistance) and severe (i.e., requires mechanical ventilation) cases within 2 weeks of onset; there is no need for more than six sessions, even for severe cases. For IAPP, the blood processing volume per session should be 1500–2000 ml (40–50 ml/kg) for 4–5 times every other day for 2 weeks, with additions incorporated during the following week depending on symptoms.

References

1. Griffin JW, Li CY, Ho TW, et al. Pathology of the motor-sensory axonal Guillain-Barré syndrome. Ann Neurol. 1996;39(1):17–28.

2. Willison HJ, Yuki N. Peripheral neuropathies and anti-glycolipid antibodies. Brain. 2002;125:2591–625.

3. Hughes RA, Cornblath DR. Guillain-Barré syndrome. Lancet. 2005;366(9497):1653–66.

4.Beghi E, Kurland LT, Mulder DW, et al. Guillain-Barré syndrome. Clinicoepidemiologic features and effect of influenza vaccine. Arch Neurol. 1985;42(11):1053–7.

5.Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Lancet. 1997; 349(9047):225–30.

6.Plasmapheresis and acute Guillain-Barré syndrome. The Guillain-Barré syndrome Study Group. Neurology. 1985;35(8):1096–104.

7. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome. Ann Neurol. 1987;22(6):753–61.

8. Haupt WF, Birkmann C, van der Ven C, et al. Apheresis and selective adsorption plus immunoglobulin treatment in Guillain-Barré syndrome. Ther Apher. 2000;4(3):198–200.

9. Diener HC, Haupt WF, Kloss TM, et al. A preliminary, randomized, multicenter study comparing intravenous immunoglobulin, plasma exchange, and immune adsorption in Guillain-Barré syndrome. Eur Neurol. 2001;46(2):107–9.

10. Appropriate number of plasma exchanges in Guillain-Barré syndrome. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Ann Neurol. 1997;41(3):298–306.

8.47 | Worksheet 47

Diseases: Hashimoto's encephalopathy

Procedure: PE, IAPP

Purpose: Removal of immunity-related substances and immunoregulation

Recommendation: 2C

Category: II

The number of references: RCT 0, CT 0, CS 0, CR 15

Description of the disease

It is a neuropsychiatric disorder that is caused by the autoimmune mechanism associated with Hashimoto's disease (chronic thyroiditis/autoimmune thyroiditis). There are many clinical symptoms, including consciousness disorders, psychological symptoms such as hallucinations/delusions and cognitive dysfunction, involuntary movements such as tremors and myoclonus, motor paralysis, cerebral ataxia, and spasms. Autoantibodies against the N-terminal α-enolase (NAE) (i.e., antibody NAE antibodies) have been reported as diagnostic markers for the serum.

Current management/treatment

Corticosteroids are the first-line treatment, and one of the characteristics of this disease is its good responsiveness to the drug. However, B cell depletion therapy with immunosuppressants, IVIG, apheresis, and anti-CD20 monoclonal antibody preparations is conducted for refractory cases given that this is an autoimmune disease.

Rationale for apheresis

Apheresis is thought to exhibit a therapeutic effect through the removal of immunity-related substances (including anti-thyroid antibodies) and immunomodulatory actions. Antibody NAE antibodies have been detected in approximately 50% of patients with Hashimoto's encephalopathy, but the pathological significance of these antibodies remains unclear. There have been case reports in which apheresis reduced the antithyroid peroxidase (TPO) antibodies but did not improve neurological symptoms, but there is also a report that summarized nine cases for which apheresis was effective.

Technical notes

There are many cases presenting with involuntary movements, and attention should be aimed in repairing the indwelling puncture site. Additionally, attention should be given to the immunoglobulin levels and the amount of fibrinogen after infection at the dwelling puncture site and after the procedure.

Duration and discontinuation/number of procedures

Not covered by insurance. Apheresis should be performed a total of 3–6 times over 7–14 days.

References

1. Tran MH, Mkhikian H, Sy M, Perez-Alvarez I, Demetriou M. Long-term plasma exchange as maintenance therapy for cerebellar-type Hashimoto's encephalopathy, a case report. Transfus Apher Sci. 2018;57:418–20.

2. Drulovic J, Andrejevic S, Bonaci-Nikolic B, Mijailovic V. Hashimoto's encephalopathy: a long-lasting remission induced by intravenous immunoglobulins. Vojnosanit Pregl. 2011;68:452–4.

3. Bektas O, Yilmaz A, Kendirli T, Siklar Z, Deda G. Hashimoto encephalopathy causing drug-resistant status epilepticus treated with plasmapheresis. Pediatr Neurol. 2012;46:132–5.

4. Boers PM, Colebatch JG. Hashimoto's encephalopathy responding to plasmapheresis. J Neurol Neurosurg Psychiatry. 2001;70:132.

5. Cook MK, Malkin M, Karafin MS. The use of plasma exchange in Hashimoto's encephalopathy: a case report and review of the literature. J Clin Apher. 2015;30:188–192.

6. Hussain NS, Rumbaugh J, Kerr D, Nath A, Hillis AE. Effects of prednisone and plasma exchange on cognitive impairment in Hashimoto encephalopathy. Neurology. 2005;64:165–6.

7. Mijajlovic M, Mirkovic M, Dackovic J, Zidverc-Trajkovic J, Sternic N. Clinical manifestations, diagnostic criteria and therapy of Hashimoto's encephalopathy: report of two cases. J Neurol Sci. 2010;288:194–6.

8. Nieuwenhuis L, Santens P, Vanwalleghem P, Boon P. Subacute Hashimoto's encephalopathy, treated with plasmapheresis. Acta Neurol Belg. 2004;104:80–3.

9. Nagpal T, Pande S. Hashimoto's encephalopathy: response to plasma exchange. Neurol India. 2004; 52:245–7.

10. Pari E, Rinaldi F, Premi E, et al. A follow-up ^{18}F-FDG brain PET study in a case of Hashimoto's encephalopathy causing drug-resistant status epilepticus treated with plasmapheresis. J Neurol. 2014;261:663–7.

11. Olmez I, Moses H, Sriram S, Kirshner H, Lagrange AH, Pawate S. Diagnostic and therapeutic aspects of Hashimoto's encephalopathy. J Neurol Sci. 2013;331: 67–71.

8.48 | Worksheet 48

Diseases: (Atypical, complement-mediated) hemolytic uremic syndrome (aHUS)

Procedure: PE

Purpose: Treatment of hemolytic uremic syndrome

Recommendation: Complement control factor abnormality Grade 2C

Acquired aHUS with anti-Factor H antibody Grade 2C

Category: Complement control factor abnormality III

Acquired aHUS with anti-Factor H antibody I

The number of references: RCT 0, CT 8, CS 17, CR 103

Description of the disease

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy that presents with intravascular hemolysis, thrombocytopenia, and acute renal failure. It is broadly classified into STEC-HUS, which is largely secondary to infection with Shiga toxin-producing Escherichia coli (STEC); atypical HUS (aHUS), which is the result of the dysregulation of complement activation associated with abnormalities in the complement regulators; and secondary HUS, which has comorbidity complications.

Current management/treatment

Rapid implementation of PE has been recommended as a first-line treatment. Once tests have ruled out thrombotic thrombocytopenic purpura, STEC infection, and secondary HUS as the underlying cause, Complement controlling treatment with eculizumab, which is a human monoclonal anti-C5 antibody, is recommended in cases of complement-mediated aHUS.

PE combined with immunosuppressant therapy is also effective for treating acquired aHUS with anti-Factor H antibodies, and eculizumab is also effective in the acute phase of these cases.

Rationale for apheresis

Removing the anti-Factor H antibodies and mutant humoral complement regulators present in the patient's plasma and replacing them with normal humoral complement regulators is critical to improving patient outcomes. In particular, aHUS with anti-humoral factor antibodies is expected to be effective in reducing the antibody titer when combined with immunosuppressants. Reports have verified that PE showed that although 83% of patients achieved hematological remission, renal sequelae remained in 80.3% of patients. Differences in effects depending on the type of pathological genetic abnormalities have also been reported. Meanwhile, replacement with a normal factor is impossible in MCP dysfunction, which involves the complement regulator on the cell membrane, so PE is thought to be ineffective in these cases.

Technical notes

One of the underlying mechanisms supporting the efficacy of PE in these conditions is the replacement of the abnormal complement regulators with normal complement regulators when fresh frozen plasma is used as the replacement solution. The transfusion volume should be set to 1–1.5 times the circulating plasma volume, and the procedure should be completed every day. Given the close relationship between these bleeding disorders and other bleeding abnormalities, such as thrombocytopenia, sufficient consideration must be given to ensuring vascular access.

Duration and discontinuation/number of procedures

There is no established protocol for the implementation period, number of implementations, or suspension of this interventions. The protocol should be determined based on the condition of the patient and responsiveness to treatment. Various tests should be used to make a definitive diagnosis when PE is introduced as the initial treatment for TMA, and these results should be used to help produce a subsequent treatment policy.

References

1. Schaefer F, Ardissino G, Ariceta G, et al. Clinical and genetic prediction of atypical hemolytic uremic syndrome phenotype and outcome. Kidney Int. 2018;94:408–18.

2. Brocklebank V, Johnson S, Sheerin TP, et al. Factor H autoantibody is associated with atypical hemolytic uremic syndrome in children in the United Kingdom and Ireland. Kidney Int. 2017;92:1261–71.

3. Greenbaum LA, Fila M, Ardissino G, et al. Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. Kidney Int. 2016;89:701–11.

4. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol. 2016;31:15–39.

5. Hans R, Sharma RR, Marwaha N, et al. Efficacy and safety of therapeutic plasma exchange by using apheresis devices in pediatric atypical hemolytic uremic syndrome patients. J Clin Apher. 2016;31:381–7.

6. Kato H, Nangaku M, Hataya H, et al. Clinical guides for atypical hemolytic uremic syndrome in Japan. Pediatrics Int. 2016;58:549–55.

7. Fakhouri F, Houmant M, Campistol JM, et al. Terminal complement inhibitor eculizumab in adult patients with atypical hemolytic uremic syndrome: a single-arm, open-label trial. Am J Kidney Dis. 2016;68:84–93.

8. Khandelwai P, gupta A, Sinha A, et al. Effect of plasma exchange and immunosuppressive medications on antibody titers and outcome in anti-complement factor H antibody-associated hemolytic uremic syndome. Pediatr Nephrol. 2015;30:451–7.

9. Licht C, Greenbaum LA, Muus P, et al. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int. 2015;87:1061–73.

10. Johnson S, Stojanovic J, Ariceta G, et al. An audit analysis of a guideline for the investigation and initial therapy of diarrhea negative (atypical) hemolytic uremic syndrome. Pediatr Nephrol. 2014;29:1967–78.

11. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic uremic syndrome. N Engl J Med. 2013;368:2169–81.

12. Taylor CM, Machin S, Wigmore SJ, et al. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. Br J Haematol. 2010;148:37–47.

13. Ariceta G, Besbas N, Johnson S, et al. Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. Pediatr Nephrol. 2009;24:687–96.

8.49 | Worksheet 49

Diseases: Hemophilia with inhibitors
Procedure: IAPP, PE, DFPP
Purpose: Removal of antibodies
Recommendation: Hemophilia with inhibitor 2C
Acquired hemophilia 2B
Category: Hemophilia with inhibitor III
Acquired hemophiliaII
The number of references: RCT 0, CT 0, CS 16, CR 84

Description of the disease

Antibody production against factor VIII is the most common. Hemophilia A treated with factor VIII produces allogeneic antibodies against infused factor VIII, which results in nonresponse to infusion and increased bleeding. Acquired hemophilia A involves the acquired production of antibodies against the patient's own factor VIII, usually resulting in significant bleeding abnormalities.

Current management/treatment

Bispecific antibody, emicizumab, is used to treat the majority of hemophilia A with inhibitor cases, but active factor VII (VIIa), activated prothrombin complex concentrate (aPCC), and the combined use of PE and factor VIII preparations are all commonly used to treat these bleeding abnormalaties. Immunotolerance therapy is also used to reduce the antibody titer. Immunosuppressive therapy is also applied in specific cases of acquired hemophilia A. VIIa, aPCC, and a combination of PE and factor VIII preparations should be evaluated in all cases of severe bleeding abnormalities.

Rationale for apheresis

Used to facilitate the removal of the anti-factor VIII antibody from both hemophilia A with inhibitor and acquired hemophilia A cases where increases in the concentration of infused factor VIII activity still exhibits some hemostatic effect. However, the long-term effects of PE on inhibitor removal have not been confirmed. IAPP has been used to combat IgG resistance in the West, but this is not yet approved in Japan. There are some Japanese reports describing DFPP as effective.

Technical notes

Implement when bleeding events cannot be sufficiently controlled, even when treated with emicizumab (for hemophilia A), VIIa, and aPCC. Insurance coverage is available for severe cases with antibody titers of 5 BU/ml or higher. There are several reports describing PE (replacement solution is FFP) or DFPP in Japan. The processed plasma volume is 1–1.5 times that of the circulating plasma volume.

Duration and discontinuation/number of procedures

Implement every day or 2–3 times a week until bleeding events are controlled. Treatment should be closely monitored and evaluated at each implementation.

References

1. Imafuku A, Sawa N, Ubara Y, Takaichi K. Acquired hemophilia A that developed during the induction of hemodialysis: the use of double-filtration plasmapheresis. Clin Nephrol. 2017;87:147–51.

2. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377:809–18.

3. Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, et al. Factor VIII–mimetic function of humanized bispecific antibody in hemophilia A. N Engl J Med. 2016;374:2044–53.

4. Leissinger CA. The literature on inhibitors: articles that influence my management of patients with hemophilia A and high-titer inhibitors. Am J Hematol. 2012;87:S23–6.

5. Zeitler H, Ulrich-Merzenich G, Hess L, Konsek E, Unkrig C, Walger P, et al. Treatment of acquired hemophilia by the Bonn-Malmö protocol: documentation of an in vivo immunomodulating concept. Blood. 2005;105:2287–93.

6. Freedman J, Garvey MB. Immunoadsorption of factor VIII inhibitors. Curr Opin Hematol. 2004;11:327–33.

7. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired hemophilia A: review and meta-analysis focused on therapy and prognostic factors. Brit J Haematol. 2003;121:21–35.

8. Guillet B, Kriaa F, Huysse MG, Proulle V, George IC, Tchernia G, et al. Protein A sepharose immunoadsorption: immunological and haemostatic effects in two cases of acquired haemophilia. Brit J Haematol. 2001;114:837–44.

9. Freiburghaus C, Berntorp E, Ekman M, Gunnarsson M, Kjellberg B, Nilsson IM. Tolerance induction using the Malmö treatment model 1982–1995. Haemophilia. 1999;5:32–9.

10. Sunagawa T, Uezu Y, Kadena K, Tokuyama K, Kinjo F, Saito A. Successful treatment of a non-haemophilic patient with inhibitor to factor VIII by double-filtration plasmapheresis. Brit J Haematol. 1999;104:465–7.

8.50 | Worksheet 50

Diseases: Heterozygous familial hypercholesterolemia

Procedure: LDL-A, DFPP, PE

Purpose: Removal of LDL

Recommendation: 1C

Category: II

The number of references: RCT 1, CT 4, CS 16, CR 13

Description of the disease

This disease is mainly caused by mutations in related genes such as genes for LDL receptors and proprotein convertase subtilisin/Kexin 9 (PCSK9). Its frequency is one in 2–300, and it has the highest frequency among hereditary metabolic diseases. The physical findings are characterized by the thickening of the Achilles tendon, cutaneous xanthoma, and juvenile corneal opacities. It has been reported that arteriosclerosis such as coronary artery disease develops at an early age, with complications of myocardial infarction occurring in 30% of men over the age of 50 years and 20% of women over the age of 60 years.

Current management/treatment

Drug therapy centered on statins is recommended, and ezetimibe or PCSK9 antibody drugs are added when the target LDL cholesterol level is not reached. In cases where the level is still insufficient or if the drugs are not tolerated, the addition of resin or probucol or the introduction of LDL-A will be required. In particular, cases of apheresis being withdrawn due to the introduction of PCSK9 antibody drugs have been found to increase, but the long-term prognosis of patients who undergo withdrawal is unknown.

Rationale for apheresis

Apheresis lowers the level of LDL cholesterol, which cause arteriosclerosis, and it also suppresses the progression of arteriosclerosis via various aspects such as the removal of Lp(a), PCSK9, or fibrinogen. In fact, the introduction of apheresis has been shown to lead to regression and inhibiting progression of coronary artery lesion, as well as reduction of the frequency of coronary artery disease.

Technical notes

LDL apheresis should be introduced in patients with severe coronary artery disease if LDL cholesterol levels cannot be controlled by drug therapy alone. Interruption of apheresis because LDL choresterol could be managed by drug therapy alone has been reported to possibly exacerbate coronary artery disease. Therefore, LDL-A should be continued in patients with severe coronary artery disease and LDL-A has already been introduced, even in case LDL cholesterol values can be managed with drug therapy alone. When using the liposorber system to patients taking ACE inhibitors, ensure that these agents are suspended prior to starting apheresis since hypotension can occur due to bradykinin.

Duration and discontinuation/number of procedures

Once every 2–4 weeks so that the average LDL cholesterol level is less than 70.

References

1. Nishimura S, Sekiguchi M, Kano T, Ishiwata S, Nagasaki F, Nishide T, et al. Effects of intensive lipid lowering by low-density lipoprotein apheresis on regression of coronary atherosclerosis in patients with familial hypercholesterolemia: Japan Low-density Lipoprotein Apheresis Coronary Atherosclerosis Prospective Study (L-CAPS). Atherosclerosis. 1999;144(2):409–17.

2. Mabuchi H, Koizumi J, Shimizu M, Kajinami K, Miyamoto S, Ueda K, et al. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group. Am J Cardiol. 1998; 82(12):1489–95.

3. Gordon BR, Kelsey SF, Dau PC, Gotto AM Jr, Graham K, Illingworth DR, et al. Long-term effects of low-density lipoprotein apheresis using an automated dextran sulfate cellulose adsorption system. Liposorber Study Group. Am J Cardiol. 1998;81(4):407–11.

4. Makino H, Tamnaha T, Harada-Shiba M. Chapter 15: LDL adsorption. In: Hemoperfusion book. 2016. p. 2364.

5. Matsuzaki M, Hiramori K, Imaizumi T, Kitabatake A, Hishida H, Nomura M, Fujii T, Sakuma I, Fukami K, Honda T, Ogawa H, Yamagishi M. Intravascular ultrasound evaluation of coronary plaque regression by low density lipoprotein-apheresis in familial hypercholesterolemia: the Low Density Lipoprotein-Apheresis Coronary Morphology and Reserve Trial (LACMART). J Am Coll Cardiol. 2002; 40(2):220–7.

6. Richter WO, Donner MG, Höfling B, Schwandt P. Long-term effect of low-density lipoprotein apheresis on plasma lipoproteins and coronary heart disease in native vessels and coronary bypass in severe heterozygous familial hypercholesterolemia. Metabolism. 1998; 47(7):863–8.

7. Yamamoto A, Harada-Shiba M, Kawaguchi A, Tsushima M. Apheresis technology for prevention and regression of atherosclerosis.Ther Apher. 2001;4:221–5.

8.51 | Worksheet 51

Diseases: Homozygous familial hypercholesterolemia

Procedure: Plasma adsorption (plasma exchange in early childhood)

Purpose: LDL removal

Recommendation: 1B

Category: I

The number of references: RCT 0, CT 2, CS 26, CR 15

Description of the disease

In this disaeas, the activity of the low-density lipoprotein (LDL) receptor is entirely or almost entirely lost bedause of pathogenic mutation in its gene. If untreated, severe LDL-cholesterolemia persists from birth, causing premature death from early-onset cardiovascular disease.

Classically, two alleles of LDLR gene mutations are present. Two allelles of pathogenic mutations occurring in combination in the APOB gene and PCSK9 gene, is also involved in homozygous FH.

Current management/treatment

Statins and PCSK9 inhibitors, which are generally used for hyper LDL-cholesterolemia, have LDL-C lowering effect via upregulation of LDL receptor. Therefore, these drugs have no or insufficient effect for this disease. The combination of ezetimibe and resin have also least effects. so therapy with LDL-A is the main form of treatment for this disease. Lomitapide, which has recently been indicated for this disease, has been approved and exhibits higher LDL lowering effects than the previously mentioned drugs, but its use alone is insufficient and should be combined with LDL-A.

Rationale for apheresis

Apheresis improves vital prognosis by adsorbing and removing LDL, which is the causative agent of arteriosclerosis. LDL-A is a treatment method that does not depend on LDL receptor function, so it can also reduce the level of LDL in patients with this disease according to the amount of processed plasma. LDL-A also helps eliminate arteriosclerosis-inducing lipoproteins other than LDL (e.g., VLDL, Lp[a]) as well as PCSK9, suppressing the expression of adhesive molecules.

This disease is rare and has a poor prognosis, so there are no randomized controlled trials of apheresis, which is considered an effective treatment from an early stage. However, LDL-A has been reported to alleviate arteriosclerosis according to the findings of angiography, ultrasonography, and computed tomography studies, and it has been reported to suppress cardiovascular events.

Technical notes

Be cautious of hemodynamics in patients who already have cardiovascular disease.

Angiotensin-converting enzyme inhibitors are contraindicated, and their use should be suspended prior to treatment.

Consider plasma exchange treatment during early childhood, when the use of an adsorption column is difficult.

Duration and discontinuation/number of procedures

As a general rule, maintenance therapy centered on LDL-A must be continued.

Apheresis can be included up to once a week under insured medical treatment.

References

1. Thompson GR, Blom DJ, Marais AD, Seed M, Pilcher GJ, Raal FJ. Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol. Eur Heart J. 2018 Apr 7; 39(14):1162–8.

2. Stein EA, Dann EJ, Wiegman A, Skovby F, Gaudet D, Sokal E, et al. Lipoprotein apheresis in the treatment of dyslipidaemia - the Czech Republic experience. J Am Coll Cardiol. 2017 Aug 29;70(9):1162–70.

3. Bláha V, Bláha M, Lánská M, Solichová D, Kujovská Krčmová L, Havel E, et al. Lipoprotein apheresis in the treatment of dyslipidaemia - the Czech Republic experience. Physiol Res. 2017 Apr 5; 66(Suppl 1):S91–S100.

4. Bruckert E, Kalmykova O, Bittar R, Carreau V, Béliard S, Saheb S, et al. Long-term outcome in 53 patients with homozygous familial hypercholesterolaemia in a single centre in France. Atherosclerosis. 2017 Feb;257:130–7.

5. Harada-Shiba M, Ikewaki K, Nohara A, Otsubo Y, Yanagi K, Yoshida M, et al. Efficacy and safety of lomitapide in Japanese patients with homozygous familial hypercholesterolemia. J Atheroscler Thromb. 2017 Apr 3;24(4):402–11.

6. Wang A, Richhariya A, Gandra SR, Calimlim B, Kim L, Quek RG, et al. Systematic review of low-density lipoprotein cholesterol apheresis for the treatment of familial hypercholesterolemia. J Am Heart Assoc. 2016 Jul 6;5(7):e003294.

7. Coker M, Ucar SK, Simsek DG, Darcan S, Bak M, Can S. Low density lipoprotein apheresis in pediatric patients with homozygous familial hypercholesterolemia. Ther Apher Dial. 2009 Apr;13(2):121–8.

8. Hudgins LC, Kleinman B, Scheuer A, White S, Gordon BR. Long-term safety and efficacy of low-density lipoprotein apheresis in childhood for homozygous familial hypercholesterolemia.Am J Cardiol. 2008 Nov 1; 102(9):1199–204.

8.52 | Worksheet 52

Diseases: HTLV-1 associated myelopathy (HAM)
Procedure: PE, IAPP, and LCAP
Purpose: Introduction and maintenance of remission
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 2, CR 2

Description of the disease

This disease is characterized by chronic progressive spastic spinal cord paralysis in human T-cell leukemia virus type 1 (HTLV-1) carriers. The main symptom is gait disturbance due to spastic paraplegia and is usually slowly progressive and chronic. It is thought to affect approximately 0.3% of HTLV-1 carriers, and the number of patients nationwide is estimated to be approximately 3000. The age of onset in usually middle-aged and older, and a female predilection is seen.

Current management/treatment

The treatment for rapidly progressing cases involves immunotherapy/antiviral therapy with the objective of adjusting excessive immune response. Oral corticosteroid maintenance therapy is generally conducted after steroid pulse therapy. Oral corticosteroids or IFN-α are administered for gradually progressing cases. HTLV-1 mainly infects chemokine receptor CCR4–expressing T cells and is important for the pathogenesis; therefore, doctor-initiated clinical trials of humanized anti-CCR4 antibodies have been conducted in refractory cases.

Rationale for apheresis

Studies have shown the effectiveness of apheresis for HAM. Comparative trials of PE and corticosteroid therapy showed that 11 of 18 patients who received PE and 14 of 20 patients who received corticosteroid therapy exhibited therapeutic effects, and both treatments had the same effect. It was reported in particular that 5 of 11 patients with PE exhibited rapid and significant improvements.

Technical notes

Apheresis for HAM can be effective in all rapidly progressing, gradually progressing, and refractory cases. However, it is more invasive than both steroid pulse therapy or oral corticosteroids, and its application should be carefully considered.

Duration and discontinuation/number of procedures

It is not covered by insurance. Previous reports involved four or six sessions of PE over 2 weeks.

References

1. Matsuo H, Nakamura T, Tsujihata M, et al: Plasmapheresis in treatment of human T-lymphotropic virus type-I associated myelopathy. Lancet. 1988;2(8620): 1109–13.

2. Itoyama Y, Minato S, Kira J, et al. Spontaneous proliferation of peripheral blood lymphocytes increased in patients with HTLV-I-associated myelopathy. Neurology. 1988;38:1302–7.

3. Matsuo H, Nakamura T, Tsujihata M, et al. Human T-lymphotropic virus type I (HTLV-I) associated myelopathy in Nagasaki: clinical features and treatment of 21 cases. Jpn J Med. 1989;28:328–34.

4. Oishi M, Mochizuki Y, Hara M, et al. Human T-lymphotropic virus type I associated myelopathy treated effectively with lymphocytapheresis using a leukocyte removal filter. Intern Med. 1995;34:1215–9.

5. Nakagawa M, Nakahara K, Maruyama Y, et al. Therapeutic trials in 200 patients with HTLV-I-associated myelopathy/tropical spastic paraparesis. J Neurovirol. 1996;2:345–55.

6. Osame M, Nakagawa M, Umehara F, et al. Recent studies on the epidemiology, clinical features and pathogenic mechanisms of HTLV-I associated myelopathy (HAM/TSP) and other diseases associated to HTLV. J Neurovirol. 1997;3:S50–1.

7. Gessain A, Mahieux R. Tropical spastic paraparesis and HTLV-1 associated myelopathy: clinical, epidemiological, virological and therapeutic aspects. Rev Neurol. 2012;168:257–69.

8. Narukawa N. Shiizaki K, Kitabata Y, et al. Plasma exchange for the treatment of human T-cell lymphotropic virus type 1 associated myelopathy. Ther Apher. 2001;5:491–3.

8.53 | Worksheet 53

Diseases: Hyper Lp(a)-emia
Procedure: LDL-A, DFPP, PE
Purpose: Removal of Lp(a)
Recommendation: 1C
Category: II
The number of references: RCT 0, CT 6, CS 6, CR 7

Description of the disease

Lp(a) is one of the atherogenic lipoproteins and protein part of which apolipoprotein (a) bounds to apolipoprotein B and . Hyper Lp(a)-emia is a condition in which a large amount of Lp(a) is present in the blood. The concentration of Lp(a) is genetically determined. Apolipoprotein (a) has structural similarities with plasminogen, and it has been reported to be closely associated with the onset and progression of atherosclerosis, either directly, or through the coagulation/fibrinolytic system. A arge amount of epidemiological data has also shown that hyper Lp(a)-emia is an independent risk factor for atherosclerosis. However, there are currently no drugs that can effectively reduce Lp(a).

Current management/treatment

Lp(a) is a risk factor for atherosclerosis and patients with atherosclerotic cardiovascular disease, especially those with high levels of Lp(a), should be treated. However, there are currently no effective treatments other than lipoprotein apheresis. The proprotein convertase subtilisin/kexin type 9 (PCSK) inhibitor, which was recently made commercially available, reduces Lp(a), but it does not come close to the effects of lipoprotein apheresis. However, hyper Lp(a)-emia is currently not indicated for lipoprotein apheresis in Japan.

Rationale for apheresis

Lp(a) is closely associated with the onset and progression of atherosclerosis, so its removal has been considered to possibly prevent the progression of this disease. It can, in fact, be removed by liposorber system or DFPP because Lp(a) contains apolipoprotein B, and its size ranges between that of VLDL and LDL. Clinical trials investigating the effects of lipoprotein apheresis on hyper Lp(a)-emia have been conducted to date, and informative data in relation to cardiovascular events have benn published.

Technical notes

Concomitant use with ACE inhibitors is contraindicated during use of a liposorber system. Caution should be paid since blood bradykinin levels will be increased during administration of ACE inhibitors, which can cause hypotension and shock.

Duration and discontinuation/number of procedures

About once every 2–3 weeks

References

1. Seidel D. The HELP-system in the treatment of severe hypercholesterolaemia: acute and long-term experience. Adv Exp Med Biol. 1991;285:155–9.

2. Pokrovsky SN, Sussekov AV, Afanasieva OI, Adamova IY, Lyakishev AA, Kukharchuk VV. Extracorporeal immunoadsorption for the specific removal of lipoprotein (a) (Lp(a) apheresis): preliminary clinical data. Chem Phys Lipids. 1994;67–68:323–30.

3. Yamaguchi H, Lee YJ, Daida H, Yokoi H, Miyano H, Kanoh T, et al. Effectiveness of LDL-apheresis in preventing restenosis after percutaneous transluminal coronary angioplasty (PTCA): LDL-apheresis angioplasty restenosis trial (L-ART). Chem Phys Lipids. 1994; 67–68:399–403.

4. Daida H, Lee YJ, Yokoi H, Kanoh T, Ishiwata S, Kato K, et al. Prevention of restenosis after percutaneous transluminal coronary angioplasty by reducing lipoprotein (a) levels with low-density lipoprotein apheresis. Low-Density Lipoprotein Apheresis Angioplasty Restenosis Trial (L-ART) Group. Am J Cardiol. 1994;73:1037–40.

5. Ullrich H, Lackner K, Schmitz G. Lipoprotein(a)-apheresis in the secondary prevention of coronary heart disease. Transfus Sci. 1996;17:511–7.

6. Jaeger BR, Richter Y, Nagel D, Heigl F, Vogt A, Roeseler E, et al. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. Nat Clin Pract Cardiovasc Med. 2009;6:229–39.

7. Leebmann J, Roeseler E, Julius U, Heigl F, Spitthoever R, Heutling D, et al. Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study. Circulation. 2013;128:2567–76.

8. Rosada A, Kassner U, Vogt A, Willhauck M, Parhofer K, Steinhagen-Thiessen E. Does regular lipid apheresis in patients with isolated elevated lipoprotein(a) levels reduce the incidence of cardiovascular events? Artif Organs. 2014;38:135–41.

9. Khan TZ, Pottle A, Pennell DJ, Barbir MS. The expanding role of lipoprotein apheresis in the treatment of raised lipoprotein(a) in ischaemic heart disease and refractory angina. Glob Cardiol Sci Pract. 2014;2014:3–12.

8.54 | Worksheet 54

Diseases: Hyperleukocytosis

Procedure: Centrifugal blood cell component removal method

Purpose: Improvement of various symptoms associated with hyperleukocytosis

Recommendation: Symptomatic 1B

Prevention 2C

Category: Symptomatic II

Prevention III

The number of references: RCT 0, CT 18, CS 23, CR 27

Description of the disease

Hyperleukocytosis (HL) is generally defined as a condition with a leukocyte count of 100 000/μl or more. Acute myeloid leukemia (AML) complications are present in approximately 5%–20% of cases. The complications associated with acute lymphocytic leukemia (ALL) are also present in 10%–30% of cases. Chronic lymphocytic leukemia and chronic myeloid leukemia can also present with HL. Complications with HL include increased risk of disseminated intravascular coagulation (DIC) and tumor lysis syndrome (TLS), as well as symptoms associated with leukostasis. The latter is a particularly major clinical complication. The leukocyte count presenting with leukostasis differs according to the disease, with its frequency increasing at more than 100 000/μl and 400 000/μl for AML and ALL, respectively. However, it is known to even occur at around 50 000/μl for AML M4 and M5.

Current management/treatment

Remission induction therapy should be promptly administered according to the underlying disease for cases with HL. The treatment for TLS and DIC should be actively administered. Combined implementation of leukocytapheresis should also be considered in cases presenting with symptoms of leukostasis (particularly lung and central nervous system symptoms). Prophylactic leukocytapheresis is not actively recommended in cases presenting only with HL with no symptoms of leukostasis.

Rationale for apheresis

There have been reports that leukocytapheresis as an initial treatment for cases presenting with HL contributed to a decrease in early mortality rates. However, its outcomes are not consistent. There are also reports that this treatment did not lead to any improvements in remission rate or overall survival over a long term.

There are reports of the effectiveness of treatment in improving symptoms of leukostasis. Therefore, the combined use of remission induction therapy and leukocytapheresis can be considered when symptoms of leukostasis are present.

Technical notes

Decreased leukocyte counts owing to leukocytapheresis are temporary. Remission induction therapy should be rapidly implemented when the patient presents with symptoms of leukostasis. The risks of apheresis complications should, therefore, be considered at this time (e.g., cardiovascular risk, hemodynamics, bleeding tendencies, and ease of blood access), and whether treatment should be administered needs to be determined. In addition, sufficient attention should be paid to the decrease in platelet counts after apheresis.

The circulating blood volume should be aimed at 1.5–2.0 times for the processed blood volume and leukocytapheresis should be performed every day or twice a day.

Replenishment with extracellular fluid or albumin preparations should be performed if the amount of cell suspension to be removed is large.

Duration and discontinuation/number of procedures

Treatment should be continued until the symptoms of leukostasis are alleviated and the leukocyte count is decreased to 50 000–100 000/μl.

References

1. Oberoi S, Lehrnbecher T, Phillips B, et al. Leukapheresis and low-dose chemotherapy do not reduce early mortality in acute myeloid leukemia hyperleukocytosis: a systematic review and metaanalysis. Leuk Res. 2014;38:460–8.

2. Giles FJ, Shen Y, Kantarjian HM, et al. Leukapheresis reduces early mortality in patients with acute myeloid leukemia with high white cell counts but does not improve long- term survival. Leuk Lymphoma. 2001;42:67–73.

3. Bug G, Anargyrou K, Tonn T, et al. Impact of leukapheresis on early death rate in adult acute myeloid leukemia presenting with hyperleukocytosis. Transfusion. 2007;47:1843–50.

4. Porcu P, Farag S, Marcucci G, et al. Leukocytoreduction for acute leukemia. Ther Apher. 2002;6:15–23.

5. Choi MH, Choe YH, Park Y, et al. The effect of therapeutic leukapheresis on early complications and outcomes in patients with acute leukemia and hyperleukocytosis: a propensity score-matched study. Transfusion. 2018;58:208–16.

6. Nguyen R, Jeha S, Zhou Y, et al. The role of leukapheresis in the current management of hyperleukocytosis in newly diagnosed childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2016;63:1546–51.

7. Creutzig U, Rössig C, Dworzak M, et al. Exchange transfusion and leukapheresis in pediatric patients with AML with high risk of early death by bleeding and leukostasis. Pediatr Blood Cancer. 2016;63:640–5.

8. Kuo KH, Callum JL, Panzarella T, et al. A retrospective observational study of leucoreductive strategies to manage patients with acute myeloid leukaemia presenting with hyperleucocytosis.Br J Haematol. 2015;168:384–94.

8.55 | Worksheet 55

Diseases: Hypertrophic pachymeningitis
Procedure: LCAP
Purpose: Immunomodulation
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 0, CR 1

Description of the disease

Hypertrophic pachymeningitis (HP) refers to a pathological state in which the pachymeninx becomes significantly thicker, mainly in the skull and spine. It is a disease that causes multiple cranial nerve disorders such as headaches, hearing loss, and facial nerve paralysis and neurological symptoms such as cerebellar ataxia and myelopathy. HP can be classified into secondary or idiopathic types. In the case of secondary HP, causes are thought to be ANCA-related vasculitis, Wegener's granulomatosis, inflammatory diseases (e.g., sarcoidosis), bacterial/fungal/tuberculosis infection, and multiorgan fibrosis. There have been recent cases in which IgG4-positive plasma cells were found in biopsied pachymeninx tissue that was diagnosed with idiopathic HP, suggesting a relationship between IgG4-related disease and idiopathic HP. The prevalence of HP in Japan was 0.949 per 100 000 people, the average age at onset was 58.3 years, and the male–female ratio was 1:0.91.

Current management/treatment

Corticosteroid therapy is often performed according to IgG4-related disease in the case of idiopathic HP. Oral maintenance therapy is gradually tapered off after steroid pulse treatment (methylprednisolone 1000 mg/day, 3 days). Combined treatment with immunosuppressants (e.g., methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide) or rituximab, a CD20-monoclonal antibody, has been reported to be effective when the effect of corticosteroid therapy is insufficient. Shunting may also be performed as a form of surgical treatment, and the excision of hypertrophic pachymeninx may be performed to alleviate the pressure imposed by the pachymeninx.

Rationale for apheresis

In idiopathic HP, especially IgG4-related HP, inflammatory infiltration by T/B lymphocytes induces collagen deposition through the activation of fibroblasts, which in turn induces collagen deposition and promotes tissue and pachymeninx hypertrophy.

Similar to the above-mentioned corticosteroid or immunosuppressant therapies, apheresis is expected to correct the patient's immunity status, although the mechanism of action is unknown.

Technical notes

Only one study has reported the effectiveness of apheresis for idiopathic hypertrophic pachymeningitis thus far. Yamamoto et al. reported that a single session of LCAP in a 48-year-old man with headaches, facial pain, unilateral tongue atrophy, and swallowing disorder who was diagnosed with idiopathic HP resulted in sustained long-term (14 months) effects. Although steroid pulse therapy was effective in this case, the patient developed steroid-induced diabetes during oral administration; therefore, apheresis was selected as an alternative for maintenance therapy.

Cellsorba (CS 100; Asahi Medical Co., Tokyo, Japan) was used, and 50 ml of whole blood was collected every minute, with a total of 3000 ml of whole blood processed over 60 min in a single session. The decrease in the CD4/8 ratio was sustained even after the completion of apheresis, and no clinical recurrence was observed for 14 months. There are no reports on plasma exchange therapy.

Duration and discontinuation/number of procedures

Required further consideration regarding the indications for LCAP.

References

1. Available from: https://www.nanbyou.or.jp/entry/3202

2. De Virgilio A, de Vincentiis M, Inghilleri M, Fabrini G, Conte M, Gallo A, et al. Idiopathic hypertrophic pachymeningitis: an autoimmune IgG4-related disease. Immunol Res. 2017 Feb;65(1):386–394. https://doi.org/10.1007/s12026-016-8863-1

3. Yonekawa T, Murai H, Utsuki S, Matsushita T, Masaki K, Isobe N, et al. A nationwide survey of hypertrophic pachymeningitis in Japan. J Neurol Neurosurg Psychiatry. 2014 Jul;85(7):732–9. https://doi.org/10.1136/jnnp-2013-306410

4. Lu LX, Della-Torre E, Stone JH, Clark SW. IgG4-related hypertrophic pachymeningitis: clinical features, diagnostic criteria, and treatment. JAMA Neurol. 2014 Jun;71(6):785–93. https://doi.org/10.1001/jamaneurol.2014.243

5. Yamamoto T, Goto K, Suzuki A, Nakamura N, Mizuno Y. Long-term improvement of idiopathic hypertrophic cranial pachymeningitis by lymphocytapheresis. Ther Apher. 2000;4(4):313–6.

8.56 | Worksheet 56

Diseases: Hyperviscosity syndrome
Procedure: PE, DFPP
Purpose: Removal of excess immunoglobulin
Recommendation: 1B
Category: I
The number of references: RCT 0, CT 3, CS 19, CR NA

Description of the disease

Hyperviscosity is a pathological condition where a predominantly monoclonal increase of immunoglobulin induces increased plasma viscosity and red blood cell aggregation. This leads to increased blood viscosity and presents with various symptoms such as bleeding tendencies, venous distension in the fundus, fundus hemorrhaging, headache, dizziness, and hearing loss. It can occur in patients with macroglobulinemia with IgM > 3–4 g/dl and multiple myeloma with polymerized IgA > 6–7 g/dl, IgG3 > 4–5 g/dl. It is a pathological condition for which apheresis was shown to be effective in the 1950s.

Current management/treatment

PE is the first line of treatment for the hyperviscosity syndrome, but underlying diseases are simultaneously treated. Primary macroglobulinemia, characterized by excessive production of monoclonal IgM, is treated as a gradually progressing non-Hodgkin's lymphoma. Multiple myelomas are treated when they produce IgA and IgG3.

Rationale for apheresis

Apheresis removes the excess monoclonal immunoglobulins, which are directly responsible for the hyperviscosity syndrome. In particular, 80% of IgMs are present in the blood vessels, and apheresis has excellent IgM removal efficiency. A small percentage of removal ability causes decreased viscosity and rapid improvement of symptoms. There are many case reports.

Technical notes

The hyperviscosity syndrome tends to cause bleeding owing to hyperviscosity of the blood. Thus, this is promptly diagnosed based on fundus findings, and PE using albumin as a replacement solution is conducted. Replacement of approximately 1–1.5 times the circulating plasma volume is conducted. Blood viscosity rapidly decreases. Attention must be paid to the deterioration of removal efficiency and membrane clogging for DFPP.

Duration and discontinuation/number of procedures

Perform daily until symptoms improve. It should be performed at the same time with chemotherapy to control the underlying disease. Maintenance therapy can be performed at regular intervals while observing immunoglobulin levels if symptoms are not sufficiently controlled by chemotherapy.

References

1. Kwaan HC. Hyperviscosity in plasma cell dyscrassias. Clin Hemorheol Microcirc. 2013;55:75–83.

2. Stone MJ, Bogen SA. Evidence-based focused review of management of hyperviscosity syndrome. Blood. 2012;119:2205–8.

3. Ansell SM, Kyle RA, Reeder CB. Diagnosis and management of Waldenström's macroglobulinemia: Mayo stratification of macroglobulinemia and risk-adapted therapy(mSMART) guidelines. Mayo Clin Proc. 2010;85:824–33.

4. Hoffkes HG, Heemann UW, Tschendorf C, et al. Hyperviscosity syndrome: efficacy and comparison of plasma exchange by plasma separation and cascade filtration in patients with immunocytoma of Wardenstrom's type. Clin Nephrol. 1995;43:335–8.

5. Adams WS, Blahd WH, Bassett SH. A method of human plasmapheresis. Proc Soc Exp Biol Med. 1952;80:377–9.

8.57 | Worksheet 57

Diseases: Inclusion body myositis (IBM)
Procedure: PE, LDL-A
Purpose: Introduction and maintenance of remission
Recommendation: 2C
Category: IV
The number of references: RCT 0, CT 0, CS 0, CR 2

Description of the disease

Inclusion body myositis (IBM) is an inflammatory myopathy characterized by the presence of structures resembling eosinophilic inclusion bodies in the nucleus or cytoplasm. It is relatively common among the elderly, who are refractory to the treatment, and exhibits slow progression. Weakness may also affect distal muscles from the early stages. Also, the serum creatine kinase (CK) levels are found to be mildly elevated. This muscular pathology is characterized by the presence of inflammatory but mild cell infiltration as well as degenerated myofibers along with rimmed vacuoles. IBM is thought to exhibit a different pathology compared to other inflammatory muscle disorders, because in case of IBM muscle degeneration is accompanied with inflammatory changes.

Current management/treatment

An effective treatment has not been established yet. There have been reports on the application of corticosteroids and high-dose immunoglobulin therapy, but there effectiveness is limited. Apheresis is also considered ineffective; however, reports indicated improvement in some cases.

Rationale for apheresis

There are no reports on the application of apheresis in controlled trials, but it is usually considered ineffective. However, CD8/MHC-1 complex was found in the IBM lesions, thereby suggesting the involvement of cell-mediated immunity. Therefore, patients with IBM may respond to immunotherapy. There are reports that indicated certain level of efficacy of immunotherapy in patients with IBM accompanied with monoclonal hypergammaglobulinemia, and thus, it might be useful to attempt other treatments for resistant and refractory cases.

Technical notes

Immunoglobulins and coagulation factors are also removed non-selectively in PE, so a replenishment solution (i.e., albumin or FFP) must be selected. LDL-A is contraindicated since it leads to excessive production of bradykinin when used in combination with ACE-I and results in a shock response.

Duration and discontinuation/number of procedures

This treatment is not covered in the insurance. There are few reports have demonstrated its effectiveness; however, such indications are limited. There are no established methods, and thus, the evaluation should be performed on a case-by-case basis using the methods in accordance with PM/DM.

References

1. Yunis EJ, Samaha FJ. Inclusion body myositis. Lab Invest. 1971 Sep;25(3):240–8.

2. Askanas V, Serratrice GS, Engel WK. Inclusionbody myositis and myopathies. Cambridge: Cambridge Univ Press; 1998.

3. Nonaka I, Sunohara N, Ishiura S, Satoyoshi E. Familial distal myopathy with rimmed vacuole and lamellar (myeloid) body formation. J Neurol Sci. 1981 Jul;51(1):141–55.

4. Askanas V, Engel WK, Alvarez RB. Enhanced detection of congo-red-positive amyloid deposits in muscle fibers of inclusion body myositis and brain of Alzheimer's disease using fluorescence technique. Neurology. 1993 Jun;43(6):1265–7.

5. Dalakas MC. Inflammatory disorders of muscle: progress in polymyositis, dermatomyositis and inclusion body myositis. Curr Opin Neurol. 2004;17:561–7.

6. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet. 2003;362:971-982.

7. Mastaglia FL, Garlepp MJ, Phillips BA, Zilko PJ. Inflammatory myopathies: clinical, diagnostic and therapeutic aspects. Muscle Nerve. 2003;27:407–25.

8. Engel AG, Hohlfeld R. In: Engel AG, et al., editors. The polymyositis and dermatomyositis syndrome. New York: McGraw-Hill; 2004. p. 1321–66.

9. Dau PC. Immunomodulation during treatment of polymyositis with plasmapheresis and immunosuppressive drugs. J Clin Apher. 1994;9(1):21–5.

10. Kiprov DD, Miller RG. Polymyositis associated with monoclonal gammopathy. Lancet. 1984 Nov 24; 2(8413):1183–6.

8.58 | Worksheet 58

Diseases: Isaacs' syndrome
Procedure: PE, DFPP
Purpose: Removal of autoantibodies
Recommendation: Grade 2B
Category: III
The number of references: RCT 0, CT 0, CS 0, CR 6

Description of the disease

Isaacs' syndrome is a disease characterized by persistent and painful muscle spasms and myotonia of the limbs and trunk along with myokymia and neuromyotonia. Muscle spasms and stiffness also occur during sleep, which further aggravate due to exercise load, cold, and ischemia. It is also accompanied by autonomic symptoms, such as excessive sweating, diarrhea, changes in skin tone, and hyperthermia due to unknown cause. It is speculated that the voltage-gated potassium channel (VGKC) complex antibodies cause functional abnormalities of the VGKC and induce hyperexcitability of peripheral nerves. Complications of thymoma, myasthenia gravis, hyperthyroidism, and systemic lupus erythematosus have also been reported. Morvan syndrome is characterized by various autonomic nervous system symptoms (e.g., arrhythmia, urinary incontinence) and central nervous system symptoms (e.g., severe insomnia, nocturnal behavioral abnormalities, hallucinations, memory impairment) in addition to the above-mentioned symptoms. The anti-VGKC complex antibody-related encephalitis is also characterized by the central nervous system symptoms (e.g., amnesia, disorientation, seizures).

Current management/treatment

There is no radical cure established so far. All diseases related to Isaacs' syndrome are rare, and there is no evidence in the form of RCTs. Drug therapies involve the application of Na channel inhibitors (e.g., carbamazepine, phenytoin, lamotrigine) with the objective to suppress the hyperexcitability of the peripheral nerves. Immunotherapy includes apheresis therapy, IVIG, and steroid pulse therapy. Resection improves clinical symptoms if the patient has thymoma or lung cancer. Elimination of the anti-VGKC complex antibody using PE is effective in the cases that are positive for the anti-VKGC complex antibody and thought to be associated with autoimmunity, refractory cases, and cases with disorders that significantly affect the day-to-day life.

Rationale for apheresis

Apheresis therapy reduces the anti-VGKC antibodies and improves clinical symptoms in anti-VGKC complex antibody-positive cases.

Technical notes

PE is recommended because the anti-VGKC complex antibody mainly corresponds to IgG4 or IgG1. The case reports indicated therapeutic effects exerted by IAPP. The therapeutic effects of PE may not appear immediately after the treatment, but may be 1–2 weeks after the treatment.

Duration and discontinuation/number of procedures

Only the cases where PE was effective have been reported, and thus, the optimal number of PE is unknown. PE is usually conducted three times a week, followed by three times during the subsequent week.

References

1. Isaacs H. A syndrome of continuous muscle-fibre activity. J Neurol Neurosurg Psychiatry. 1961; 24(4):319–25.

2. Ahmed A, Simmons Z. Isaacs syndrome: a review. Muscle Nerve. 2015;52(1):5–12.

3. Irani SR, Vincent A. Voltage-gated potassium channel-complex autoimmunity and associated clinical syndromes. Handb Clin Neurol. 2016;133:185–97.

4. Nakatsuji Y, Kaido M, Sugai F, et al. Isaacs' syndrome successfully treated by immunoadsorption plasmapheresis. Acta Neurol Scand. 2000;102(4):271–3.

5. Ansell J, Kirby S, Benstead T. A case of Isaacs' syndrome with associated central nervous system findings. Muscle Nerve. 1997;20(10):1324–7.

6. Song J, Jing S, Quan C, et al. Isaacs syndrome with CASPR2 antibody: A series of three cases. J Clin Neurosci. 2017;41:63–6.

7. Bin Waqar SH. Waves in extremities: a rare report of isolated Isaacs' syndrome. Cureus. 2019 May 17;11(5): e4687.

8. Ishii A, Hayashi A, Ohkoshi N, et al. Clinical evaluation of plasma exchange and high dose intravenous immunoglobulin in a patient with Isaacs' syndrome. J Neurol Neurosurg Psychiatry. 1994;57(7):840–2.

9. Jaben EA, Winters JL. Plasma exchange as a therapeutic option in patients with neurologic symptoms due to antibodies to voltage-gated potassium channels: a report of five cases and review of the literature. J Clin Apher. 2012;27(5):267–73.

8.59 | Worksheet 59

Diseases: Lambert-Eaton myasthenic syndrome
Procedure: PE
Purpose: Removal of autoantibodies
Recommendation: Grade 2C
Category: II
The number of references: RCT 0, CT 0, CS 7, CR 5

Description of the disease

Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular junction disorder characterized by proximal muscle weakness, autonomic neuropathy, and decreased tendon reflex. Autoantibodies of the presynaptic P/Q type voltage-gated calcium channels (VGCC) are found in 85%–90% of LEMS cases, and it is caused by a decrease in acetylcholine secretion from the neuromuscular junction. The initial symptoms of proximal muscle weakness in the lower limbs and gait disturbance are observed in 80% of cases. Neurological findings include decreased tendon reflex and autonomic neuropathy (e.g., dry mouth, constipation, decreased sweating), as well as cerebellar ataxia. The diagnosis of the disorder is based on detecting proximal muscle weakness mainly in the lower limbs, as well as P/Q-VGCC autoantibodies, and the outcomes of related to the waxing phenomenon in electrophysiological examinations. Malignant tumors (e.g., small cell lung cancer [SCLC], Hodgkin's lymphoma, thymic adenocarcinoma) are common complications, and the disorder may include paraneoplastic neurological syndrome. LEMS with SCLC is common in men aged 50–60 years. Non-neoplastic LEMS has been reported for all ages, with the predominant age, based on a bimodal peak, falling between 35 and 60 years. Half of the cases are found in females.

Current management/treatment

LEMS treatment involves the early detection of malignant tumors and radical treatment. Treatment for the underlying disease is required for cases with malignant tumors. Symptomatic treatments include the use of cholinesterase inhibitors and 3,4-diaminopyridine (not approved for insurance in Japan); their effectiveness have been confirmed in a randomized double-blind trial. Immunotherapy is also used to control autoantibody production. If a patient presents with advanced weakness and progress is slow, IVIG (2000 mg/kg, 2–5 days) and PE are administered in addition to corticosteroids and immunosuppressants.

Rationale for apheresis

Apheresis therapy is performed to remove autoantibodies, but there are no reports on comparative studies for LEMS involving large samples. PE is mainly used, and there are only case reports on the therapeutic effects of IAPP. The therapeutic effects of PE appear at a relatively early stage, and they are observed over several weeks although they are relatively temporary. Apheresis therapy is not covered by insurance in Japan; however, multiple case reports have been published, and its clinical effectiveness has been confirmed.

Technical notes

It has been reported that PE was conducted 5–10 times over 3 weeks or 5–10 times every 5–7 days; however, no treatment protocol has been established. Be aware of hypotension due to decreased plasma volume, metabolic alkalosis due to repeated PE, infection and thrombi, and hypocalcemia (and the muscle spasms and arrhythmia caused by it), among others.

Duration and discontinuation/number of procedures

Not covered by insurance. The amount of plasma processed is 1–1.5 times the total plasma volume. There are no established PE protocols for LEMS.

References

1. O'Neill JH, Murray NMF, Newsom-Davis J. The Lambert-Eaton myasthenic syndrome – a review of 50 cases. Brain. 1988;111:577–96.

2. Titulaer MJ, Wirtz PW, Kuks JB, et al. The Lambert-Eaton myasthenic syndrome 1988–2008: a clinical picture in 97 patients. J Neuroimmunol. 2008;201:153–8.

3. Titulaer MJ, Maddison P, Sont JK, et al. Clinical Dutch-English Lambert-Eaton Myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. J Clin Oncol. 2011;29:902–8.

4. Lennon VA, Kryzer TJ, Griesmann GE, et al. Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. N Engl J Med. 1995;332:1467–74.

5. Maddison P. Treatment in Lambert-Eaton myasthenic syndrome. Ann N Y Acad Sci. 2012;1275:78–84.

6. Skeie GO, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol. 2010;17:893–902.

7. Vedeler CA, Antoine JC, Giometto B, et al. Paraneoplastic neurological syndromes. In: Gilhus NE, Barnes MP, Brainin M, editors. European handbook of neurological management. 2nd ed. Oxford:Blackwell Publishing Ltd; 2011. p. 447–457.

8. Newsom-Davis J, Murray NM. Plasma exchange and immunosuppressive drug treatment in the Lambert-Eaton myasthenic syndrome. Neurology. 1984;34:480–5.

8.60 | Worksheet 60

Diseases: Multifocal motor neuropathy
Procedure: PE
Purpose: Removal of autoantibodies
Recommendation: 1C
Category: IV
The number of references: RCT 1, CT 0, CS 0, CR 8

Description of the disease

Multifocal motor neuropathy (MMN) is an acquired chronic demyelinating peripheral neuropathy with the main symptoms of left-right asymmetry without sensory impairment, muscle weakness that is predominantly distal to the upper limbs, and muscular atrophy. Although it pathophysiology is unclear, IgM-type GM1 antibodies have been detected in approximately half of MMN cases, and some kind of autoimmune mechanism has been assumed.

Current management/treatment

The first-line treatment is intravenous immunoglobluin (IVIG). The therapeutic effect of IVIG against MMN has been confirmed in double-blind, randomized controlled trials and is effective in 80% of cases. Moreover, corticosteroid therapy and apheresis can actually worsen pathological conditions and are not recommended as treatments for MMN. There is a lack of evidence on the therapeutic effects of immunosuppressants, such as azathioprine and cyclophosphamide, or molecular-targeted drugs, such as rituximab and eculizumab.

Rationale for apheresis

There have been cases of MMN in which neurological symptoms and conduction block became significantly exacerbated by PE, and apheresis is ineffective against MMN.

Technical notes

The effectiveness of apheresis against this disease has not been demonstrated and is not recommended. The usage of apheresis therapy for this disease is not covered by insurance.

Duration and discontinuation/number of procedures

Apheresis therapy is not recommended.

References

1. Parry GJ, Clarke S. Multifocal acquired demyelinating neuropathy masquerading as motor neuron disease. Muscle Nerve. 1988;11:103–7.

2. Delmont E, Halstead S, Galban-Horcajo F, et al. Improving the detection of IgM antibodies against glycolipids complexes of GM1 and galactocerebroside in multifocal motor neuropathy using glycoarray and ELISA assays. J Neuroimmunol. 2015;278:159–61.

3. Umapathi T, Hughes RA, Nobile-Orazio E, Léger JM. Immunosuppressant and immunomodulatory treatments for multifocal motor neuropathy. Cochrane Database Syst Rev. 2015;3:CD003217. https://doi.org/10.1002/14651858.CD003217.pub5

4. Van den Berg LH, Lokhorst H, Wokke JH. Pulsed high-dose dexamethasone is not effective in patients with multifocal motor neuropathy. Neurology. 1997;48:1135.

5. Carpo M, Cappellari A, Mora G, et al. Deterioration of multifocal motor neuropathy after plasma exchange. Neurology. 1998;50:1480–2.

6. Claus D, Specht S, Zieschang M. Plasmapheresis in multifocal motor neuropathy: a case report. J Neurol Neurosurg Psychiatry. 2000;68:533–5.

7. Lehmann HC, Hoffmann FR, Fusshoeller A Meyer zu Hörste G, et al. The clinical value of therapeutic plasma exchange in multifocal motor neuropathy. J Neurol Sci. 2008;271:34–9.

8. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—first revision. J Peripher Nerv Syst. 2010;15:295–301. https://doi.org/10.1111/j.1529–8027.2010.00290.x

8.61 | Worksheet 61

Diseases: Multiple Sclerosis
Procedure: PE IAPP
Purpose: Calming of pathologic conditions
Recommendation: 1A (PE), 1B (IAPP)
In the exacerbation period
Category: II (RR-MS), III (SP-MS, PP-MS)
The number of references: RCT 2, CT 0, CS 29, CR NA

Description of the disease

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, characterized by temporal and spatial lesions. its cause is unknown, but it is thought to be an autoimmune disease mainly involving the cell-mediated immunity that targets the central nervous system. Typical symptoms include, but are not limited to, monocular vision loss due to optic neuritis, weakness or hypoesthesia of the limbs due to myelitis, diplopia due to brain stem lesions, and ataxia due to cerebellar lesions. The clinical course is classified as follows: clinically isolated syndrome (CIS), recurrent remission (RR-MS), and primary or secondary progressive (PP-MS, SP-MS). Several patients demonstrate a progressive course (secondary) 10–20 years after onset, with progressive neuropathy. MS lesions appear throughout the central nervous system and are recognized in the white matter as focal areas of demyelination, inflammation, and glial reactions. Humoral and cellular autoimmunity and genetic and environmental factors play major roles in the pathophysiology of MS. The incidence is 8–9 per 100 000 people in Japan, with the male–female ratio being 1:3 and a relatively high incidence among women.

Current management/treatment

Disease-modifying agents for RR-MS have recently been developed. Interferon-β preparations, immunomodulatory monoclonal antibodies, chemotherapeutic agents, and oral agents are available. These drugs control the clinical recurrence of MS and the development of new white matter lesions observed on brain MRI. Meanwhile, the development of therapeutic agents for advanced MS has progressed slowly. Azathioprine, cyclophosphamide, and IVIG have not been conventionally used. The standard treatment for acute MS attacks in adult and pediatric MS and CIS is high-dose intravenous corticosteroid use. Apheresis therapy or combination therapy with intravenous corticosteroids is recommended for cases where insufficient therapeutic effects are observed with intravenous corticosteroids.

Rationale for apheresis

Weiner et al. conducted an RCT for RR-MS and divided patients between a PE with combined ACTH and CPA use group and a sham group. They observed significant improvements in the PE group 4 weeks after treatment relative to the sham group, but no long-term effects were observed, and this facilitated the calming and remission of MS exacerbation. Weinshenker et al. conducted PE for central demyelinating diseases (including MS) for which intravenous corticosteroids were ineffective, and theyconfirmed efficacy in 8/11 patients and 1/11 patients in the PE and sham PE groups, respectively. A cross-over trial conducted on the ineffective patients showed short-term improvements in 8/19 patients in the PE group, and it was concluded that PE should be actively used for cases where the therapeutic effect during the acute exacerbation period is insufficient. Keegan et al. also performed PE for 59 cases of central demyelinating disease and found that it was effective in 44% of cases. The therapeutic effects were particularly high for NMOSD and Marburg-type MS, and they reported that treatment responsiveness was correlated with early treatment. There have been no RCTs on the therapeutic effects of IAPP on RR-MS. However, case reports have indicated its effectiveness, and similar therapeutic effects of IAPP and PE have been reported by a study of 207 clinical reports. An RCT by the Canadian cooperative MS study group stated that PE was not effective for PP-MS, as well as the chronic phases of SP-MS and PP-MS.

Technical notes

A total of 5–7 sessions of PE or IAPP is recommended for MS cases that do not respond to intravenous corticosteroid therapy during the exacerbation of RR-MS. Starting treatment at an early stage (i.e., within 14–20 days of onset) is a predictor of treatment responsiveness. The therapeutic effects of PE are not recommended when more than 60 days have elapsed since onset. The efficacy of blood purification therapy for PP-MS has also not been confirmed.

Duration and discontinuation/number of procedures

Five to seven sessions of PE or IAPP are recommended during the early stage of RR-MS. No additional treatment has been proven to be effective. Blood purification therapy with SP-MS and PP-MS is not recommended.

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. N Engl J Med. 2000;343:938–52.

2. Weiner HL, Dau PC, Khatri BO, et al. Double-blind study of true vs. sham plasma exchange in patients treated with immunosuppression for acute attacks of multiple sclerosis. Neurology. 1989;39:1143–9.

3. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol. 1999;46:878–86.

4. Keegan M, Pineda AA, McClelland RL, et al. Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology. 2002;58:143–6.

5. Heigl F, Hettich R, Arendt R, et al. Immunoadsorption in steroid refractory multiple sclerosis: clinical experience in 60 patients. Atheroscler Suppl. 2013;14:167–73.

6. Schimrigk S, Faiss J, Köhler W, et al. Escalation therapy of steroid refractory multiple sclerosis relapse with tryptophan immunoadsorption - observational multicenter study with 147 patients. Eur Neurol. 2016;75:300–6.

7. The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. The Canadian Cooperative Multiple Sclerosis Study Group. Lancet. 1991;337:441–6.

8. Cortese I, Chaudhry V, So YT, et al. Evidence-based guideline update:plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2011;76:294–300.

9. Vamvakas EC, Pineda AA, Weinshenker BG. Meta-analysis of clinical studies of the efficacy of plasma exchange in the treatment of chronic progressive multiple sclerosis. J Clin Apher. 1995;10:163–70.

8.62 | Worksheet 62

Diseases: Myasthenia gravis
Procedure: PE, IAPP, and DEPP
Purpose: Removal of autoantibodies
Recommendation: Grade 1B
Category: I
The number of references: RCT 11, CT 16, CS 15, CR NA

Description of the disease

Myasthenia gravis (MG) is a disease in which autoantibodies against membrane proteins present in the posterior synaptic membrane of the neuromuscular junction of skeletal muscles inhibit synaptic transmission at the junction, resulting in muscle fatigue. Many of these autoantibodies are anti-acetylcholine receptor (AchR) antibodies, but some of them are anti-muscle-specific receptor tyrosine kinase (MuSK) and anti-LDL receptor-related protein 4 (Lrp4) antibodies. Most MG cases present as ptosis and diplopia, 70% of which shift to the systemic type with limb weakness and dysphagia. The eye muscle type is for cases in which only eye symptoms occur in the entire disease course. Symptoms vary across days, worsen with continued exercise, and improve with rest (easy fatiguability). Cases can quickly worsen with infection or stress (acute exacerbation), and crises requiring respiratory management may emerge.

Current management/treatment

MG is treated with immunotherapy, aimed at disease suppression, as well as corticosteroids and immunosuppressants, aimed at remission. Apheresis therapy, IVIG, and steroid pulse therapy are used to treat acute exacerbations. Anticholinesterase inhibitors are used for symptomatic treatment. Patients aged 50 years or younger and exhibiting complications of thymoma undergo thymectomy at an early stage. Thymectomy is not supported for anti-MuSK- or anti-Lrp4-antibody-positive MG. IVIG involves intravenous infusions of immunoglobulin at 400 mg/kg/day for 5 days, while IVMP involves those of methylprednisolone at 500–1000 mg/day for 3–5 days. Steroid pulse therapy during acute exacerbations can lead to crises; therefore, IVIG and immunosuppressants are often combined. For the long-term management of MG, immunosuppressants with corticosteroids and calcineurin inhibitors (cyclosporine and tacrolimus) are used. Complement inhibitors (eculizumab) have recently been covered by insurance for anti-AchR-antibody-positive MG cases in which IVIG or PE shows no significant effects. The effectiveness of anti-CD20 monoclonal antibodies (rituximab) has also been reported in treatment-resistant anti-MuSK-antibody-positive MG (off-label use in Japan).

Rationale for apheresis

Plasmapheresis is indicated for the exacerbation of MG before thymectomy and in cases that do not sufficiently respond to corticosteroid therapy. Blood purification therapy does not have long-term efficacy but is a short-term therapy to manage acute exacerbations. PE, IAPP, and DFPP remove blood anti-AchR antibodies and improve the disease state. They do not differ in therapeutic effects on anti-AchR-positive MG. The IgG subclass of anti-MuSK antibodies mainly comprises IgG4. Anti-AchR antibodies mainly arise from IgG1 and IgG3, and the adsorption rate of IgG4 is low in IaPP by Immusorba TR; therefore, PE or DFPP is suited for anti-MuSK-antibody-positive MG.

Technical notes

Apheresis therapy, which is powerful and fast-acting, involves using IVIG to manage MG in a short period of time. In addition, it actively introduces calcineurin inhibitors at an early stage to minimize oral corticosteroids. Therefore, it is recommended early in the onset of MG (early fast-acting treatment [EFT]). Actively conducting apheresis therapy, IVIG administrations, and steroid pulse therapy, thereby introducing a remission state in a short time period, is important during acute exacerbation. IVIG and PE have similar effects on severe MG. The efficacy is higher when PE is introduced early during hospitalization to patients with severe MG with respiratory distress. PE and IAPP have been indicated as the possible long-term treatment for refractory MG.

Duration and discontinuation/number of procedures

There is no optimal schedule for apheresis therapy. PE is usually conducted 5–6 times with the circulating plasma volume (equivalent to 4%–5% body weight/session) for 10–14 days combined with corticosteroids and immunosuppressants. It is then repeated every 2–3 weeks until clinical symptoms improve and anti-AChR antibody titer values reduce (i.e., intermediate PE). Intensive PE improves muscle strength and has therapeutic effects lasting 4–6 weeks. Apheresis therapy, IVIG administrations, and steroid pulse therapy have been actively performed in the early stage of MG in recent years. Further, EFT, which introduces calcineurin inhibitors, has been conducted. Patients who require long-term and high-dose corticosteroids are administered with additional apheresis therapy every 4–6 weeks (maintenance PE). Their neurological symptoms improve, and the corticosteroid dose amount and side effects are reduced.

References

1. Higuchi O, Hamuro J, Motomura M, et al. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Ann Neurol. 2011; 69(2):418–22.

2. Oosterhuis HJ, Limburg PC, Hummel-Tappel E, et al. Anti-acetylcholine receptor antibodies in myasthenia gravis. Part 2. Clinical and serological follow-up of individual patients. J Neurol Sci. 1983;58(3):371–85.

3. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med. 2016;375(6):511–22.

4. Howard JF Jr., Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017;16:976–86.

5. Gajdos P, Chevret S, Toyka K. Plasma exchange for myasthenia gravis. Cochrane Database Syst Rev. 2002;4: CD002275.

6. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016;87(4):419–25.

7. Barth D, Nabavi Nouri M, Ng E, et al. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology. 2011;76(23):2017–23.

8. Köhler W, Bucka C, Klingel R. A randomized and controlled study comparing immunoadsorption and plasma exchange in myasthenic crisis. J Clin Apher. 2011;26(6):347–55.

9. Schneider-Gold C, Krenzer M, Klinker E, et al. Immunoadsorption versus plasma exchange versus combination for treatment of myasthenic deterioration. Ther Adv Neurol Disord. 2016;9(4):297–303.

8.63 | Worksheet 63

Diseases: Necrotizing myopathy
Procedure: PE, IAPP, and CAP
Purpose: Introduction and maintenance of remission
Recommendation: Grade 2C
Category: IV
The number of references: RCT 0, CT 0, CS 1, CR 2

Description of the disease

Necrotizing myopathy has a clinical course similar to that of polymyositis but is characterized by myopathological findings, mainly including necrotic regenerative fibers with almost no inflammatory cell infiltration. A muscle biopsy is performed for the diagnosis. The disease has immune-mediated, paraneoplastic, collagenous, and drug-induced causes. Immune-mediated causes are associated with anti-signal recognition particle (SRP) and anti HMGCoA reductase (HMGCR) antibodies. Anti-SRP-antibody-positive cases manifest as severe muscle weakness and swallowing dysfunction. Many cases are resistant to corticosteroids, and combined treatments with IVIG or immunosuppressants are required. Anti-HMGCR-antibody-positive cases are statin-related myopathies with relatively favorable therapeutic responsiveness, while antibody-negative cases often exhibit malignant tumor complications.

Current management/treatment

If the case has a background of statin preparation administration suspension, antiviral agent administration, and treatments for malignant tumors, treatments for these should be conducted. There are no comparative trials, but many cases show treatment resistance compared to polymyositis or dermatomyositis and require multiple immunosuppressants and IVIG. Evidence is limited for the effectiveness of apheresis, and case reports are few.

Rationale for apheresis

Cases in which anti-HMGCR or anti-SRP antibodies are identified have a high possibility for antibody-dependent complement activation or macrophage-induced muscle damage; therefore, apheresis is expected to have therapeutic effects.

Technical notes

Investigations with small sample sizes and case reports have shown apheresis to be effective, but no comparative trials with other treatment methods using a large sample size has shown clear therapeutic effects; therefore, apheresis should be considered only for refractory cases with resistivity to various other treatments.

Duration and discontinuation/number of procedures

It is not covered by insurance. No studies have shown clear efficacy, and indications are limited.

References

1. Liang C, Needham M. Necrotizing autoimmune myopathy. Curr Optin Rheunmatol. 2011:23;612–9.

2. Kassardjian CD, Lennon VA, Alfugham NB, et al. Clinical features and treatment outcomes of necrotizing autoimmune myopathy. JAMA Neurol. 2015;72:996–1003.

3. Momomura M, Miyamae T, Nozawa T, et al. Serum levels of anti-SRP54 antibodies reflect disease activity of necrotizing myopathy in a child treated effectively with combinatorial methylprednisolone pulses and plasma exchanges followed by intravenous cyclophosphamide. Mod Rheumatol. 2014;24:529–31.

4. Ramanathan S, Langguth D, Hardy TA, et al. Clinical course and treatment of anti-HMGCR antibody-associated necrotizing autoimmune myopathy. Neurol Neuroimmunol Neuroinflamm. 2015;2:e96.

8.64 | Worksheet 64

Diseases: Neuro-Behçet's disease
Procedure: PE
Purpose: Immunomodulation
Recommendation: 2C
Category: IV
The number of references: RCT 0, CT 0, CS 0, CR 4

Description of the disease

Behçet's disease is a syndrome based on systemic vasculitis of unknown cause, of which neuro-Behçet's disease is a syndrome in which nerve tissue is affected. Central neuropathy is more common than peripheral neuropathy. Disease types are classified between acute and chronically progressive types. The acute type consists of either acute- or subacute-onset meningoencephalitis, where there is a significant increase in the number of cerebrospinal fluid cells, and where hyperintensity lesions were sometimes observed in brain MRI and FLAIR images. The chronically progressive type involves the gradual progress of dementia-like neuropsychiatric symptoms and ataxic gait, resulting in the decay of personality. IL-6 in the cerebrospinal fluid continuously shows abnormally high levels, and MRI shows atrophy of the brainstem.

Current management/treatment

This differs depending on the acute or chronically progressive types. Oral corticosteroids and steroid pulse therapy are used for the acute type. Oral corticosteroids and colchicine are used to prevent seizures. Methotrexate and infliximab are used as treatment for the chronically progressive type. Cyclosporine may induce acute neurological symptoms, so dosing should be discontinued and not used as a therapeutic drug in cases where the administration is conducted prior to the onset of symptoms.

Rationale for apheresis

There is no reported evidence of the usefulness of apheresis against neuro-Behçet's disease. Basic treatment consists of oral and intravenous medicines. Apheresis should be an emergency treatment option when serious dysfunction is a concern.

Technical notes

There is no reported evidence of the therapeutic efficacy of apheresis against neuro-Behçet's disease.

Duration and discontinuation/number of procedures

There is no reported evidence of the therapeutic efficacy of apheresis against neuro-Behçet's disease.

References

1. Afshin Borhani-Haghighi et al. Neuro-Behcet's disease: an update on diagnosis, differential diagnoses, and treatment, Mult Scler Relat Disord. 2020;39:1–15.

2. Wechsler B, et al. Medical treatment of Behcet's disease, J Mal Vasc. 1988;13(3):262–9.

3. Caruso P, Moretti R. Focus on neuro-Behcer's disease: a review, Neurol India. 2018;66:1619–28.

4. Virginia G, et al, Treatment of Behcet's disease-an update, Semin Arthritis Rheum. 2001;30:299–312.

8.65 | Worksheet 65

Diseases: Neuromyelitis optica spectrum disorders (NMOSD)

Procedure: PE, IAPP

Purpose: Removal of autoantibodies/complements

Recommendation: 1B

Category: II

The number of references: RCT 0, CT 3, CS 20, CR NA

Description of the disease

Neuromyelitis optica (NMO) is an autoimmune inflammatory disease that centers on optic neuritis and myelitis and anti-aquaporin 4 (AQP4) antibodies in serum involved in its pathology. A group of common pathological conditions that produce a unique autoantibody named anti-AQP4 antibody has recently been widely proposed as NMO spectrum disorders (NMOSD). Furthermore, international diagnostic criteria have been proposed, which classified the disorder as anti-AQP4 antibody-positive NMOSD, anti-AQP4 antibody-negative NMOSD, or unmeasured NMOSD. Blindness is a common symptom of optic neuritis in NMOSD, and lesions in the optic chiasma can cause binocular visual impairment. Myelitis often presents with long lesions extending to three or more vertebral bodies in the MRI sagittal section and is often located in the central part of the spinal cord in axial sections. Serum anti-AQP4 antibodies are NMO-specific autoantibodies that are positive in approximately 70% of cases. A total of 80%–90% of NMO cases are recurrent, and some exhibit a monophasic course. The male–female ratio is 1:9, and the disease is common among women, with an average age of onset of 39 years. Autoantibodies against the myelin oligodendrocyte glycoprotein (MOG) (i.e., MOG-IgG) have been identified in anti-AQP4-negative NMOSD cases, and anti-MOG antibody-positive nerve-related diseases have also been proposed.

Current management/treatment

NMO treatment is divided into acute exacerbation and remission phases, similar to MS. Steroid pulse therapy is the first-line treatment from an early stage of the acute exacerbation phase of NMO. Apheresis therapy is selected for cases that are resistant to corticosteroid treatment. The effectiveness of early combined therapy (ECT), which combines steroid pulse therapy and apheresis therapy, has recently been reported, and oral corticosteroids and immunosuppressants (e.g., azathioprine, tacrolimus, cyclosporine) have been used with the objective of controlling recurrence in the remission phase of NMO. Other treatments include mycophenolate mofetil, mitoxantrone, rituximab, IVIG, and eculizumab.

Rationale for apheresis

Weinshenker et al. conducted an RCT where PE and sham PE treatment were administered to 11 cases each for a total of 22 cases of central inflammatory demyelinating disease (including 12 cases of severe acute exacerbation of MS where steroid pulse therapy was ineffective, 2 cases of NMO, and 1 case of recurrent myelitis). PE was conducted every other day over 2 weeks, and a cross-over study was performed for the ineffective cases. Results showed moderate or more rapid improvement in 8/19 cases (42.1%), with PE more effective than sham PE. Watanabe et al. conducted PE on six cases of NMO where corticosteroid therapy was ineffective, which resulted in improvements and effectiveness in three cases. Keegan et al. examined a retrospective trial of 59 cases with inflammatory demyelinating disease and found a high improvement rate in NMO, with moderate or higher improvement in 6/10 patients (60%) and reporting that PE should be conducted early during onset. Nomura et al. investigated the efficacy of IAPP against NMO and conducted IAPP on 21 cases that were resistant to corticosteroid therapy, where improvements in clinical symptoms were observed in 5/21 cases (71%). There have also been reports that PE was regularly repeated as maintenance therapy for recurrent NMOSD in order to control recurrence.

Technical notes

Despite the administration of steroid pulse therapy as a treatment for the acute exacerbation phase of NMO, its therapeutic effects have not been sufficiently observed, or some cases exhibited further progression in neurological symptoms. Apheresis therapy is chosen as a second-line treatment in such cases. Conducting apheresis therapy from an early stage has recently been recommended for severe cases presenting with quadriplegia and respiratory distress during the acute exacerbation phase. Oji et al. measured QIgG, which predicts the responsiveness of the acute exacerbation phase of NMO to corticosteroid therapy, and recommended ECT for cases with high QIgG levels. There have also been reports that PE was effective for steroid therapy-resistant optic neuritis cases presenting with severe visual impairment.

Duration and discontinuation/number of procedures

Similar to MS, apheresis therapy for NMO should be actively performed in cases where the effects of steroid pulse therapy are insufficient during the acute exacerbation phase. Up to seven implementations a month for a series of pathological conditions is acceptable.

References

1. Wingerchuk DM, Lennon VA, Luchinetti CF, et al. The spectrum of neuromyelitis optica. Lancet Neurol. 2007;6:805–15.

2. Wingerchuk DM, Lennon VA, Pittock SJ, et al. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006;23;66(10):1485–9.

3. Wingerchuk DM, Banwell B, Bennett JL, et al. International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177–89.

4. Jarius S, Kleiter I, Ruprecht K, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 3: brainstem involvement - frequency, presentation and outcome. J Neuroinflammation. 2016;13(1):281.

5. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease, Ann Nwurol. 1999;46:878–86.

6. Watanabe S, Nakashima I, Misu T, et al. Therapeutic efficacy of plasma exchange in NMO-IgG-opsitive patients with neuromyelitis optica, Mult Scler. 2007;13:128–32.

7. Keegan M, Pineda AA, McClelland RL, et al. Plasma exchange for severe attacks of CNS demyelination: predictors of response, Neurology. 2002;58:143–6.

8. Sherman E, Han MH. Acute and chronic management of neuromyelitis optica spectrum disorder. Curr Treat Options Neurol. 2015;17(11):48.

9. Miyamoto K, Kusunoki S. Intermittent plasmapheresis prevents recurrence in neuromyelitis optica. Ther Apher Dial. 2009;13(6):505–8.

10. Kleiter I, Gahlen A, Borisow N, et al. Apheresis therapies for NMOSD attacks: a retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm. 2018;5(6):e504.

11. Oji S, Tanaka S, Kojima M, et al. Quotient of cerebrospinal fluid/serum immunoglobulin G as a predictive factor for non-responders to intravenous methylpredonisolone therapy in patients with relapsing neruomyelitis optica sepctrum disorder: implication for early initiation of plasmapheresis. Clin Exper Neuroimmunol. 2016;7:272–80.

12. Deschamps R, Gueguen A, Parquet N, et al. Plasma exchange response in 34 patients with severe optic neuritis. J Neurol. 2016;263(5):883–7.

8.66 | Worksheet 66

Diseases: Neuropsychiatric SLE (NPSLE)

Procedure: IAPP, PE, DFPP

Purpose: Removal of autoantibodies and immune complexes

Recommendation: 2C

Category: II

The number of references: RCT 0, CT 0, CS 5, CR 11

Description of the disease

Systemic lupus erythematosus, which is a disease that presents with inflammatory lesions throughout the body (e.g., in skin/mucosa, muscles/joints, kidneys, nerves, lungs, cardiovascular system, digestive organs, blood) due to various autoantibodies and immune complexes, have especially presented with diffuse psychiatric symptoms (e.g., consciousness disorder [acute confusion], cognitive dysfunction, mood disorder, anxiety disorder, psychotic disorder), central neurological symptoms (e.g., headache, convulsions, involuntary movement [movement disorder], myelopathy, aseptic meningitis, epilepsy, cerebrovascular disorder, demyelinating disease), or peripheral neurological symptoms (e.g., mononeuritis, neuropathy, myasthenia gravis). This has come to be collectively referred to as neuropsychiatric systemic lupus erythematosus (NPSLE) which was previously known as central nervous system lupus. This is one of the intractable conditions of SLE along with lupus nephritis, and it is associated with poor prognosis, complications of lesions in other organs, and decreased quality of life.

Current management/treatment

Treatments include corticosteroids (oral, pulse therapy), immunosuppressants (e.g., azathioprine, mycophenolic acid, cyclosporine A, methotrexate, cyclophosphamide), rituximab, immunoglobulin, blood purification therapy, and even autologous peripheral blood stem cell transplantation. Antiplatelet and anticoagulant therapies are used in the case of complications with antiphospholipid antibody syndrome. Steroids are Grade 1A/2A/B, and all others except for cyclophosphamide pulse are Grade 3D.

Rationale for apheresis

Microangiopathy as well as the production of autoantibodies against nerve cells and inflammatory mediators in the medullary cavity are presumed as pathological conditions; it is thought that the removal of autoantibodies (e.g., anti-ribosome P antibody, anti-Ro antibody, antiphospholipid antibody, anti-NMDA-NR2 antibody) and the reduction of inflammatory cytokines (e.g., IL-6, TNFα) and complements/immune complexes are effective. RCTs and CTs have been conducted only on lupus nephritis, but there have been some case reports on concomitant therapy with steroids and cyclophosphamide pulses for severe and refractory cases. A review comparing monotherapy or combined therapy with cyclophosphamide for 26 serious cases that were not responsive to existing treatments indicated that 74% showed improvements and 13% were stabilized, with many of these showing responses in a few days and some dependent on concomitant therapy, but several cases exhibiting long-term maintenance with regular implementation of blood purification therapy alone. There was also a report where the combination of the steroid cyclophosphamide and blood purification therapy for 13 relapse events in 10 refractory cases resulted in improvements after an average of 3 weeks (1.5–8 weeks), with 54% showing complete remission in 7 weeks (2–22 weeks), with the remaining cases all exhibiting partial remission. There have also been reports of cases where double membrane filtration plasma exchange therapy was significantly effective against psychiatric symptoms even when cyclophosphamide was ineffective, and cases where immunoadsorption therapy was effective for cases where such treatments were not possible due to side effects.

Technical notes

Pay attention to the infections or the presence of coagulation/bleeding tendencies at the puncture site, and route fixation (in cases of consciousness disorder or involuntary movement)

Duration and discontinuation/number of procedures

NPSLE refers to CNS lupus and is covered by insurance. In the current literature, treatment is conducted at a frequency of 1–3 times per week according to pathological conditions. This is implemented 4–20 times in the case of combined therapy, and cyclophosphamide is added for rebound prevention. Adjust as appropriate with a target of once every 2 weeks in the case of maintenance therapy.

References

1. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999 Apr;42(4):599–608.

2. Piga M, Chessa E, Peltz MT, Floris A, Mathieu A, Cauli A. Demyelinating syndrome in SLE encompasses different subtypes: do we need new classification criteria? Pooled results from systematic literature review and monocentric cohort analysis. Autoimmun Rev. 2017; 16(3):244–52.

3. Hanly JG, Urowitz MB, et al. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: an international inception cohort study. Arthritis Rheum. 2007 Jan;56(1):265–73.

4. Magro-Checa C, Zirkzee EJ, Huizinga TW, Steup-Beekman GM. Management of neuropsychiatric systemic

lupus erythematosus: current approaches and future perspectives. Drugs. 2016;76(4):459–83.

5. Popescu A, Kao AH. Neuropsychiatric systemic lupus erythematosus. Curr Neuropharmacol. 2011; 9(3):449–57.

6. Gokhale YA, Bhide S, Rajadhyaksha S, Bichile LS, Hase NK. Plasmapheresis: an adjunct therapy in severe progressive neuropsychiatric lupus. J Assoc Physicians India. 2001;49:986–9.

7. Neuwelt CM. The role of plasmapheresis in the treatment of severe central nervous system neuropsychiatric systemic lupus erythematosus. Ther Apher Dial. 2003;7(2):173–82.

8. Bartolucci P, Bréchignac S, Cohen P, Le Guern V, Guillevin L. Adjunctive plasma exchanges to treat neuropsychiatric lupus: a retrospective study on 10 patients. Lupus. 2007;16(10):817–22.

9. Sugawara H, Takizawa H, Shimamura Y, Moniwa N, Hasegawa K, Ogawa Y. Anti-glomerular basement membrane disease accompanied by systemic lupus erythematosus presenting central nervous system involvement. CEN Case Rep. 2017;6:1–4.

10. Kelley BP,Corrigan JJ, Patel SC, Griffith BD. Neuropsychiatric lupus with antibody-mediated striatal encephalitis. AJNR Am J Neuroradiol. 2018 Dec; 39(12):2263–9.

8.67 | Worksheet 67

Diseases: NMDAR encephalitis

Procedure: PE, IAPP

Purpose: Removal of immunity-related substances, immunoregulation

Recommendation: 1C

Category: I

The number of references: RCT 0, CT 0, CS 10, CR 40

Description of the disease

Autoimmune encephalitis is caused by autoantibodies that recognize the extracellular steric epitopes on the NR1 subunit of the n-methyl-D-aspartate-D (NMDA) receptor, which is one of the ion channel glutamate receptors (i.e., anti-NMDAR antibodies). It causes acute encephalitis due to autoantibodies for glutamate receptors, which are excitatory neurotransmitters in the brain, and NMDA-type glutamate receptors. The five symptoms of this disease are (1) schizophrenia-like psychiatric symptoms, (2) seizures, (3) nonresponsive/catatonic confusion, (4) central hypoventilation, and (5) bizarre involuntary movements. It predominantly occurs in young women and is associated with a high rate of ovarian teratoma complications.

Current management/treatment

Treatments such as steroid pulse therapy, apheresis therapy, and IVIG are used for controlling or halting autoantibody production and anti-inflammation. Tumor resection is performed in patients with tumors. The first-line treatment is corticosteroids, and this can be used alone or in combination with IVIG or apheresis therapy. B-cell depletion therapy using immunosuppressants and anti-CD20 monoclonal antibody preparations is implemented for refractory cases. The management of involuntary movements, convulsions, respiration, and infectious diseases is important.

Rationale for apheresis

Apheresis is thought to demonstrate therapeutic effects through the removal of autoantibodies (anti-NMDAR antibodies). This antibody belongs to the IgG1 and IgG3 subclasses, but it is thought that it does not cause complement-mediated tissue damage; it decreases NMDAR functionality, instead, by promoting the internalization of NMDAR. Therefore, the significance of removing complements is thought to be low. The results of the retrospective analysis of the therapeutic effects of corticosteroids and apheresis therapy showed combined therapy was administered for 10 of 14 cases, with three and seven cases showing improvements after corticosteroids and apheresis therapy, respectively. A study of 241 children showed therapeutic effects in 66.7% of cases receiving a combination of corticosteroids and apheresis therapy. However, no RCTs investigating the efficacy of apheresis therapy have been conducted, and the evidence is insufficient. Reports have also indicated that IAPP and PE have similar efficacies.

Technical notes

Ensure that the indwelling puncture site is fixed since several cases present with involuntary movements. Be aware of any infection of the indwelling puncture site, as well as the immunoglobulin and fibrinogen concentrations after apheresis implementation.

Duration and discontinuation/number of procedures

Not covered by insurance. PE or IAPP should be administered a total of 4–7 times every other day.

References

1. DeSena AD, Noland DK, Matevosyan K, et al. Intravenous methylprednisolone versus therapeutic plasma exchange for treatment of anti-N-methyl-D-aspartate receptor antibody encephalitis: a retrospective review. J Clin Apher. 2015;30:212–6.

2. Kohler W, Ehrlich S, Dohmen C, et al. Tryptophan immunoadsorption for the treatment of autoimmune encephalitis. Eur J Neurol. 2015;22:203–6.

3. Mann AP, Grebenciucova E, Lukas RV. Anti-N-methyl-D-aspartate-receptor encephalitis: diagnosis, optimal management, and challenges. Ther Clin Risk Manag. 2014;10:517–25.

4. Pham HP, Daniel-Johnson JA, Stotler BA, Stephens H, Schwartz J. Therapeutic plasma exchange for the treatment of anti-NMDA receptor encephalitis. J Clin Apher. 2011;26:320–5.

5. Suleiman J, Dale RC. The recognition and treatment of autoimmune epilepsy in children. Dev Med Child Neurol. 2015;57:431–40.

6. Zekeridou A, Karantoni E, Viaccoz A, et al. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J Neurol. 2015;262:1859–66.

7. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12:157–65.

8. Dogan Onugoren M, Golombeck KS, Bien C, et al. Immunoadsorption therapy in autoimmune encephalitides. Neurol Neuroimmunol Neuroinflamm. 2016;3:e207.

9. Suppiej A, Nosadini M, Zuliani L, et al. Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review. Brain Dev. 2016;38:613–22.

10. Fassbender C, Klingel R, Kohler W. Immunoadsorption for autoimmune encephalitis. Atheroscler Suppl. 2017;30:257–63.

11. de Montmollin E, Demeret S, Brule N, et al. Anti-N-methyl-d-aspartate receptor encephalitis in adult

patients requiring intensive care. Am J Respir Crit Care Med. 2017;195:491–9.

12. Heine J, Ly LT, Lieker I, et al. Immunoadsorption or plasma exchange in the treatment of autoimmune encephalitis: a pilot study. J Neurol. 2016;263:2395–2402.

13. Nauen DW. Extra-central nervous system target for assessment and treatment in refractory anti-N-methyl-d-aspartate receptor encephalitis. J Crit Care. 2017;37:234–6.

14. Leel N, Thakkar HS, Drake D, Bouhadiba N. Ovarian teratoma associated with anti-NMDA (N-methyl D-aspartate) receptor encephalitis. BMJ Case Rep. 2018;2018.

8.68 | Worksheet 68

Diseases: Palmoplantar pustulosis

Procedure: Granulocyte and monocyte adsorptive apheresis

Purpose: Activated granulocyte/monocyte removal

Recommendation: 1C

Category: III

The number of references: RCT 0, CT 0, CS 2, CR 3

Description of the disease

Palmoplantar pustulosis is a chronic intractable inflammatory skin disease, in which aseptic pustules repeatedly occur on the palms and soles. It can be complicated by bone and joint symptoms in some cases. The cause of disease onset is still largely unknown; however, several factors, such as focal infections, metal allergies, and smoking, might be triggering factors.

Current management/treatment

Topical steroids, topical active vitamin D3, topical combinations of both, UV therapy, etretinate, cyclosporine, oral methotrexate, tumor necrosis factor (TNF)-α inhibitors, interleukin (IL)-17 inhibitors, IL-23 inhibitors, and other biological preparations have been used for treatment. Removal of the caustive agent (e.g., treatment of the infected lesion or removal of the dental metal) can also be effective in some cases.

Rationale for apheresis

Granulocyte and monocyte adsorption apheresis selectively removes activated *granulocytes and monocytes/macrophages* that underlie the pathology of pustular psoriasis. Removal of these cells decrease the proinflammatory cytokines in the blood. In addition, it has various immunomodulatory effects, including reduction of active naïve cell mobilization from the bone marrow, decrease in inflammatory macrophages, and induction of regulatory T cells and bone marrow-derived inhibitory cells. However, treatment of palmoplantar pustulosis is currently not covered under insurance.

Technical notes

Select an appropriate blood vessel to perform the insertion technique while paying attention to the infection risk at the needle insertion site. Try to select an insertion site with unaffected healthy skin, if possible. Wiping with alcohol cotton is sufficient when piercing healthy skin. Disinfect with isodine when there are pustules or erosions near the insertion site.

Duration and discontinuation/number of procedures

For a single treatment session, process 1800 ml of blood for 60 min at a flow rate of 30 ml/min. Treatment should be repeated once or twice a week, 5–10 sessions per series. Insured coverage is approved for once-a-week treatment per course, up to five times. Determine whether to suspend or continue treatment by evaluating the effectiveness based on some factors, such as the severity of skin and subjective symptoms.

References

1. Kanekura T, Yoshii N, Yonezawa T, Kawabata H, Saruwatari H, Kanzaki T. Treatment of pustular psoriasis with granulocyte and monocyte adsorption apheresis. J Am Acad Dermatol. 2003;49:329–32.

2. Kanekura T, Hiraishi K, Kawahara K, Maruyama I, Kanzaki T. Granulocyte and monocyte adsorption apheresis (GCAP) for refractory skin diseases caused by activated neutrophils and psoriatic arthritis: evidence that GCAP removes Mac-1-expressing neutrophils. Ther Apher Dial. 2006;10:247–56.

3. Sakanoue M, Takeda K, Kawai K, Kanekura T. Granulocyte and monocyte adsorption apheresis for refractory skin diseases due to activated neutrophils, psoriasis, and associated arthropathy. Ther Apher Dial. 2013;17:477–83.

4. Fujisawa T, Tawada C, Mizutani Y, Doi T, Yoshida S, Ogura S, et al. Efficacy of granulocyte and monocyte adsorption apheresis for treatment of palmoplantar pustulosis. Ther Apher Dial. 2014;18:238–43.

5. Arimura A, Fujii K, Ibusuki A, Hatanaka M, Sakanoue M, Higashi Y, et al. Granulocyte and monocyte adsorption apheresis for palmoplantar pustulosis with extrapalmoplantar lesions and pustulotic arthro-osteitis. J Dermatol. 2018;45:e167–8.

8.69 | Worksheet 69

Diseases: PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection)/Sydenham's chorea

Procedure: PE, IAPP

Purpose: Removal of anti-nerve antibodies

Recommendation: PANDAS 1B/Sydenham's chorea 2B

Category: PANDAS II/Sydenham's chorea III

The number of references: RCT 1, CT 0, CS 2, CR 7

Description of the disease

A neuropsychiatric disorder associated with group A beta-hemolytic streptococcus (GABHS) infection and is thought to be caused by an autoimmune mechanism involving autoantibodies (anti-neural antibodies) against nerve cells in the basal ganglia. It predominantly occurs in pediatric patients. Sydenham's chorea is a neurological symptom of rheumatic fever with decreased muscle tonus, emotional instability, and chorea. Tic-like movements may be observed. Acute development of PANDAS follows GABHS infection, and it is diagnosed by the following five criteria: (1) presence of obsessive-compulsive disorder or tic disorders, (2) onset from prepuberty (from age three to prepuberty), (3) sudden onset or sudden exacerbation or repeated relapse and remission, (4) association with GABHS infection at the time of onset, and (5) chorea. Neurological abnormalities, such as tics, may be observed.

Current management/treatment

In addition to antibacterial therapy for GABHS infection, treatments include corticosteroids, IVIG, and apheresis therapy given that this is an autoimmune disease.

Rationale for apheresis

Apheresis is thought to demonstrate therapeutic effects through the removal of immunity-related substances (e.g., autoantibodies [anti-nerve antibodies]), as well as immunomodulatory actions. The results of RCTs that investigated the therapeutic effects of apheresis therapy, IVIG, and corticosteroids in 18 patients with Sydenham's chorea showed that apheresis therapy resulted in a decrease in the average chorea severity score of 50% one month after implementation. The results of a placebo-controlled study investigating the efficacies of high-dose intravenous immunoglobulin therapy and apheresis in 30 PANDAS patients showed significant improvements in neurological symptoms after 1 month relative to the placebo group, and these therapeutic effects lasted for 1 year.

Technical notes

There are several pediatric cases, as well as cases presenting with involuntary movements, and care should be taken to secure and fix the indwelling puncture site. It is important to be aware of any infection of the indwelling puncture site, as well as the immunoglobulin and fibrinogen concentrations after apheresis.

Duration and discontinuation/number of procedures

Not covered by insurance. Perform PE or IAPP for a total of 3–6 times over 7–14 days.

References

1. Garvey MA, Snider LA, Leitman SF, Werden R, Swedo SE. Treatment of Sydenham's chorea with intravenous immunoglobulin, plasma exchange, or prednisone. J Child Neurol. 2005;20:424–9.

2. Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. JAMA 1992;268:2069–73.

3. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. 1998;155:264–71.

4. Esposito S, Bianchini S, Baggi E, Fattizzo M, Rigante D. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: an overview. Eur J Clin Microbiol Infect Dis. 2014;33:2105–9.

5. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). Arch Pediatr Adolesc Med. 2002;156:356–61.

6. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet. 1999;354:1153–8.

7. Cortese I, Chaudhry V, So YT, Cantor F, Cornblath DR, Rae-Grant A. Evidence-based guideline update: plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2011;76:294–300.

8. Latimer ME, L'Etoile N, Seidlitz J, Swedo SE. Therapeutic plasma apheresis as a treatment for 35 severely ill children and adolescents with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. J Child Adolesc Psychopharmacol. 2015;25:70–5.

9. Tucker DM, Leckman JF, Scahill L, et al. A putative poststreptococcal case of OCD with chronic tic disorder, not otherwise specified. J Am Acad Child Adolesc Psychiatry. 1996;35:1684–91.

10. Elia J, Dell ML, Friedman DF, et al. PANDAS with catatonia: a case report. Therapeutic response to

lorazepam and plasmapheresis. J Am Acad Child Adolesc Psychiatry. 2005;44:1145–50.

11. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. Biol Psychiatry. 2005;57:788–92.

12. Teixeira AL Jr., Maia DP, Cardoso F. Treatment of acute Sydenham's chorea with methyl-prednisolone pulse-therapy. Parkinsonism Relat Disord. 2005;11:327–30.

8.70 | Worksheet 70

Diseases: Paraneoplastic neurological syndrome (PNS)

Procedure: PE

Purpose: Removal of anti-neuronal antibodies

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 1, CS 12, CR 19

Description of the disease

Paraneoplastic neurological syndrome (PNS) presents with neurological symptoms from the central to peripheral nerves, neuromuscular junction, and muscles due to remote effects of the tumor. It is not considered to be resulting from the direct infiltration of tumor cells, metastasis, or chemotherapy for tumors, or side effects, metabolic disorders, or opportunistic infections from radiation therapy. The European Federation of Neurological Societies (EFNS)/PNS Euronetwork declared the following neurological syndromes to be typical of classical PNS: encephalomyelitis, limbic encephalitis, optic neuritis, paraneoplastic retinopathy, opsoclonus myoclonus syndrome, subacute sensory neuropathy, chronic pseudointestinal obstruction, Lambert-Eaton myasthenic syndrome, and dermatomyositis. The index of suspiscion is high for tumor complications with classical PNS, with or without anti-neuronal antibodies. PNS detects characteristic autoantibodies associated with clinical disease types (i.e., anti-neuronal antibodies); therefore, anti-neuronal antibodies are directly linked to medical care in terms of therapeutic responsiveness and diagnostic markers.

Anti-neuronal antibodies are of two types: those against intracellular antigens and those against the surface of nerve cell membranes (1). Antibodies against intracellular antigens include those with an established clinical significance: Hu, Yo, Ri, Ma2, CV/CRMP5, and amphiphysin antibodies. There is a high probability of tumor complications regardless of the presence/absence of tumors when these antibodies are positive. Zic4 and SOX-1 antibodies predict the complication of small cell lung cancer, and anti-GAD antibodies are positive in Stiff-person syndrome and cerebellar ataxia (2). Antibodies against the surface of nerve cell membranes, which do not necessarily indicate tumor complications, include the voltage gated potassium channel (VGKC) complex, NMDA receptor, AMPA receptor, GABAB, and glycine receptor antibodies. The frequency of tumor complications is high but only approximately 70%; therefore, the presence of these antibodies does not indicate PNS, and some autoimmune pathologies do not coexist with tumors. These are antibodies that react with antigen epitopes on the surface of nerve cell membranes, mostly on the anterior and posterior synaptic membranes. It is assumed that the antibodies themselves play a major role in the pathogenesis owing to the correlation between antibody titers and the neural function prognosis as well as its effectiveness in immunotherapy. However, patients with VGCC antibody-positive cerebellar ataxia are less likely to respond to immunotherapy, unlike those with antibodies corresponding to other nerve cell membrane surface antigens.

Current management/treatment

The basis of treatment is to consider the causative tumor and immune pathology and include supportive therapy for symptoms. Treating the tumor is important for stopping antigen stimulation and should be rapidly conducted along with the treatment of the immune pathology. Immunotherapy has high therapeutic responsiveness for anti-neuronal-antibody-positive PNS against nerve cell membrane antigens. Meanwhile, effects of immunotherapy are poor for anti-neuronal-antibody-positive PND against intracellular antigens. Immunotherapy has no established guideline but is conducted according to therapeutic strategies for NMDA receptor-antibody-positive encephalitis. First-line treatments include methylprednisolone pulse therapy, IVIG administrations, PE, and IAPP. When these were tried individually or in combination and a poor therapeutic response is obtained or steroid therapy is desired, cyclophosphamide pulse therapy, rituximab therapy, or other immunosuppressants is considered.

Rationale for apheresis

Evidence is lacking for apheresis therapy as a treatment of PNS. Anti-neuronal antibodies against nerve cell membrane surface antigens are involved in immune pathology; therefore, improvements in neurological symptoms can be expected from the removal of autoantibodies. VGCC, NMDAR, VGKC, and AMPAR antibodies correlate with antibody titers and the neurological prognosis. Clinical symptoms are alleviated with the removal of antibodies for VGKC- and VGCC-antibody-positive PNS, and complete remission occurs in over half of the cases with the combination of tumor removal and immunotherapy for NMDAR-antibody-positive PNS (neither resulting from apheresis alone).

Technical notes

The EFNS/PNS Euronetwork Task Force has published management guidelines. No therapeutic effects can be expected with immunotherapy (corticosteroids, PE, and IVIG) for limbic encephalitis, subacute sensory neuropathy, and subacute cerebellar degeneration. Immunotherapy can be expected to be effective against opsoclonus-myoclonus syndrome in children but not in adults and against Lambert-Eaton myasthenic syndrome.

The tumor treatment and immunotherapy improve the prognosis of anti-neuronal-antibody-positive PNS against nerve cell membrane surface antigens.

Duration and discontinuation/number of procedures

It is not covered by insurance. Per the recommendation, PE or IAPP is administered twice weekly for 2–4 weeks to determine effects.

References

1. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004;75:1135–40.

2. Solimena M, Folli F, Aparisi R, et al. Autoantibodies to GABA-ergic neurons and paraneoplastic beta cells in stiff-man syndrome. N Engl J Med. 1990;322:1555–60.

3. Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. J Neurol. 2010;257:509–17.

4. Dalmau J, Lancaster E, Matinez-Hermandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10:63–74.

5. Antoine JC, Camdessanché JP. Treatment options in paraneoplastic disorders of the peripheral nervous system. Curr Treat Options Neurol. 2013;15:210–23.

6. Blyakhman I, Chakravarthy K. Update review and treatment recommendations on paraneoplastic neurologic syndromes and chronic pain. Pain Physician. 2013;22:433–55.

7. Grativvol RS, Cavalcante WCP, Castro LHM, et al. Updates in diagnosis and treatment of paraneoplastic neurologic syndromes.

8. Dalmau J, Gleichmann AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7:1091–8.

9. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain. 2004;127:701–12.

10. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009;65:424–34.

11. Vedeler CA, Antoine JC, Giometto B, et al. Management of paraneoplastic neurological syndromes: report of an EFNS task force. Eur J Neurology. 2006;13:682–90.

8.71 | Worksheet 71

Diseases: Paraproteinemic demyelinating polyneuropathies/chronic acquired demyelinating polyneuropathies (CADP)

Procedure: PE, IAPP

Purpose: Removal of autoantibodies contained in M protein, immunomodulation

Recommendation: IgG/IgA: 1B

IgM: 1C

Anti-MAG antibody positive: 2C

Category: IgG/IgA: I

IgM: I

Anti-MAG antibody positive: III

The number of references: RCT 1, CT 0, CS 18, CR NA

Description of the disease

A general term for peripheral neuropathy associated with paraproteinemia (monoclonal immunoglobulinemia, M proteinemia) and several other diseases. Monoclonal proliferation of B cells or plasma cells is observed in the background and is clinically accompanied by monoclonal gammopathy of undetermined significance (MGUS), but it can be accompanied by multiple myeloma, malignant lymphoma, cryoglobulinemia, amyloidosis, and other blood disorders. It involves autoantibodies with activity against the glycoprotein myelin-associated glycoprotein (MAG), glycolipid sulfated glucuronyl paragloboside (SGPFG), and ganglioside when the M protein is IgM type, and the M protein may be directly involved in peripheral neuropathy. Anti-MAG antibody-positive cases characterized by the involvement of antibody activity against MAG in the onset of neuropathy are most common in older men, and the main symptom is gradual progressive sensory disorder or sensorimotor disorder in the distal limbs. Direct peripheral neuropathy due to the M protein has not been established for the IgG and IgA types.

Current management/treatment

Treatments include the use of various immunosuppressants and anti-CD20 monoclonal antibody preparations in addition to corticosteroids, IVIG, and apheresis therapy. Corticosteroids, IVIG, and apheresis therapy are administered for CIDP as part of treatment for demyelinated neuropathy with IgG/IgA-type monoclonal immunoglobulinemia (M proteinemia). Treatment for the underlying disease is important, and treatments for hematological malignancies (e.g., autologous peripheral blood stem cell transplantation, chemotherapy) may be administered.

Rationale for apheresis

Apheresis is thought to demonstrate a therapeutic effect through the removal of immunity-related substances (e.g., autoantibodies that are contained in the M protein, complements in plasma) as well as immunomodulatory actions. The subanalysis results of RCTs for neuropathy with M proteinemia showed that apheresis therapy was effective for the IgG/IgA type and ineffective for the IgM type. However, efficacy was subsequently confirmed for all the groups. Therefore, the most promising therapeutic effects may be expected in the presence of the IgG- or IgA-type MGUS, but therapeutic effects may also be expected for the IgM-type MGUS. Eight case series that reported the results of apheresis therapy as monotherapy for anti-MAG antibody-positive cases indicated improvements in 24 of 48 cases. However, these effects were often transient and insufficient, and recurrence was reported for almost all cases after treatment was discontinued. The effects are uncertain for multifocal motor neuropathy.

Technical notes

Be aware of any infection at the indwelling puncture site, as well as the immunoglobulin level and fibrinogen amount after implementation.

Duration and discontinuation/number of procedures

Not covered by insurance. Up to seven times per month in a single series according to insured coverage for CIDP. Up to once a week in a single series for 3 months according to the insured coverage for multiple myeloma and macroglobulinemia. All other cases are not covered by insurance. Usually performed 5–6 times in total over 10–14 days.

References

1. Dyck PJ, Low PA, Windebank AJ, et al. Plasma exchange in polyneuropathy associated with monoclonal gammopathy of undetermined significance. N Engl J Med. 1991;325:1482–6.

2. Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst Rev. 2006:CD002827.

3. Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst Rev. 2016;10:CD002827.

4. Dalakas MC, Rakocevic G, Salajegheh M, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. Ann Neurol. 2009;65:286–93.

5. Nobile-Orazio E, Meucci N, Baldini L, Di Troia A, Scarlato G. Long-term prognosis of neuropathy associated with anti-MAG IgM M-proteins and its relationship to immune therapies. Brain. 2000;123(Pt 4):710–7.

6. Oksenhendler E, Chevret S, Leger JM, Louboutin JP, Bussel A, Brouet JC. Plasma exchange and chlorambucil in

polyneuropathy associated with monoclonal IgM gammopathy. IgM-associated Polyneuropathy Study Group. J Neurol Neurosurg Psychiatry. 1995;59:243–7.

7. Vallat JM, Magy L, Ciron J, Corcia P, Le Masson G, Mathis S. Therapeutic options and management of polyneuropathy associated with anti-MAG antibodies. Expert Rev Neurother. 2016;16:1111–9.

8. Gorson KC, Ropper AH, Weinberg DH, Weinstein R. Treatment experience in patients with anti-myelin-associated glycoprotein neuropathy. Muscle Nerve. 2001;24(6):778–86.

9. Allen D, Lunn MP, Niermeijer J, Nobile-Orazio E. Treatment for IgG and IgA paraproteinaemic neuropathy. Cochrane Database Syst Rev. 2007:CD005376.

10. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society—first revision. J Peripher Nerv Syst. 2010;15:185–95.

11. Simmons Z, Albers JW, Bromberg MB, Feldman EL. Long-term follow-up of patients with chronic inflammatory demyelinating polyradiculoneuropathy, without and with monoclonal gammopathy. Brain. 1995;118(Pt 2):359–68.

12. Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology. 1997;48:321–8.

8.72 | Worksheet 72

Diseases: Pemphigoid
Procedure: PE, DFPP
Purpose: Autoantibody removal
Recommendation: 1C
Category: II
The number of references: RCT 0, CT 3, CS 5, CR 222

Description of the disease

Pemphjgoid is one of the autoimmune bullous disease that causes edematous erythema and tight blisters with frequent pruritus on the skin of the entire body. Oral mucosal lesions may occur. The Nikolsky's sign seen in pemphigus is generally negative for pemphigoids. The etiology is thought to be that IgG autoantibodies bind to the epidermal basement membrane antigen (i.e., hemidesmosome constituent proteins BP180 [Type 17 collagen] or BP230) and induce subepidermal blisters.

Current management/treatment

The main treatment is oral corticosteroid therapy which acts to suppress autoantibody production. Combined therapies include immunosuppressants, apheresis therapy, and high-dose intravenous γ-globulin therapy. Topical therapy is also used locally to prevent infection, protect erosions, and promote epithelialization. Patients may also be responsive to an oral combination of tetracycline (or minocycline) and nicotinamide or oral diaminodiphenyl sulfone.

Rationale for apheresis

Symptoms improve with the removal and reduction of the pathogenic substance that is the autoantibody (i.e., previously-mentioned anti-BP180 antibody or anti-BP230 antibody) from the blood of the patient.

Technical notes

Catheter placement should avoid erosions, and an appropriate blood vessel should be selected while paying attention to infection. The amount of plasma processed should be 1–1.5 times the amount of circulating plasma in the patient. The patient should be inspected as appropriate after implementation for hypoalbuminemia and hypogammaglobulinemia, and skin lesion observations (e.g., presence of signs of infection, bleeding lesions) should be made while keeping in mind the possibility of decreases in the coagulation factor 8 in the case of DFPP. Replenishment should be provided when necessary.

Duration and discontinuation/number of procedures

Implement two to three times a week, either every day or every other day. Treatment is completed when the antibody titer decreases, blister formation stops, and erosions become epithelialized. Insured coverage is up to two times a week for 3 months. However, this can be extended another 3 months if the case is moderate or severe.

References

1. Yamada H, Yaguchi H, Takamori K, Ogawa H. Plasmapheresis for the treatment of pemphigus vulgaris and bullous pemphigoid. Ther Apher. 1997;1:178–82.

2. Roujeau JC, Guillaume JC, Morel P, et al. Plasma exchange in bullous pemphigoid, Lancet. 1984;2:486–8.

3. Takamori K, Yamada H, Morioka S, Ogawa H. Long term remission succssfully achieved in severe types of pemphigus vulgaris and bullous pempjigoid by the use of plasmaphersis. Eur J Dermatol. 1993;3:433–7.

4. Nakamura K, Matsukura K, Kouno M. Therapeutic experience of plasmapheresisi with three cases of recalcitrant bulloud pemphigoid. Jpn J Apheresis. 2015;34:219–25.

5. Wada N, Yamada H, Yaguchi H, Takamori K, Ogawa H. Evaluation of plasma exchange therapy in the treatment of pemphigus vulgaris and bullous pemphigoid: summary of 42 cases in Juntendo University. Jpn J Dermatol. 1996;106:1903–8.

6. Yaguchi H, Yamada H, Takamori K, Ogawa H. Evaluation of plasma exchange therapy in the treatment of bullous pemphigoid. Jpn J Apheresis. 2000;19180–3.

7. Hunziker T, Schwarzenbach HR, Krebs A, Nydegger UE, et al. Plasma exchange in pemphigus vulgaris. Schweiz Med Wochenschr. 1981;111:1637–42.

8.73 | Worksheet 73

Diseases: Pemphigus
Procedure: PE, DFPP
Purpose: Autoantibody removal
Recommendation: Grade 1C
Category: II
The number of references: RCT 0, CT 5, CS 6, CR 193

Description of the disease

Pemphigus is one of the autoimmune bullous disease which results in the development of lesions on the skin and mucous membranes. Painful and intractable erosions and ulcers form on the oral mucosa. The flaccid blisters and erosions form on the skin. The blisters are fragile and tend to attach, on the margines, to other blisters. Similarly, the erosions are also often painful, and adjacent erosions may fuse to form larger plaques. Applying pressure to a seemingly normal section of skin results in the epidermis peeling off and presenting with erosion. This is called Nikolsky's sign. The etiology is thought to be that IgG autoantibodies bind to desmoglein, which is an interepidermal adhesion factor, inducing blisters by impairing its adhesion function.

Current management/treatment

The main treatment is oral corticosteroid therapy, which suppresses autoantibody production. Combined therapies include immunosuppressants, apheresis therapy, and high-dose intravenous γ-globulin therapy. Topical therapy is also used locally to prevent infection, protect erosions, and promote epithelialization.

Rationale for apheresis

Symptoms improve with the removal and reduction of the pathogenic substance that is the autoantibody (i.e., previously mentioned anti-desmoglein 3 antibody and anti-desmoglein 1 antibody) from the blood of the patient.

Technical notes

Catheter placement should avoid erosions, and an appropriate blood vessel should be selected while paying attention to infection. The amount of plasma processed should be 1–1.5 times the amount of circulating plasma in the patient. The patient should be inspected as appropriate after implementation for hypoalbuminemia and hypogammaglobulinemia, and skin lesion observations (e.g., presence of signs of infection, bleeding lesions) should be made while keeping in mind the possibility of decreases in the coagulation factor 8 in the case of DFPP. Replenishment should be provided when necessary.

Duration and discontinuation/number of procedures

Implement treatment two to three times a week, either every day or every other day. Treatment is completed when the antibody titer decreases, blister formation stops, and erosions become epithelialized. Insured coverage is up to two times a week for 3 months. However, this can be extended another 3 months if the case is more severe.

References

1. Yamada H, Yaguchi H, Takamori K, Ogawa H. Plasmapheresis for the treatment of pemphigus vulgaris and bullous pemphigoid. Ther Apher. 1997；1:178–82.

2. Ikeda S, Komiyama E, Ogawa H. The prognosis of pemphigus patients will be significantly improved in the future. Arch Dermatol Res. 2003；295(Suppl 1):S69–70.

3. Sondergaard K, Carstens J, Jørgensen J, Zachariae H. The steroid-sparing effect of long-term plas-mapheresis in pemphigus. Acta Derm Venereol. 1995；75:150–2.

4. Sondergaard K, Carstens J, Zachariae H. The steroid-sparing effect of long-term plasmapheresis in pemphigus: an update. Ther Apher. 1997；1:155–8.

5. Yoshiike K, Shiozawa E, Yamada H, Ogawa H. A study on the therapy and prognosis of pemphigus vulgari vulgaris. Jpn J Dermatol. 1990;100:773–8.

6. Tan Lim R, Bystryn JC. Effect of plasmapheresis therapy on circulating levels of pemphigus antibodies. J Am Acad Dermatol. 1990;22:35–40.

7. Ruocco V, Astarita C, Pisani M. Plasmapheresis as an alternative of adjunctive therapy in problem case of pemphigus. Dermatologica. 1984;168 219–23.

8. Takamori K, Yamada H, Morioka S, Ogawa H. Long term remission succssfully achieved in severe types of pemphigus vulgaris and bullous pempjigoid by the use of plasmaphersis. Eur J Dermatol. 1993;3:433–7.

9. Higashihara T, Kawase M, Kobayashi M, Hara M, Matsuzaki H, Uni R, et al. Evaluating the efficacy of double-filtration plasmaphresis in treating five patients with drug-resistant pemphigus. Ther Apher Dial. 2017;21:243–7.

10. Wada N, Yamada H, Yaguchi H, Takamori K, Ogawa H. Evaluation of plasma exchange therapy in the treatment of pemphigus vulgaris and bullous pemphigoid: summary of 42 cases in Juntendo University Jpn J Dermatol:1996;106:1903–8.

11. Sakuma M, Ogawa H. An investigation of the severity of pemphigus and effect of various treatments. Jpn J Dermatol. 1998;108:225–33.

12. Hunziker T, Schwarzenbach HR, Krebs A, Nydegger UE, et al. Plasma exchange in pemphigus vulgaris. Schweiz Med Wochenschr. 1981;111:1637–42.

8.74 | Worksheet 74

Diseases: POEMS syndrome
Procedure: Simple plasma exchange
Purpose: Introduction of remission
Recommendation: 2C
Category: IV
The number of references: RCT 0, CT 0, CS 0, CR 24

Description of the disease

This syndrome is characterized by monoclonal plasma cell proliferation, requires multiple neuropathies, and varying symptoms. POEMS exhibits clinical features of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes. Abnormally elevated vascular endothelial growth factor (VEGF) in serum is associated with the pathological condition.

Current management/treatment

A standard treatment has not been established, but currently, patients with sporadic plasmacytoma undergo surgical resection or local radiation therapy for the tumor. Systemic chemotherapy is provided if the presence of plasmacytoma is unknown or if multiple bone lesions are present. Chemotherapy is performed similar to that for multiple myeloma, which is also a proliferative disorder of plasma cells. Molecular-targeted therapies, such as thalidomide, lenalidomide, or bortezomib, have been used. IVIG and apheresis are ineffective.

Rationale for apheresis

Reports indicated worsened serum M-protein and neurological symptoms following melphalan and PE, indicating that PE was ineffective. Apheresis is ineffective and not recommended for this syndrome.

Technical notes

Apheresis is not effective or recommended for this syndrome and is not covered by insurance.

Duration and discontinuation/number of procedures

Apheresis is not recommended.

References

1. Bardwick PA, Zvaifler NJ, Gill GN. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. Medicine. 1980;59:311–22.

2. Dispenzieri A. POEMS syndrome: 2017 update on diagnosis, risk stratification, and management. Am J Hematol. 2017;92:814–29. https://doi.org/10.1002/ajh.24802

3. Watanabe O, Arimura K, Kitajima I, et al. Greatly raised vascular endothelial growthfactor (VEGF) in POEMS syndrome. Lancet. 1996;347:702.

4. Li J, Zhang W, Jiao L, et al. Combination of melphalan and dexamethasone for patients with newly diagnosed POEMS syndrome. Blood. 2011;117:6445–9.

5. Dispenzieri A, Moreno-Aspitia A, Suarez GA, et al. Peripheral blood stem cell transplantation in 16 patients with POEMS syndrome, and a review of the literature. Blood. 2004;104:3400–7.

6. Kuwabara S, Misawa S, Kanai K, et al. Thalidomide reduces serum VEGF levels and improves peripheral neuropathy in POEMS syndrome. J Neurol Neurosurg Psychiatry. 2008;79:1255–7.

7. Royer B, Merlusca L, Abraham J, et al. Efficacy of lenalidomide in POEMS syndrome: a retrospective study of 20 patients. Am J Hematol. 2013;88:207–12.

8. Tang X, Shi X, Sun A, et al. Successful bortezomib-based treatment in POEMS syndrome. Eur J Haematol. 2009;83:609–10.

9. Dispenzieri A. POEMS syndrome. Hematology Am Soc Hematol Educ Program. 2005:360–7.

8.75 | Worksheet 75

Diseases: Polycythemia vera

Procedure: Centrifugal blood component removal method

Purpose: Removal of red blood cells, and replacement with physiological saline

Recommendation: 1B

Category: I

The number of references: RCT 0, CT 3, CS 6, CR NA

Description of the disease

Myeloproliferative neoplasm that causes significant absolute increases in the amount of red blood cells and total blood volume and is usually characterized by leukocytosis, thrombocytosis, and splenomegaly. JAK2 V617F mutation is found in over 95% of cases.

Current management/treatment

The basic treatment policy ensures the maintanence of Ht below 45% using phlebotomy and prevent thrombosis through oral administration of bayaspirin. Hydroxycarbamide (HU) should be administered orally if Ht cannot be controlled using phlebotomy. The administration of ruxolitinib, which is a JAK2 inhibitor, has recently included for coverage under insurance when existing treatments, such as HU, are insufficient and ineffective.

Rationale for apheresis

Removal of the target red blood cells can be performed through a single session of erythrocyte apheresis while reducing the effect on hemodynamics by simultaneously replacing the red blood cells with the same amount of physiological saline. Multiple reports have indicated that this method was more efficient compared to phlebotomy using the back method, and the burden on patients is expected to be reduced through decreasing the number of treatments and hospital visits.

Technical notes

This treatment exerts a smaller effect on the hemodynamics than implementing phlebotomy using the back method, and this can be performed even in patients with cardiac dysfunction. However, the fluctuations in the vitals must be monitored during the implementation. ACD-A solution must be used as an anticoagulant at a ratio of 13:1. Symptoms due to hypocalcemia are usually not experienced during erythrocyte apheresis aiming for Ht 55%–60% to 45%, and prophylactic Ca supplementation is not required. However, the materials used for erythrocyte apheresis in Japan can not be reimbursed through insurance as of August 2020.

Duration and discontinuation/number of procedures

It is import to conduct erythrocyte apheresis with a target Ht of less than 45%. Targe values can generally be achieved with just one session, and follow-up observations should subsequently be conducted until Ht increases again.

References

1. Tefferi A. Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol. 2012;87:284–93.

2. Tefferi A, Vannucchi AM, Barbui T. Polycythemia vera treatment algorithm 2018. Blood Cancer J. 2018 Jan 10;8(1):3.

3. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med. 2013;368:22–33.

4. Marchioli R, Vannucchi AM, Barbui T. Treatment target in polycythemia vera. N Engl J Med. 2013;368:1556.

5. Liu H, Liu H, Shen J, Sun C, Guo C, Lin H, et al. A clinical analysis of erythrocytapheresis for the treatment of polycythemia. Transfus Apher Sci. 2013;48:229–33.

6. Evers D, Kerkhoffs JL, Van Egmond L, Schipperus MR, Wijermans PW. The efficiency of therapeutic erythrocytapheresis compared to phlebotomy: a mathematical tool for predicting response in hereditary hemochromatosis, polycythemia vera, and secondary erythrocytosis. J Clin Apher. 2014 Jun;29(3):133–8.

7. Vecchio S, Leonardo P, Musuraca V, D'Ettoris AR, Geremicca W. A comparison of the results obtained with traditional phlebotomy and with therapeutic erythrocytapheresis in patients with erythrocytosis. Blood Transfus. 2007;5:20–3.

8. Kaboth U, Rumpf KW, Liersch T, Vehmeyer K, Krieter D, Kaboth W. Advantages of isovolemic large-volume erythrocytapheresis as a rapidly effective and long-lasting treatment modality for red blood cell depletion in patients with polycythemia vera. Ther Apher. 1997;1:131–4.

8.76 | Worksheet 76

Diseases: Post-transplantation recurrent focal segmental glomerulosclerosis (FSGS)

Procedure: PE

Purpose: Prevention of post-transplantation recurrent FSGS

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 4, CS 3, CR 1

Description of the disease

Focal segmental glomerulosclerosis (FSGS) is a renal disease that presents with intractable nephrotic syndrome and progresses to end-stage renal failure. It has a high recurrence rate even after transplantation and can lead to graft loss. The presence of a proteinuria-inducing humoral factor that circulates in the blood has been presumed to be the cause of recurrence after transplantation; however, this factor has not been identified as of yet.

Current management/treatment

Reports have indicated PE, RIT, and the combined use of both treatments as a way to prevent the recurrence of post-transplantation FSGS.

Rationale for apheresis

The removal of proteinuria-inducing humoral factors in the patient's plasma is thought to be effective; however, this has not yet been proven. There have been reports that the above-mentioned preventive treatment prior to surgery resulted in a lower recurrence rate compared to historical controls, and that the urinary protein amount was low even during recurrence. However, there are also reports indicating no differences in the recurrence rate or amount of urinary protein. The number of reported cases is limited; additionally, there is no established consensus on its effects.

Technical notes

A volume of 1–2 times the circulating plasma is replaced with either 3.3%–8% (most are at 5%) albumin solution or FFP in PE. The blood coagulation time should be monitored and replacement with FFP should be conducted prior to surgery in order to avoid bleeding complications at the time of the kidney transplantation.

Duration and discontinuation/number of procedures

The number of PE implementations prior to surgery has varied widely from 3 to 10 times depending on the report. This is currently not covered by the insurance in Japan.

References

1. Park HS, Hong Y, Sun IO, Chung BH, Kim HW, Choi BS, et al. Korean J Intern Med. 2014 Jul;29(4):482–8.

2. Audard V, Kamar N, Sahali D, Cardeau-Desangles I, Homs S, Remy P, et al. Transpl Int. 2012 May;25(5): e62–6.

3. Gonzalez E, Ettenger R, Rianthavorn P, Tsai E, Malekzadeh M. Pediatr Transplant. 2011 Aug;15(5):495–501.

4. Hickson LJ, Gera M, Amer H, Iqbal CW, Moore TB, Milliner DS, et al. Transplantation. 2009 Apr 27; 87(8):1232–9.

5. Mahesh S, Del Rio M, Feuerstein D, Greenstein S, Schechner R, Tellis V, et al. Pediatr Transplant. 2008 Sep;12(6):682–8.

6. Gohh RY, Yango AF, Morrissey PE, Monaco AP, Gautam A, Sharma M, et al. Am J Transplant. 2005 Dec; 5(12):2907–12.

7. Matalon A, Markowitz GS, Joseph RE, Cohen DJ, Saal SD, Kaplan B, et al. Clin Nephrol. 2001 Oct; 56(4):271–8.

8. Ohta T, Kawaguchi H, Hattori M, Komatsu Y, Akioka Y, Nagata M, et al. Transplantation. 2001 Mar 15;71(5):628–33.

8.77 | Worksheet 77

Diseases: Post-transplantation recurrent focal segmental glomerulosclerosis (FSGS)

Procedure: PE

Purpose: Treatment of post-transplantation recurrent FSGS

Recommendation: 1B

Category: I

The number of references: RCT 0, CT 9, CS 17, CR 0

Description of the disease

Focal segmental glomerulosclerosis (FSGS) is a renal disease that presents with intractable nephrotic syndrome and progresses to end-stage renal failure. It has a high recurrence rate even after transplantation and can lead to graft loss. The presence of a proteinuria-inducing humoral factor that circulates in the blood has been presumed to be the cause of recurrence after transplantation; however, this factor has not been identified as of yet.

Current management/treatment

The treatment of post-transplantation recurrent FSGS includes immunosuppressants prior to recurrence (steroids, CNI, and MMF), as well as PE, steroid pulse therapy, rituximab, and ACEI/ARB, either as monotherapy or concomitant therapy.

Rationale for apheresis

The removal of proteinuria-inducing humoral factors in the patient's plasma is presumed to be effective. The humoral factors have not yet been identified; however, no reports on recurrent FSGS cases showed that remission was achieved without PE. The response rate (complete remission or partial remission) of PE (under the concomitant therapy in the previous section) was 50%–100% based on articles included in this systematic review. Although there are differences between reports, the humoral factors are thought to be involved, given that the PE decreases proteinuria in recurrent cases following the completion of PE or proteinuria-increasing cases.

Technical notes

A volume of 1–2 times the circulating plasma is replaced with either 3.3%–8% (most are at 5%) albumin solution or FFP in PE. Several reports stated that PE should ideally be started immediately after the diagnosis of recurrence. The immunoglobulin levels may decrease alongside elevated proteinuria during recurrence and this may be worsened by PE. Therefore, attention must be paid to hypogammaglobulinemia. There have also been reports of transplanted kidney bleeding as a complication; therefore, caution is required for coagulation factor depletion.

Duration and discontinuation/number of procedures

The number of implementations when including international reports varies widely from several times to over 100 times; additionally, there is no established number of implementations or interval. There have been reports even among cases that were responsive to the initial treatment where multiple recurrences occurred after the suspension of the treatment, or when proteinuria worsened with decreases in the frequency of PE. The optimal discontinuation time is unknown.

References

1. Cleper R, Krause I, Bar Nathan N, Mor M, Dagan A, Weissman I, et al. Clin Transplant. 2016 Oct;30 (10):1324–31.

2. Staeck O, Slowinski T, Lieker I, Wu K, Rudolph B, Schmidt D, et al. Transplantation. 2015 Dec;99(12): 2593–7.

3. Fencl F, Vondrák K, Rosík T, Zieg J, Chadimová M, Háček J, et al. Minerva Pediatr. 2016 Oct;68(5): 348–54.

4. Park HS, Hong Y, Sun IO, Chung BH, Kim HW, Choi BS, et al. Korean J Intern Med. 2014 Jul;29(4): 482–8.

5. Straatmann C, Kallash M, Killackey M, Iorember F, Aviles D, Bamgbola O, et al. Pediatr Transplant. 2014 Feb;18(1):29–34.

6. Kandus A, Ponikvar R, Buturović-Ponikvar J, Bren AF, Oblak M, Mlinšek G, et al. Ther Apher Dial. 2013 Aug;17(4):438–43.

7. Audard V, Kamar N, Sahali D, Cardeau-Desangles I, Homs S, Remy P, et al. Transpl Int. 2012 May;25(5): e62–6.

8. Gungor O, Sen S, Kircelli F, Yilmaz M, Sarsik B, Ozkahya M, et al. Transplant Proc. 2011 Apr;43(3):853–7.

9. Gonzalez E, Ettenger R, Rianthavorn P, Tsai E, Malekzadeh M. Pediatr Transplant. 2011 Aug;15(5): 495–501.

10. Schachter ME, Monahan M, Radhakrishnan J, Crew J, Pollak M, Ratner L, et al. Clin Nephrol. 2010 Sep;74(3):173–81.

11. Tsagalis G, Psimenou E, Nakopoulou L, Laggouranis A. Artif Organs. 2011 Apr;35(4):420–5.

12. Fuentes GM, Meseguer CG, Carrion AP, Hijosa MM, Garcia-Pose A, Melgar AA, et al. Pediatr Nephrol. 2010 Mar;25(3):529–34.

13. Moroni G, Gallelli B, Quaglini S, Banfi G, Montagnino G, Messa P. Transpl Int. 2010 Feb;23(2): 208–16.

14. Hickson LJ, Gera M, Amer H, Iqbal CW, Moore TB, Milliner DS, et al. Transplantation. 2009 Apr 27; 87(8):1232–9.

15. Canaud G, Zuber J, Sberro R, Royale V, Anglicheau D, Snanoudj R, et al. Am J Transplant. 2009 May;9(5):1081–6.

16. Mahesh S, Del Rio M, Feuerstein D, Greenstein S, Schechner R, Tellis V, et al. Pediatr Transplant. 2008 Sep;12(6):682–8.

17. Garcia CD, Bittencourt VB, Tumelero A, Antonello JS, Malheiros D, Garcia VD. Transplant Proc. 2006 Jul–Aug;38(6):1904–5.

18. Pardon A, Audard V, Caillard S, Moulin B, Desvaux D, Bentaarit B, et al. Nephrol Dial Transplant. 2006 Apr;21(4):1053–9.

19. Gohh RY, Yango AF, Morrissey PE, Monaco AP, Gautam A, Sharma M, et al. Am J Transplant. 2005 Dec; 5(12):2907–12.

20. Pradhan M, Petro J, Palmer J, Meyers K, Baluarte HJ. Pediatr Nephrol. 2003 Sep;18(9):934–8.

21. Matalon A, Markowitz GS, Joseph RE, Cohen DJ, Saal SD, Kaplan B, et al. Clin Nephrol. 2001 Oct; 56(4):271–8.

22. Greenstein SM, Delrio M, Ong E, Feuerstein D, Schechner R, Kim D, et al. Pediatr Nephrol. 2000 Oct; 14(12):1061–5.

23. Ohta T, Kawaguchi H, Hattori M, Komatsu Y, Akioka Y, Nagata M, et al. Transplantation. 2001 Mar 15;71(5):628–33.

24. Dall'Amico R, Ghiggeri G, Carraro M, Artero M, Ghio L, Zamorani E, et al. Am J Kidney Dis. 1999 Dec; 34(6):1048–55.

25. Andresdottir MB, Ajubi N, Croockewit S, Assmann KJ, Hibrands LB, Wetzels JF. Nephrol Dial Transplant. 1999 Nov;14(11):2650–6.

8.78 | Worksheet 78

Diseases: Progressive multifocal leukoencephalopathy (PML) associated with natalizumab

Procedure: PE

Purpose: Removal of natalizumab

Recommendation: 1C

Category: III

The number of references: RCT 0, CT 0, CS 4, CR NA

Description of the disease

Progressive multifocal leukoencephalopathy (PML) is caused by the central nervous system infection of the JC virus (JCV). It has affected more than 70% of healthy adults in Japan. Rarely, when the host's immune function is reduced, it involves invasion of the infected B cells in the central nervous system, thereby infecting oligodendrosites and astrosites and resulting in demyelination. Natalizumab (NTZ) is a pathogenic modifier for relapse-/remission-type multiple sclerosis and a humanized monoclonal antibody (IgG4) for α4-integrin, which inhibits the transfer of activated lymphocytes to brain parenchymal tissue. PML has recently garnered attention as a complication of monoclonal antibody therapy. The incidence rate of general PML is 0.9 per million people, while that of NTZ-related PML (NTZ-PML) is relatively high at 1.1–28 per million people.

Current management/treatment

No effective treatment has been established for general PML. Early detection of PML, temporary or permanent suspension of NTZ use, and apheresis therapy to remove NTZ, particularly when NTZ has recently been administered, have been considered for NTZ-PML. However, in the case of NTZ-PML, cell-mediated immunity is enhanced by removing NTZ with PE and performing immune reconstitution, causing rapid immune reconstitution inflammatory syndrome (IRIS). NTZ-PML causes IRIS more often than PML related to other drugs, and the prognosis is poor after the disease has developed.

Rationale for apheresis

In blood, NTZ has a long half-life of 365 ± 132 h and can remain long after its suspension; therefore, apheresis can be an effective removal method. However, it does not improve the prognosis or outcome. It also belongs to the IgG4 subclass, and IAPP cannot absorb or remove IgG4.

Technical notes

Handling the subsequent IRIS is important in apheresis therapy for asymptomatic PML. Severe PML-IRIS is associated with vital prognosis, so steroid pulse therapy should also be considered. IAPP should not be used with the objective of removing NTZ.

Duration and discontinuation/number of procedures

Per the recommendation, albumin-replacement PE is usually conducted every alternate day for five sessions in a single course.

References

1. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;17:366:1870–80.

2. Ho PR, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol. 2017;16:925–33.

3. Wenning W, Haghikia A, Laubenberger J, Clifford DB, Behrens PF, Chan A, et al. Treatment of progressive multifocal leukoencephalopathy associated with natalizumab. N Engl J Med. 2009;361:1075–80.

4. Lindå H, von Heijne A, Major EO, Ryschkewitsch C, Berg J, Olsson T, et al. Progressive multifocal leukoencephalopathy after natalizumab monotherapy. N Engl J Med. 2009;361:1081–7.

5. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol. 2010;9:438–46.

6. Vermersch P, Kappos L, Gold R, Foley JF, Olsson T, Cadavid D, et al. Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. Neurology. 2011;76:1697–1704.

7. Dahlhaus S, Hoepner R, Chan A, Kleiter I, Adams O, Lukas C, et al. Disease course and outcome of 15 monocentrically treated natalizumab-associated progressive multifocal leukoencephalopathy patients. J Neurol Neurosurg Psychiatry. 2013;84:1068–74.

8. Available from: http://www.ms-supportnavi.com/med/tys/products/08.html

9. Landi D, De Rossi N, Zagaglia S, Scarpazza C, Prosperini L, Albanese M, et al. No evidence of beneficial effects of plasmapheresis in natalizumab-associated PML. Neurology. 2017;88:1144–52.

10. Available from: https://www.uptodate.com/contents/progressive-multifocal-leukoencephalopathy-treatment-andprognosis?/souece=see_link&sectionName=Natalizumab-associated%20PML&anchor=H56321583#56321583

11. Clifford DB. Neurological immune reconstitution inflammatory response: riding the tide of immune recovery. Curr Opin Neurol. 2015;28:295–301.

12. Ikazabo RNN, Mostosi C, Quivron B, Delberghe X, El Hafsi K, Lysandropoulos AP. Immune-reconstitution inflammatory syndrome in multiple

sclerosis patients treated with natalizumab: a series of 4 cases. Clin Ther. 2016 Mar;38(3):670–5.

13. Vennegoor A, Rispens T, Van Oosten BW, Wattjes MP, Wondergem MJ, Teunissen CE, et al. Application of serum natalizumab levels during plasma exchange in MS patients with progressive multifocal leukoencephalopathy. Mult Scler. 2015 Apr;21(4):481–4.

14. Takao M. Targeted therapy and progressive multifocal leukoencephalopathy (PML): PML in the era of monoclonal antibody therapies. Brain Nerve. 2013 Nov;65(11):1363–74.

15. Wattjes MP, Verhoeff L, Zentjens W, Killestein J, van Munster ET, Barkhof F, et al. Punctate lesion pattern suggestive of perivascular inflammation in acute natalizumab-associated progressive multifocal leukoencephalopathy: productive JC virus infection or preclinical PML-IRIS manifestation? J Neurol Neurosurg Psychiatry. 2013 Oct;84(10):1176–7.

16. Subramanyam M, Plavina T, Khatri BO, Fox RJ, Goelz SE. The effect of plasma exchange on serum anti-JC virus antibodies. Mult Scler. 2013 Jun;19(7):912–9.

17. Gwathmey K, Balogun RA, Burns T. Neurologic indications for therapeutic plasma exchange: 2011 update. J Clin Apher. 2012;27(3):138–45.

8.79 | Worksheet 79

Diseases: Psoriatic arthritis

Procedure: Granulocyte and monocyte adsorption apheresis

Purpose: Removal of activated granulocytes and monocytes

Recommendation: 1C

Category: II

The number of references: RCT 0, CT 0, CS 4, CR 1

Description of the disease

Psoriatic arthritis is a disease that causes psoriatic rash-associated peripheral arthritis, axial arthritis, enthesitis, and dactylitis. According to the Moll & Wright classification, it is classified into five subtypes: asymmetric oligoarthritis, symmetric polyarthritis, distal interphalangeal joint inflammation, spondyloarthritis, and arthritis mutilans.

Current management/treatment

Current treatment options include nonsteroidal anti-inflammatory drugs for mild joint symptoms. For moderate symptoms, cyclosporine, methotrexate, or phosphodiesterase (PDE)4 inhibitors are administered. Biological therapies, such as tumor necrosis factor (TNF)-α inhibitors, interleukin (IL)-17 inhibitors, and IL-23 inhibitors, should be reserved for patients who do not respond to the abovementioned treatments or who rapidly progress.

Rationale for apheresis

Granulocyte and monocyte adsorption apheresis selectively removes activated *granulocytes and monocytes/macrophages* that underlie the pathology of pustular psoriasis. Removal of these cells decrease the proinflammatory cytokines in the blood. In addition, it has various immunomodulatory effects, including reduction of active naïve cell mobilization from the bone marrow, decrease in inflammatory macrophages, and induction of regulatory T cells and bone marrow-derived inhibitory cells.

Technical notes

Select an appropriate blood vessel to perform the insertion technique while paying attention to the infection risk at the needle insertion site. Carefully apply anticoagulants (heparin, low-molecular-weight heparin, or nafamostat mesylate) for patients with a history of hypersensitivity.

Duration and discontinuation/number of procedures

For a single treatment session, process 1800 ml of blood for 60 min at a flow rate of 30 ml/min. Treatment should be repeated once or twice a week, 5–10 sessions per series. Insured coverage is approved for once-a-week treatment per course, up to five times. Determine whether to suspend or continue treatment by evaluating the effectiveness based on the severity of subjective symptoms, such as joint swelling and pain.

References

1. Kanekura T, Seishima M, Honma M, Etou T, Eto H, Okuma K, et al. Therapeutic depletion of myeloid lineage leukocytes by adsorptive apheresis for psoriatic arthritis: efficacy of a non-drug intervention for patients refractory to pharmacologics. J Dermatol. 2017;44:1353–9.

2. Kanekura T, Kawabata H, Maruyama I, Kanzaki T. Treatment of psoriatic arthritis with granulocyte and monocyte adsorption apheresis. J Am Acad Dermatol. 2004;50:242–6.

3. Kanekura T, Hiraishi K, Kawahara K, Maruyama I, Kanzaki T. Granulocyte and monocyte adsorption apheresis (GCAP) for refractory skin diseases caused by activated neutrophils and psoriatic arthritis: evidence that GCAP removes Mac-1-expressing neutrophils. Ther Apher Dial. 2006;10:247–56.

4. Sakanoue M, Takeda K, Kawai K, Kanekura T. Granulocyte and monocyte adsorption apheresis for refractory skin diseases due to activated neutrophils, psoriasis, and associated arthropathy. Ther Apher Dial. 2013;17:477–83.

5. Fujisawa T, Moriya C, Shibuya Y, Kanoh H, Seishima M. Combination therapy of infliximab and granulocyte and monocyte adsorption apheresis for refractory pustular psoriasis with psoriatic arthritis. Acta Derm Venereol. 2013;93:364–5.

8.80 | Worksheet 80

Diseases: Pustular psoriasis
Procedure: GMA
Purpose: Activated granulocyte / monocyte removal
Recommendation: 1C
Category: II
The number of references: RCT 0, CT 0, CS 12, CR 7

Description of the disease

Pustular psoriasis (generalized type) is a skin disease, in which the skin of the entire body rapidly becomes feverish, and aseptic pustules frequently occur. Histopathologically, subcorneal pustules are characterized by spongiform pustules of Kogoj. Psoriasis vulgaris rash may or may not precede the presentation, and repeated recurrence usually occurs.

Current management/treatment

Treatments, such as topical steroids, topical active vitamin D3, topical combinations of both, UV therapy, etretinate, cyclosporine, oral methotrexate, tumor necrosis factor (TNF)-α inhibitors, interleukin (IL)-17 inhibitors, IL-23 inhibitors, and other biological preparations are used.

Rationale for apheresis

Granulocyte and monocyte adsorption apheresis selectively removes activated granulocytes and monocytes/macrophages that underlie the pathology of pustular psoriasis. Removal of these cells decrease the proinflammatory cytokines in the blood. In addition, it has various immunomodulatory effects, including reduction of active naïve cell mobilization from the bone marrow, decrease in inflammatory macrophages, and induction of regulatory T cells and bone marrow-derived inhibitory cells.

Technical notes

Select an appropriate blood vessel to perform the insertion technique while paying attention to the infection risk at the needle insertion site. Try to select an insertion site with unaffected healthy skin, if possible. Wiping with alcohol cotton is sufficient when piercing healthy skin. Disinfect with isodine when there are pustules or erosions near the insertion site.

Duration and discontinuation/number of procedures

For a single treatment session, process 1,800 mL of blood for 60 minutes at a flow rate of 30 mL/min. Treatment should be repeated once or twice a week, 5-10 sessions per series. Insured coverage is approved for once-a-week treatment per course, up to five times. Determine whether to suspend or continue treatment by evaluating the effectiveness based on some factors, such as the severity of skin and subjective symptoms.

References

1. Ikeda S, Takahashi H, Suga Y et al. Therapeutic depletion of myeloid lineage leukocytes in patients with generalized pustular psoriasis indicates a major role for neutrophils in the immunopathogenesis of psoriasis. J Am Acad Dermatol 2013; 68: 609–617.

2. Kanekura T, Yoshii N, Yonezawa T, Kawabata H, Saruwatari H, Kanzaki T. Treatment of pustular psoriasis with granulocyte and monocyte adsorption apheresis. J Am Acad Dermatol 2003; 49: 329–332.

3. Kanekura T, Hiraishi K, Kawahara K, Maruyama I, Kanzaki T. Granulocyte and monocyte adsorption apheresis (GCAP) for refractory skin diseases caused by activated neutrophils and psoriatic arthritis: evidence that GCAP removes Mac-1-expressing neutrophils. Ther Apher Dial 2006; 10: 247–256.

4. Sakanoue M, Takeda K, Kawai K, Kanekura T. Granulocyte and monocyte adsorption apheresis for refractory skin diseases due to activated neutrophils, psoriasis, and associated arthropathy. Ther Apher Dial. 2013;17:477–483.

5. Seishima M, Mizutani Y, Shibuya Y, Nagasawa C, Aoki T. Efficacy of granulocyte and monocyte adsorption apheresis for pustular psoriasis. Ther Apher Dial 2008; 12: 13-18.

6. Shukuya R, Hasegawa T, Niwa Y, Okuma K, Ikeda S. Granulocyte and monocyte adsorption apheresis for generalized pustular psoriasis. J Dermatol 2011; 38: 1130–1134.

7. Fujisawa T, Suzuki S, Mizutani Y, Doi T, Yoshida S, Ogura S, Seishima M. Granulocyte and monocyte adsorption apheresis for generalized pustular psoriasis: therapeutic outcomes in three refractory patients. Ther Apher Dial 2015; 19: 336–341.

8.81 | Worksheet 81

Diseases: Pyoderma gangrenosum

Procedure: Granulocyte and monocyte adsorption apheresis

Purpose: Removal of activated granulocytes and monocytes

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 2, CR 24

Description of the disease

Pyoderma gangrenosum is a painful disease that starts with pustules resembling folliculitis, resulting in intractable skin ulcers frequently on the lower body. Pathology shows neutrophil infiltration in the dermis and is sterile. It is a chronic progressive disease with common recurrence, where tissue healing results in scar formation. It is often accompanied by ulcerative colitis, Crohn's disease, rheumatoid arthritis, malignant lymphoma, leukemia, and other diseases.

Current management/treatment

Current treatment options include systemic treatments (corticosteroids, immunosuppressive drugs, and non-steroidal anti-inflammatory drugs), topical therapies (corticosteroids and topical tacrolimus), and surgery (debridement and skin implantation). Tumor necrosis factor (TNF)-α inhibitors have been recently used in patients who are refractory to other treatments.

Rationale for apheresis

Granulocyte and monocyte adsorption apheresis selectively removes activated granulocytes and monocytes/macrophages that underlie the pathology of pustular psoriasis. Removal of these cells decrease the proinflammatory cytokines in the blood. In addition, it has various immunomodulatory effects, including reduction of active naïve cell mobilization from the bone marrow, decrease in inflammatory macrophages, and induction of regulatory T cells and bone marrow-derived inhibitory cells. However, treatment of pyoderma gangrenosum is currently not covered under insurance.

Technical notes

Select an appropriate blood vessel to perform the insertion technique while paying attention to the infection risk at the needle insertion site.

Duration and discontinuation/number of procedures

For a single treatment session, process 1800 ml of blood for 60 min at a flow rate of 30 ml/min. Treatment should be repeated once or twice a week, 5–10 sessions per series. Treatment is not covered by insurance. Determine whether to suspend or continue treatment by evaluating the effectiveness based on some factors, such as eruption size, depth, infiltration, and subjective symptom severity.

References

1. Russo I, Miotto S, Colpo A, Marson P, Tison T, Ferrazzi A, et al. Successful treatment of pyoderma gangrenosum with granulocyte and monocyte adsorption apheresis. Int Wound J. 2017;13:282–4.

2. Ohno M, Koyama S, Ohara M, Shimamoto K, Kobayashi Y, Nakamura F, et al. Pyoderma Gangrenosum with ulcerative colitis successfully treated by the combination of granulocyte and monocyte adsorption apheresis and corticosteroids. Intern Med. 2016;55:25–30.

3. Ikeda K, Hamada T, Otsuka M, Iwatsuki K. Beneficial effects of neutrophil-targeted therapy for pyoderma gangrenosum associated with ulcerative colitis. Eur J Dermatol. 2011;21:804–5.

4. Hanafusa T, Azukizawa H, Umegaki N, Tani M, Yamaguchi Y, Katayama I. Clinical implications of leukocytapheresis using a centrifugal cell separator for steroid-resistant pyoderma gangrenosum associated with inflammatory bowel disease. J Dermatol. 2011;38:507–10.

5. Kawakami T, Yamazaki M, Soma Y. Reduction of interleukin-6, interleukin-8, and anti-phosphatidylserine-prothrombin complex antibody by granulocyte and monocyte adsorption apheresis in a patient with pyoderma gangrenosum and ulcerative colitis. Am J Gastroenterol. 2009;104:2363–4.

6. Okuma K, Mitsuishi K, Hasegawa T, Tsuchihashi H, Ogawa H, Ikeda S. A case report of steroid and immunosuppressant-resistant pyoderma gangrenosum successfully treated by granulocytapheresis. Ther Apher Dial. 2007;11:387–90.

7. Seishima M, Mizutani Y, Shibuya Y, Nagasawa C, Aoki T. Efficacy of granulocyte and monocyte adsorption apheresis for three cases of refractory pyoderma gangrenosum. Ther Apher Dial. 2007;11:177–82.

8. Kanekura T, Kawahara K, Maruyama I, Kanzaki T. Treatment of pyoderma gangrenosum with granulocyte and monocyte adsorption apheresis. Ther Apher Dial. 2005;9:292–6.

9. Kanekura T, Maruyama I, Kanzaki T. Granulocyte and monocyte adsorption apheresis for pyoderma gangrenosum. J Am Acad Dermatol. 2002;47:320–1.

8.82 | Worksheet 82

Diseases: Rapidly progressive interstitial pneumonia associated with anti-MDA5 antibody-positive dermatomyositis

Procedure: PE

Purpose: Improvement of interstitial pneumonia

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 2, CR 8

Description of the disease

The anti-melanoma differentiation-associated gene 5 (MDA5) antibody is found in approximately 23%–58% of patients with dermatomyositis and amyopathic dermatomyositis; of these, 71% develop rapidly progressive interstitial pneumonia. These cases have treatment resistance and an extremely poor prognosis with a 2-year survival rate of 28.6%. Multidrug immunosuppressive therapy has reportedly increased this to 75%, but 25% of patients still die of respiratory failure within 6 months of onset. Hyperferritinemia, old age, and delayed treatment are risk factors. It has also been reported that patients with poor therapeutic response (e.g., decreased anti-MDA5 antibody titer, decreased IL-18) have poor prognosis.

Current management/treatment

There is no established cure. In addition to high-dose steroid administration, combined therapy with calcineurin inhibitors (e.g., cyclosporine, tacrolimus) and immunosuppressants (e.g., cyclophosphamide) has been shown to be effective. Azathioprine and mycophenolate mofetil can also be selected. Immunoglobulin therapy, rituximab, tofacitinib, and basiliximab have also been reported to be effective in addition to PE and PMX-DHP for refractory cases.

Rationale for apheresis

The enhanced expression of Type I interferon-related genes has been reported in dermatomyositis. The high concentrations of ferritin and IL-18 found in rapidly progressive interstitial pneumonia associated with anti-MDA5 antibody-positive dermatomyositis suggest that the activation of monocytes and macrophages may be associated with pathological conditions. The direct removal of these various cytokines and other unknown pathogens in the circulating blood is presumed to be the effective mechanism of apheresis.

Technical notes

Mainly PE is conducted. There have been some reports where PMX-DHP was also effective. Apheresis should be used in combination with other therapies as soon as possible after considering the severity of the pathological condition. The plasma exchange volume should be 1–1.5 times the circulating plasma volume (PV). Albumin or FFP should be used as the replenishment solution during PE. Nafamostat mesylate or heparin should be selected as the anticoagulant. The insurance coverage of PE for rapidly progressive interstitial pneumonia associated with anti-MDA5 antibody-positive dermatomyositis is pending.

Duration and discontinuation/number of procedures

A total of 4–15 sessions of PE have been reported in case reports to be efficacious. It has been suggested that treatment should be administered 2–3 times a week, every day or every other day, with the objective of correcting hypercytokinemia. There have also been reports on the effectiveness of two PMX-DHP sessions. The guidelines for the duration of treatment do not provide substantial evidence, but it is desirable to confirm the decrease in ferritin, which is thought to reflect pathological conditions.

References

1. Gono T, Kawaguchi Y, Ozeki E, Ota Y, Satoh T, Kuwana M, et al. Serum ferritin correlates with activity of anti-MDA5 antibody associated acute interstitial lung disease as a complication of dermatomyositis. Mod Rheumatol. 2011;21(2):223–7.

2. Gono T. Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. Rheumatology. 2012;51(9):1563–70.

3. Sato S, Kuwana M, Fujita T, Suzuki Y. Anti-CADM-140/MDA5 autoantibody titer correlates with disease activity and predicts disease outcome in patients with dermatomyositis and rapidly progressive interstitial lung disease. Mod Rheumatol. 2013;23(3):496–502.

4. Muro Y, Sugiura K, Akiyama M. Limitations of a single-point evaluation of anti-MDA5 antibody, ferritin, and IL-18 in predicting the prognosis of interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. Clin Rheumatol. 2013;32(3):395–8.

5. Gono T, Kaneko H, Kawaguchi Y, Hanaoka M, Kataoka S, Kuwana M, et al. Cytokine profiles in polymyositis and dermatomyositis complicated by rapidly progressive or chronic interstitial lung disease. Rheumatology. 2014;53(12):2196–203.

6. Abe Y, Matsushita M, Tada K, Yamaji K, Takasaki Y, Tamura N. Clinical characteristics and change in the antibody titres of patients with anti MDA5 antibody-positive inflammatory myositis.Rheumatology. 2017;56(9):1492–7.

7. Nakashima R. Clinical significance of myositis-specific autoantibodies. Immunol Med. 2018;41(3):103–12.

8. Moghadam-Kia S, Oddis CV, Aggarwal R. Anti-MDA5 antibody spectrum in western world. Curr Rheumatol Rep. 2018;20(12):78.

9. Fujita Y, Fukui S, Suzuki T, Ishida M, Endo Y, Tsuji S, et al. Anti-MDA5 antibody-positive dermatomyositis complicated by autoimmune-associated hemophagocytic syndrome that was successfully treated with immunosuppressive therapy and plasmapheresis. Intern Med. 2018. [Epub ahead of print].

10. Endo Y, Koga T, Suzuki T, Hara K, Ishida M, Fujita Y, et al. Successful treatment of plasma exchange for rapidly progressive interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis: a case report. Medicine. 2018;97(15):e0436.

11. Fujiki Y, Kotani T, Isoda K, et al. Evaluation of clinical prognostic factors for interstitial pneumonia in anti-MDA5 antibody-positive dermatomyositis patients. Mod Rheumatol. 2018;28(1):133–40.

8.83 | Worksheet 83

Diseases: Refractory nephrotic syndrome

Procedure: PE*DFPP*LDL-A

Purpose: Induction and maintenance of remission of nephrotic syndrome

Recommendation: (PE, DFPP) None
(LDL-A) 2C

Category: (PE, DFPP) III
(LDL-A) III

The number of references (PE, DFPP) (LDL-A): RCT 0, 0, CT 0, 1, CS 1, 9, CR 5, 20

Description of the disease

Nephrotic syndrome is characterized by a large amount of urinary protein based on increased protein permeability due to renal glomerular disorders and associated hypoalbuminemia. Refractory nephrotic syndrome is diagnosed in those individuals who do not achieve complete remission (urinary protein < 0.3 g/day) or incomplete remission Type I (0.3 g/day ≤ urinary protein < 1.0 g/day) even after undergoing various treatments (including steroids and immunosuppressants) for a certain time period (6 months, or more than 4 months).

Current management/treatment

Corticosteroids and immunosuppressants are used as an initial treatment. PE or DFPP/LDL-A is conducted to reduce proteinuria in cases where complete remission or incomplete remission Type I could not be attained with these standard treatments. The use of rituximab (covered by insurance) and mycophenolate mofetil (not covered by insurance) have also been considered in recent years in addition to apheresis therapy.

Rationale for apheresis

PE seeks to remove the permeability factor(s) that cause nephrotic syndrome. LDL-A has been reported to improve dyslipidemia as well as adsorb permeability factors, and improve cytokine balance, and the intracellular drug transport mechanism. Apheresis has been reported to induce complete remission or incomplete remission type I and improve the renal prognosis in cases who did not respond to existing treatments with steroids and immunosuppressants.

Technical notes

Immunoglobulin and coagulation factors are also nonselectively removed in PE; therefore, a replacement solution (albumin or fresh frozen plasma) must be selected accoding to the comorbidities. LDL-A is contraindicated in the patients on ACE-I because the combined use of ACE-I may cause excessive production of bradykinin and cause shock.

Duration and discontinuation/number of procedures

As indicated in the guidelines of several countries, the necessity and effectiveness of PE must be determined on a case-by-case basis. LDL-A use is covered by the insurance up to 12 times in a 3-month period per series when conventional drug therapy is ineffective, and when the serum cholesterol levels do not drop below 250 mg/dL during the nephrotic state in the patient with focal segmental glomerulosclerosis. The case series reported to date adopted a protocol that was performed twice a week for the first 3 weeks followed by once a week for the subsequent 6 weeks.

References

1. Muso E, Mune M, Fujii Y, Imai E, Ueda N, Hatta K, et al.; Kansai FGS LDL Apheresis Treatment (K-FLAT) Study Group. Significantly rapid relief from steroid-resistant nephrotic syndrome by LDL apheresis compared with steroid monotherapy. Nephron. 2001; 89(4): 408–15.

2. Hattori M, Chikamoto H, Akioka Y, Nakakura H, Ogino D, Matsunaga A, et al. A combined low-density lipoprotein apheresis and prednisone therapy for steroid-resistant primary focal segmental glomerulosclerosis in children. Am J Kidney Dis. 2003; 42(6): 1121–30.

3. Muso E, Mune M, Yorioka N, Nishizawa Y, Hirano T, Hattori M, et al. Beneficial effect of low-density lipoprotein apheresis (LDL-A) on refractory nephrotic syndrome (NS) due to focal glomerulosclerosis (FGS). Clin Nephrol. 2007; 67(6): 341–4.

4. Miyata H, Uno K, Ono T, Yashiro M, Fukatsu A, Kita T, et al. Low density lipoprotein apheresis ameliorates interferon-gamma production in patients with nephrotic syndrome. Ther Apher Dial. 2012; 16(2): 189–94.

5. Muso E, Mune M, Hirano T, Hattori M, Kimura K, Watanabe T, et al. Immediate therapeutic efficacy of low-density lipoprotein apheresis for drug-resistant nephrotic syndrome: evidence from the short-term results from the POLARIS Study. Clin Exp Nephrol. 2015; 19(3): 379–86.

6. Muso E, Mune M, Hirano T, Hattori M, Kimura K, Watanabe T, et al. A Prospective Observational Survey on the Long-Term Effect of LDL Apheresis on Drug-Resistant Nephrotic Syndrome. Nephron Extra. 2015; 5(2): 58–66.

7. Wada T, Nangaku M. A circulating permeability factor in focal segmental glomerulosclerosis: the hunt continues. Clin Kidney J. 2015; 8(6): 708–15.

8. Suzuki H, Tsukamoto T, Muso E. Rituximab-Resistant Nephrotic Syndrome With Successful Induction of Remission by Low-Density Lipoprotein Apheresis. Ther Apher Dial. 2017; 21(3): 295–6.

9. Shabaka A, Tato Ribera A, Fernández-Juárez G. Focal Segmental Glomerulosclerosis: State-of-the-Art and Clinical Perspective. Nephron. 2020; 144(9): 413–27.

10. Muso E, Sakai S, Ogura Y, Yukawa S, Nishizawa Y, Yorioka N, et al. Favorable therapeutic efficacy of low-density lipoprotein apheresis for nephrotic syndrome with impaired renal function.

Ther Apher Dial. 2021 May 31. doi: 10.1111/1744-9987.13694. Online ahead of print.

11. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group Collaborators expand. Kidney Int. 2021; 100(4S):S1–S276.

8.84 | Worksheet 84

Diseases: Refsum's disease
Procedure: PE, DFPP
Purpose: Removal of plasma phytanic acid
Recommendation: 2C
Category: II
The number of references: RCT 0, CT 0, CS 4, CR 12

Description of the disease

An autosomal recessive disorder characterized by anosmia/early onset retinitis pigmentosa, peripheral neuropathy, sensorineural hearing loss, cerebellar ataxia, and ichthyosis. In this disease, the levels of unmetabolized phytanic acid increase in the blood and its accumulation is seen in the adipose tissue, liver, kidneys, and myelin sheath due to a deficiency of phytanic-CoA hydroxylase localized in peroxisomes. Skeletal abnormalities are congenital. The associated visual impairment, deafness, and anosmia progress slowly, while peripheral neuropathy, cerebellar ataxia, arrhythmia, and ichthyosis rapidly worsen (1). Although this disease mostly occurs in infancy, adult cases have also been reported. It is often encountered in the United Kingdom and Northern Europe, and no cases have been reported in Japan to date.

Current management/treatment

The basic treatment is diet therapy, which entails limiting the consumption of dairy products, meat, and fat that have high phytanic acid content. Hunger and stress should be avoided, and a high-calorie diet is recommended. Improving visual, hearing, and odor impairments is difficult with diet therapy alone; plasma exchange is effective for acute arrhythmia and muscular symptoms due to the high concentration of phytanic acid owing to its redistribution from adipose tissue, peripheral neuropathy, and cerebellar ataxia.

Rationale for apheresis

Plasma phytanic acid has a high molecular weight because it binds to lipoproteins such as low-density lipoprotein (LDL) and very low-density lipoprotein; it cannot be removed by dialysis, but it can be removed by simple plasma exchange therapy, double filtration plasma exchange therapy, or LDL apheresis (lipapheresis). Immediate relief is seen in arrhythmia, and the effect is often seen rapidly within 1–3 weeks for peripheral neuropathy, deafness, ataxia, and pruritus; improvements in gait disturbance are also seen in a few months. This treatment is indicated in cases where diet therapy alone does not result in improvements and is effective not only for cases of acute exacerbation but also for maintenance. Phytanic acid concentration is an indicator.

Technical notes

Many cases are pediatric cases; therefore, ensure that blood access is secured/fixed. Pay attention to infections at the puncture site and coagulation/bleeding tendencies.

Duration and discontinuation/number of procedures

The treatment is not covered by insurance. Aim for 1–2 times per week, for a total of 3–4 times (equivalent to intake amount of 10–70 days). Implement treatment two times a week for the first few months depending on the disease state and reduce the frequency of administration. Implement the treatment about 10 times in the first 6 months; there are cases where the subsequent 6 months is left open as an interval, and treatment is added for another 6 months. In addition, there are maintenance therapies where treatment is administered once a week or every other week for several years.

References

1. Gibberd FB, Billimoria JD, Goldman JM, Clemens ME, Evans R, Whitelaw MN, et al. Heredopathia atactica polyneuritiformis: Refsum's disease. Acta Neurol Scand. 1985;72(1):1–17.

2. Lundberg A, Lilja LG, Lundberg PO, Try K. Heredopathia atactica polyneuritiformis (Refsum's disease). Experiences of dietary treatment and plasmapheresis. Eur Neurol. 1972;8(6):309–24.

3. Gibberd FB, Billimoria JD, Page NG, Retsas S. Heredopathia atactica polyneuritiformis (Refsum's disease) treated by diet and plasma-exchange. Lancet. 1979;17(1):575–8.

4. Hungerbühler JP, Meier C, Rousselle L, Quadri P, Bogousslavsky J. Refsum's disease: management by diet and plasmapheresis. Eur Neurol. 1985;24(3):153–9.

5. Marroun I, Delèvaux I, André M, Droullé AG, Aumaître O. Refsum's disease with severe neuropathy: efficiency of the diet and plasmapheresis. Rev Med Interne. 2005;26(6):523–5.

6. Gutsche HU, Siegmund JB, Hoppmann I. Lipapheresis: an immunoglobulin-sparing treatment for Refsum's disease. Acta Neurol Scand. 1996;94(3):190–3.

7. Straube R, Gäckler D, Thiele A, Muselmann L, Kingreen H, Klingel R. Membrane differential filtration is safe and effective for the long-term treatment of Refsum syndrome—an update of treatment modalities and pathophysiological cognition. Transfus Apher Sci. 2003 Aug;29(1):85–91.

8. Zolotov D, Wagner S, Kalb K, Bunia J, Heibges A, Klingel R. Long-term strategies for the treatment of Refsum's disease using therapeutic apheresis. Clin Apher. 2012;27(2):99–105.

9. Penovich PE, Hollander J, Nusbacher JA, Griggs RC, MacPherson J. Note on plasma exchange therapy in Refsum's disease. Adv Neurol. 1978;21:151–3.

10. Harari D, Gibberd FB, Dick JP, Sidey MC. Plasma exchange in the treatment of Refsum's disease (heredopathia atactica polyneuritiformis). J Neurol Neurosurg Psychiatry. 1991;54(7):614–7.

11. Dickson N, Mortimer JG, Faed JM, Pollard AC, Styles M, Peart DA. A child with Refsum's disease: successful treatment with diet and plasma exchange. Dev Med Child Neurol. 1989;31(1):92–7.

12. Gibberd FB. Plasma exchange for Refsum's disease. Transfus Sci. 1993;14(1):23–6.

13. Leppert D, Schanz U, Burger J, Gmür J, Blau N, Waespe W. Long-term plasma exchange in a case of Refsum's disease. Eur Arch Psychiatry Clin Neurosci. 1991;241(2):82–4.

14. Weinstein R. Phytanic acid storage disease (Refsum's disease): clinical characteristics, pathophysiology and the role of therapeutic apheresis in its management. J Clin Apher. 1999;14(4):181–4.

15. Moser HW, Braine H, Pyeritz RE, Ullman D, Murray C, Asbury AK. Therapeutic trial of plasmapheresis in Refsum disease and in Fabry disease. Birth Defects Orig Artic Ser. 1980;16(1):491–7.

8.85 | Worksheet 85

Diseases: Renal failure with unstable hemodynamics
Procedure: CHDF
Purpose: Renal replacement therapy
Recommendation: NA
Category: I
The number of references: RCT 0, CT 0, CS 0, CR 4172

Description of the disease

A condition intolerable to intermittent renal replacement therapy due to the unstable hemodynamics despite the presence of renal failure with life-threatening complications such as fatal hyperkalemia and fluid overload.

Current management/treatment

Intermittent hemodialysis dialysis may become available after the stabilization of hemodynamics. Continuous hemodiafiltration (CHDF) is recommended for patients with persistent hemodynamic instability and is often implemented when available.

Rationale for apheresis

Apheresis is effective as renal support and can often be implemented even for patients with unstable hemodynamics

Technical notes

The patient will need to be restrained for long periods of time due to continued implementation. There is also an increased risk of bleeding due to continuous administration of anticoagulants. The treatment also puts a heavy burden on the medical staff in terms of medical safety.

Duration and discontinuation/number of procedures

Most cases of acute kidney injury can be weaned off CHDF within 10 days by recovery of renal function or stabilization of hemodynamics to be suitable for intermittent renal replacement therapy .

References

1. Kellum JA, Angus DC, Johnson JP, et al. Continuous versus intermittent renal replacement therapy: a meta-analysis. Intensive Care Med. 2002;28:29–37.

8.86 | Worksheet 86

Diseases: Rheumatoid arthritis (RA)/Malignant RA (MRA)

Procedure: LCAP, PE, DFPP, IAPP

Purpose: Control of activity and improvement of pathological condition

Recommendation: 2B

Category: II

The number of references: RCT 1, CT 1, CS 14, CR 5

Description of the disease

RA is a systemic inflammatory disease primarily presenting as chronic and progressive polyarthritis and is characterized by destructive synovitis and various immune disorders. Triggers causing this autoimmune phenomenon include genetic (e.g., specific gene mutations) and environmental (e.g., smoking, periodontal disease, infectious diseases) factors. In RA, the bones and joints are deformed, resulting in dysfunction and deterioration of vital prognoses. The intractable clinical condition which causes not only joint symptoms but also extra-articular symptoms mainly because of vasculitis is called MRA.

Current management/treatment

Start treatment with methotrexate (MTX); if contraindicated, administer other anti-rheumatic drugs instead (csDMARDs). If the target is not reached but no poor prognostic factors are observed, consider a second dose of csDMARDs. If the treatment target is not reached and poor prognostic factors are present, select treatments with biological preparations or Janus kinase (JAK) inhibitors. If the treatment target is still not reached, consider switching to another biological preparation or JAK inhibitor.

Rationale for apheresis

Randomly sampled, placebo-controlled, double-blind comparative trials for drug-refractory RA patients showed significant improvements relative to the control group in single- and multiple-facility studies. Those studies which investigated the effects of mass processing using a commercially available large column at multiple facilities reported better therapeutic effects of LCAP. A multicenter joint study on MRA showed improvements in extra-articular symptoms, in addition to improvements in physical activity.

Technical notes

A blood exchange volume of LCAP is implemented at 3000 ml/body–100 ml/kg. There are no available replacement solution. If the patient does not exhibit allergies, 40 mg/h of nafamostat mesylate are continuously infused. PE is also used for MRA.

Duration and discontinuation/number of procedures

One session per week up to five sessions of LCAP can be conducted in a single course under insurance. PE is also used for MRA. In this case, there is no particular limit on the number of times at once a week, and this can be implemented until pathological conditions improve while combined with other treatments.

References

1. Azuma T, Ishimaru H, Hatta K, Kori Y. Improved response to infliximab after leukocytapheresis in a patent with rheumatoid arthritis. Mod Rheumatol. 2007;17:253–5.

2. Eguchi K, Saito K, Kondo M, Hidaka T, Ueki Y, Tanaka Y. et al. Enhanced effect of high-dose leukocytapheresis using a large filter in rheumatoid arthritis. Mod Rheumatol. 2007;17:481–5.

3. Hidaka T, Suzuki K, Matsuki Y, Takamizawa-Matsumoto M, Kataharada K, Ishizuka T, et al. Filtration leukocytapheresis therapy in rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 1999;42:431–7.

4. Hidaka T, Suzuki K. Efficacy of filtration leukocytapheresis on rheumatoid arthritis with vasculitis. Ther Apher. 1997;1:212–4.

5. Itoh Y, Takeshita Y, Ozawa Y, Tohma S, Umemura S. A case report of leukocytapheresis for refractory leg ulcers complicated with rheumatoid arthritis. Ther Apher Dial. 2006;10:419–24.

6. Izumi Y, Tominaga M, Iwanaga N, Huang M, Tanaka F, Aratake K, et al. Twenty-four-week follow-up examination of a leukocytapheresis therapy in rheumatoid arthritis. Mod Rheumatol. 2006;16:20–3.

7. Kempe K, Tsuda H, Yang K, Yamaji K, Kanai Y, Hashimoto H. Filtration leukocytapheresis therapy in the treatment of rheumatoid arthritis patients resistant to or failed with methotrexate. Ther Apher Dial. 2004;8:197–205.

8. Kitagaichi M, Kusaoi M, Tsukahara T, Murayama G, Nemoto T, Sekiya F, et al. Safety and efficacy of the leukocytapheresis procedure in eighty-five patients with rheumatoid arthritis. Transfus Apher Sci. 2016;55:225–32.

9. Maeshima K, Torigoe M, Iwakura M, Yamanaka K, Ishii K. Successful leukocytapheresis therapy in a patient with rheumatoid arthritis on maintenance hemodialysis. Mod Rheumatol. 2015;25:154–7.

10. Ogawa H, Matsumoto Y. The efficacy of plasmapheresis or leukocytapheresis for articular and extraarticular manifestations of rheumatoid arthritis. Ther Apher. 1997;1:330–5.

11. Sakai Y, Sakai S, Otsuka T, Ohno D, Murasawa T, Munakata K, Mizuno K. Efficacy of high-throughput

leukocytapheresis for rheumatoid arthritis with a reduced response to infliximab. Ther Apher Dial. 2009;13:179–85.

12. Sawada J, Kimoto O, Suzuki D, Shimoyama K, Ogawa N. Investigation of the clinical usefullness of leukocytapheresis on rheumatoid arthritis resistant to or failed with the other treatments. Nihon Rinsho Meneki Gakkai Kaishi. 2009;32:499–505. [Japanese].

13. Ueki Y, Nakamura H, Kanamoto Y, Miyazaki M, Yano M, Matsumoto K, et al. Comparison of lymphocyte depletion and clinical effectiveness on filtration leukocytapheresis in patients with rheumatoid arthritis. Ther Apher. 2001;5:455–61.

14. Ueki Y, Sagawa A, Tanimura K, Yamada A, Yamamoto K, Tsuda H, et al. A multicenter study of leukocytapheresis in rheumatoid arthritis. Clin Exp Rheumatol. 2007;25:810–6.

15. Ueki Y, Yamasaki S, Kanamoto Y, Kawazu T, Yano M, Matsumoto K, et al. Evaluation of filtration leucocytapheresis for use in the treatment of patients with rheumatoid arthritis. Rheumatology. 2000;39:165–71.

16. Yoshida S, Takeuchi T, Maeda Y, Kimura Y, Hata K, Hiramatsu Y, et al. Ultrasound evaluation of the effects of leukocytapheresis on rheumatoid arthritis. Ther Apher Dial. 2014;18:509–14.

8.87 | Worksheet 87

Diseases: Severe sepsis and septic shock
Procedure: AN69ST-CHDF
Purpose: Cytokine removal
Recommendation: None
Category: I
The number of references: RCT 0, CT 0, CS 0, CR 0

Description of the disease

Sepsis is defined as "a condition in which infection induces serious organ dysfunction." The host response to infectious insult is dysregulated, leading to life-threatening organ damage (a state of hypercytokinemia due to excessive production of cytokines, which, when exacerbated and prolonged, leads to organ failure and shock attributed to tissue oxygen metabolism disorder and mediator-induced direct organ damage).

Septic shock is a subset of sepsis and is defined as "a condition in which acute circulatory dysfunction causes severe cell damage and metabolic disorders which potentially increase mortality."

Current management/treatment

Multidisciplinary approach to administering appropriate type and dose of antimicrobial agents, intravenous injection of immunoglobulin (IVIG), fluid resuscitation, catecholamines, steroids, and so on.

Rationale for apheresis

The AN-69ST membrane can remove cytokines by adsorption. A multicenter, prospective, observational study conducted in Japan to demonstrate the efficacy of AN69ST-CHDF reported decreased 28-day mortality rate, as well as decreased blood lactate and cytokines (IL-1β, IL-6, IL-8, IL-10, TNF-α, HMGB1) levels and elevated mean blood pressure 72 h after the initiation of AN-69ST-CHDF.

Technical notes

Implement gradually so as not to affect hemodynamics.

Duration and discontinuation/number of procedures

Use for 7 days. Stop use if recovered earlier.

References

1. Hirasawa H, Oda S, Nakamura M, et al. Continuous hemodiafiltration with a cytokine-adsorbing hemofilter for sepsis. Blood Purif. 2012;34:164–70.

2. Shiga H, Hirasawa H, Nishida O, et al. Continuous hemodiafiltration with a cytokine-adsorbing hemofilter in patients with septic shock: a preliminary report. Blood Purif. 2014;38:211–8.

8.88 | Worksheet 88

Diseases: Shiga toxin-producing Escherichia coli hemolytic uremic syndrome (STEC-HUS)

Procedure: PE

Purpose: Treatment of hemolytic uremic syndrome

Recommendation: Central nervous system symptoms present Grade 2C

Central nervous system symptoms absent Grade 1C

Category: Central nervous system symptoms present III

Central nervous system symptoms absent IV

The number of references: RCT 0, CT 1, CS 2, CR 24

Description of the disease

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy that presents with intravascular hemolysis, thrombocytopenia, and acute renal failure. It is broadly classified into STEC-HUS, which is largely secondary to the Shiga toxin-producing Escherichia coli (STEC); atypical HUS (aHUS), resulting from the dysregulation of complement activation associated with abnormal induction of the complement regulators; and secondary HUS, which is closely associated with various comorbidity complications.

Current management/treatment

Aggressive implementation of infusion should be considered prior to HUS onset given the fact that several case reports have described improved patient outcomes for HUS in STEC-HUS cases who receive early infusion based therapies. However, supportive care such as water balance and electrolyte management (including dialysis therapy), blood transfusion for anemia, and antihypertensive therapy should remain the primary focus following the initial onset of HUS. The efficacy of PE based interventions in these settings has not been confirmed, and it is not recommended as a general rule. However, reports have shown its utility in several severe cases in both Germany and Japan in 2011, and its implementation has been considered in severe cases such as those with encephalopathy complications.

Rationale for apheresis

This treatment is expected to remove the Shiga toxin and their associated cytokines during STEC-HUS, but its efficacy has not been confirmed, and PE is not recommended as a general rule. Reports have indicated its efficacy in some more severe cases where there was some central nervous system involvement, given these case reports it is possible that PE may have some utility in the treatment of specific cases following a careful review of the safety profile of the individual patient.

Technical notes

It is critical to pay close attention to ensuring vascular access due to the increased risk of bleeding associated with thrombocytopenia. It is desirable to conduct this treatment in facilities with sufficient experience in the procedure especially when performed on infants. Use washed red blood cells or albumin preparations in order to avoid contamination with plasma components in HUS infections secondary to pneumococcal infection as the infusion of these plasma components may in fact worsen the condition.

Duration and discontinuation/number of procedures

There is no established protocol for the implementation period, number of implementations, or suspension of these protocols. Physicians should determine the protocol based on patient condition and responsiveness to treatment.

References

1. Grisaru S, Xie J, Samuel S, et al. Association between hydration status, intravenous fluid administration, and outcomes of patients infected with Shiga toxin-producing *Escherichia coli*: a systematic review and meta-analysis. JAMA Pediatr. 2017;17:68–76.

2. Igarashi T, Ito S, Sako M, et al. Guidelines for the management and investigation of hemolytic uremic syndrome. Clin Exp Nephrol. 2014;18:525–57.

3. Menne J, Nitschke M, Stingele R, et al. Validation of treatment and strategies for enterohaemorrhagic *Escherichia coli* O104:H4 induced haemolytic uraemic syndrome: case-control study. BMJ. 2012;345:e4565.

4. Kielstein JT, Beutel G, Fleig S, et al. Best supportive care and therapeutic plasma exchange with or without eculizumab in Shiga-toxin-producing *E. coli* O104:H4 induced haemolytic-uraemic syndrome: an analysis of the German STEC-HUS registry. Nephrol Dial Transplant. 2012;27:3807–15.

5. Balestracci A, Martin SM, Toledol I, et al. Dehydration at admission increased the need for dialysis in hemolytic uremic syndrome children. Pediatr Nephrol. 2012;27:1407–10.

6. Hicky CA, Beattie TJ, Cowieson J, et al. Early volume expansion during diarrhea and relative nephroprotection during subsequent hemolytic uremic syndrome. Arch Pediatr Adolesc. 2011;165:884–9.

7. Colic E, Dieperink H, Titlestad K, et al. Management of an acute outbreak of diarrhoea-associated haemolytic uraemic syndrome with early plasma exchange in adults from southern Denmark: an observational study. Lancet. 2011;378:1089–93.

8. Michael M, Elliot EJ, Craig JC, et al. Interventions for hemolytic uremic syndrome and thrombotic

thrombocytopenic purpura: a systematic review of randomaized controlled trials. Am J Kidney Dis. 2009;53:259–72.

9. Michael M, Elliott EJ, Ridley GF, et al. Cochrane database of systematic reviews 2009, Issue 1. Art.No.: CD003595.

10. Ake JA, Jalacic S, Ciol MA, et al. Relative nephroprotection during *Escherichia coli* O157:H7 infections: association with intravenous volume expansion. Pediatrics. 2005;115:e673–80.

8.89 | Worksheet 89

Diseases: Sjogren syndrome

Procedure: PE, DFPP

Purpose: Removal of autoantibodies and coagulation factors

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 3, CR 24

Description of the disease

It is an autoimmune disease that causes the appearance of various autoantibodies and hypergammaglobulinemia and manifests mainly as chronic salivary adenitis and keratoconjunctivitis sicca. It often involves complications with other autoimmune diseases. It systematically damages the exocrine glands throughout the body and manifests as inflammatory symptoms of the joints, thyroid glands, lungs, liver, stomach, kidneys, and skin. It can cause vasculitis- or microinfarct-induced myositis, peripheral neuritis, myelitis, dorsal root ganglionitis, and so on in the nervous system. Central nervous system symptoms include meningitis, meningeal encephalitis, multiple sclerosis-like pathology, subacute encephalitis, spasms, cognitive impairments, headache, psychosis, chorea, motor neuronal diseases, myelitis, and optic neuritis. Peripheral neurological symptoms include sensory/sensorimotor neuritis, cerebral neuritis, multiple mononeuritis, dorsal root ganglionitis, multiple root neuritis, small fiber neuritis, autonomic neuropathy, and myositis (1). It is associated with many complications such as thrombotic thrombocytopenic purpura (TTP) and neuromyelitis optica spectrum disorder (NMOsd).

Current management/treatment

Treatments include symptomatic care for dry symptoms and disorders of each organ; and penicillamine, steroid therapy (oral and pulse), immunosuppressants (mizoribine, azathioprine, cyclosporine, mycophenolate mofetil; methotrexate and cyclophosphamide for refractory cases), blood purification therapy, and IVIG therapy for symptomatic relief (Grade 3D). Rituximab is also used for refractory cases, and bortezomib use has also been considered recently.

Rationale for apheresis

Apheresis is effective by removing autoantibodies and correcting the coagulation system. Clinical features can be similar to those of multiple sclerosis/neuromyelitis optica, and the treatment should include steroid therapy for rapid exacerbation cases (e.g., transverse myelitis, optic neuritis, and neoplastic lesions) for response in 1–2 weeks (2). The therapeutic response varies with the disease type: Mononeuritis multiplex and cerebral neuritis are responsive to steroid therapy, and sensory neuropathy and polyradiculoneuritis are responsive to immunoglobulin; however, ataxic sensory disorders are refractory to treatment and may require blood purification therapy. Double filtration plasma exchange therapy in addition to simple plasma exchange are effective.

Technical notes

The presence of infection at the puncture site, presence of coagulation/bleeding tendencies, and route fixation (when there is disturbance of consciousness or involuntary movement) should be kept in mind.

Duration and discontinuation/number of procedures

It is not covered by insurance. Depending on pathological conditions, a single course should involve 1–3 sessions/week for a total of 5–9 sessions. Adjustments should be made as appropriate according to IgG and fibrinogen values.

References

1. Kampylafka EI, Alexopoulos H, Dalakas MC, Tzioufas AG. Immunotherapies for neurological manifestations in the context of systemic autoimmunity. Neurotherapeutics. 2016;13(1):163–78.

2. Lee HJ, Chang SH, Kang EH, Lee YJ, Song YW, Ha YJ. A case of primary Sjögren's syndrome presenting as mass-like encephalitis, with progression to neuromyelitis optica spectrum disorder. Arch Rheumatol. 2017;32(4):353–7.

3. Schattner A, Friedman J, Klepfish A. Thrombotic thrombocytopenic purpura as an initial presentation of primary Sjögren's syndrome. Clin Rheumatol. 2002;21(1):57–9.

4. Furukawa T, Matsui N, Tanaka K, Izumi Y, Kaji R. A case of neuromyelitis optica spectrum disorder (NMOSD) with Sjögren's syndrome manifested only brain involvement by preceding parotitis. Rinsho Shinkeigaku. 2017;57(2):77–81.

5. Xu X, Zhu T, Wu D, Zhang L. Sjögren's syndrome initially presented as thrombotic thrombocytopenic purpura in a male patient: a case report and literature review. Clin Rheumatol. 2018:37(5):1421–6.

6. Lalji A, Izbudak I, Birnbaum J. Cortical blindness and not optic neuritis as a cause of vision loss in a Sjogren's syndrome (SS) patient with the neuromyelitis optica spectrum disorder (NMOSD): challenges of ascribing demyelinating syndromes to SS: a case report. Medicine. 2017 Aug;96(34):e7454.

7. Konttinen YT, Kinnunen E, von Bonsdorff M, Lillqvist P, Immonen I, Bergroth V, et al. Acute transverse myelopathy successfully treated with plasmapheresis and prednisone in a patient with primary Sjögren's syndrome. Arthritis Rheum. 1987;30(3):339–44.

8. Yoon KH, Fong KY, Koh DR, Suri R. Central pontine myelinolysis—a rare manifestation of CNS Sjogren's syndrome. Lupus. 2000;9(6):471–3.

9. Rogers SJ, Williams CS, Román GC. Myelopathy in Sjögren's syndrome: role of nonsteroidal immunosuppressants. Drugs. 2004;64(2):123–32.

10. Bak E, Yang HK, Hwang JM. Optic neuropathy associated with primary Sjögren's syndrome: a case series. Optom Vis Sci. 2017;94(4):519–26.

11. Gerraty RP, McKelvie PA, Byrne E. Aseptic meningoencephalitis in primary Sjögren's syndrome. Response to plasmapheresis and absence of CNS vasculitis at autopsy. Acta Neurol Scand. 1993;88(4):309–11.

12. Ging K, Mono ML, Sturzenegger M, Zbinden M, Adler S, Genitsch V, et al. Peripheral and central nervous system involvement in a patient with primary Sjogren's syndrome: a case report. J Med Case Rep. 2019 May 25;13(1):165.

13. Takakura Y, Murai H, Furuya H, Ochi H, Kira J. A case of brachial amyotrophic diplegia accompanied with Sjögren's syndrome presenting good response to immunotherapies in the early course of the disease. Rinsho Shinkeigaku. 2005;45(5):346–50.

14. Chen WH, Yeh JH, Chiu HC. Plasmapheresis in the treatment of ataxic sensory neuropathy associated with Sjögren's syndrome.Eur Neurol. 2001;45(4):270–4.

15. Kujawska-Danecka H, Masiak A, Smoleńska Z, Zdrojewski Z. Involvement of the peripheral nervous system in systemic connective tissue diseases: report on clinical cases. Ann Acad Med Stetin. 2011;57(3):33–8.

16. Sawamura M, Oishi W, Nakanishi E, Maruhama S, Kim G, Harada K. Case of ataxic sensory neuronopathy associated with Sjögren's syndrome. Rinsho Shinkeigaku. 2014;54(5):413–6.

17. Hebbar M, Hebbar-Savean K, Hachulla E, Brouillard M, Hatron PY, Devulder B. Participation of cryoglobulinaemia in the severe peripheral neuropathies of primary Sjögren's syndrome. Ann Med Interne. 1995;146(4):235–8.

18. Mori K, et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. Brain. 2005 Nov;128(Pt 11):2518–34.

19. Chiu HC, Chen WH, Yeh JH. Double filtration plasmapheresis in the treatment of inflammatory polyneuropathy. Ther Apher. 1997;1(2):183–6.

8.90 | Worksheet 90

Diseases: Stevens-Johnson syndrome (SJS)
Toxic epidermal necrolysis (TEN)
Procedure: PE, DFPP
Purpose: Removal of drugs, apoptosis-inducing factors, and cytokines
Recommendation: IC
Category: II
The number of references: RCT 0, CT 2, CS 10, CR 74

Description of the disease

It is a serious disease with systemic symptoms including high fever and malaise, and with erythema and erosion appearing on the mucous membranes (e.g., lips, oral membrane, eyes, and vulva), and on a wide range of skin. Most incidents are caused by drugs.The disease is called Stevens-Johnson syndrome when the area of epidermal exfoliation is less than 10% of the body surface area, and the case of 10% or greater is toxic epidermal necrolysis.

Current management/treatment

Systemic administration of corticosteroids. High doses of steroids, including steroid pulse therapy, are given in severe cases. Apheresis therapy or high-dose intravenous γ-globulin therapy should be combined when steroids are not effective.

Rationale for apheresis

Symptoms improve with the removal of the causative drug and its metabolites, apoptosis-inducing factors, and cytokines, from the blood.

Technical notes

Indwelling catheter should be aseptically placed in an appropriate blood vessel with avoiding erosion area. The amount of processed plasma is set at 1–1.5 times of circulating plasma in the patient. Hypersensitivity reactions to anticoagulant after placement must be noted. The patient is kept under observation after implementation for hypoalbuminemia and hypogammaglobulinemia, and the replenishment is provided when necessary.

Duration and discontinuation/number of procedures

Implement two to three times a week, either every day or every other day. It is permitted to administer treatment up to eight times per series.

The time of suspension is decided by the effectiveness and side effects of the treament, which are evaluated by the extent of eruptions, and the general condition of the patient.

References

1. Han F, Zhang J, Guo Q, et al. Successful treatment of toxic epidermal necrolysis using plasmapheresis: a prospective observational study. J Crit Care. 2017;42:65–8.

2. Furubacke A, Berlin G, Anderson C, Sjöberg F. Lack of significant treatment effect of plasma exchange in the treatment of drug-induced toxic epidermal necrolysis? Intensive Care Med. 1999;25:1307–10.

3. Koštál M, Bláha M, Lánská M, et al. Beneficial effect of plasma exchange in the treatment of toxic epidermal necrolysis: a series of four cases. J Clin Apher. 2012;27:215–20.

4. Zimmermann S, Sekula P, Venhoff M, et al. Systemic immunomodulating therapies for Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA Dermatol. 2017;153:514–22.

5. Yamane Y, Matsukura S, Watanabe Y, et al. Retrospective analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in 87 Japanese patients-treatment and outcome. Allergol Int. 2016;65:74–81.

6. Yamada H, Takamori K. Status of plasmapheresis for the treatment of toxic epidermal necrolysis in Japan. Ther Apher Dial. 2008;12:355–9.

8.91 | Worksheet 91

Diseases: Stiff-person syndrome (SPS)
Procedure: PE
Purpose: Control of SPS disease activity
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 6, CR 21

Description of the disease

Stiff-person syndrome (SPS) is a rare autoimmune neurological disorder that mainly presents with persistent muscle rigidity and painful and paroxysmal muscle spasms. Symptoms are progressive and are triggered by physical sensations such as sound or touch as well as emotional changes such as anxiety or fear. The pathological condition is speculated to involve abnormal muscle tone caused by disorders of the nervous system (GABAergic, glycinergic) for relaxing the muscles. Antibodies for glutamic acid decarboxylase (GAD), amphiphysin, gephyrin, and glycine-related substances have been reported as autoantibodies involved in SPS. Complications of malignant tumors (e.g., breast cancer, lung cancer, colon cancer, Hodgkin's disease) can occur, and there is also a group that is considered to be paraneoplastic syndrome (paraneoplastic SPS).

Current management/treatment

First-line treatment involves anxiolytics (benzodiazepam drugs such as diazepam and clonazepam), muscle relaxants (baclofen, tizanidine), antiepileptic drugs (gabapentin, sodium valproate), and analgesics as symptomatic therapy. IVIG and immunosuppressants (tacrolimus, azathioprine, rituximab) are used as immunotherapy. Apheresis therapy is used as adjuvant therapy for patients with poor response to first-line therapy, and there are some reports where patients were responsive to PE.

Rationale for apheresis

There are some reports where apheresis therapy was effective, and there are several retrospective studies, but no RCTs exist. Some type of improvement in symptoms have been reported in 50%–60% of SPS cases where PE was conducted. It was reported that an anti-GAD antibody-positive case exhibited decreased serum anti-GAD antibody titer and improved clinical symptoms each time PE was conducted. Meanwhile, there were several reports where PE, DFPP, and IAPP were effective in anti-GAD antibody-negative cases.

Technical notes

Apheresis therapy for SPS is known as an adjuvant therapy. The indications and feasibility of IVIG should be considered first for immunotherapy, and apheresis therapy should be considered only in cases where responsiveness to other immunotherapies was insufficient or ineffective. Apheresis therapy should be carefully selected in cases where complications of autonomic neuropathy such as orthostatic hypotension and arrhythmia are observed.

Duration and discontinuation/number of procedures

The plasma processing amount in one session of PE should be 1–1.5 times the plasma volume (PV) of the patient, and 5% albumin solution should be used for the replenishment solution. A single course should consist of 4–5 sessions of PE, with a single course conducted over 8–14 days, and implementation of the second and subsequent courses should be considered when symptoms improve. Additionally, cases where regular PE was conducted yearly as maintenance treatment and were responsive have been reported.

References

1. Albahra S, Yates SG, Joseph D, et al. Role of plasma exchange in stiff person syndrome. Transfus Apher Sci. 2019;58(3):310–2.

2. Ballint B, Meinck HM. Pragmatic treatment of Stiff person spectrum disorders. Mov Disord Clin Pract. 2018;5:394–401.

3. Sarva H, Deik A, Ullah, et al. Clinical spectrum of stiff person syndrome: a review of recent reports. Tremor Other Hyperkinet Mov. 2016;6:340.

4. Batti AB, Gazali ZA. Recent advances review on treatment of stiff person syndrome in adults and pediatric patients. Cureus. 2015;7(12):e427.

5. Farooqi MS, Lai Y, Lancaster E, et al. Therapeutic plasma exchange and immunosuppressive therapy in a patient with anti-GAD antibody-related epilepsy: quantification of the antibody response. J Clin Apher. 2015; 30(1):8–14.

6. Pagano MB, Murinson BB, Tobian AA, et al. Efficacy of therapeutic plasma exchange for treatment of stiff-person syndrome. Transfusion. 2014;54(7):1851–6.

7. De la Casa-Fages B, Anaya F, Gabriel-Ortemberg M, Grandas F. Treatment of stiff-person syndrome with chronic plasmapheresis. Mov Disord. 2013;28(3):396–7.

8. Rakocevic G, Floeter MK. Autoimmune stiff person syndrome and related myelopathies: understanding of electrophysiological and immunological processes. Muscle Nerve. 2012;45(5):623–34.

9. Mckeon A, Robinson MT, McEvoy KM, et al. Stiff-man syndrome and variants: clinical course, treatments and outcomes. Arch Neurol. 2012;69:230–8.

10. Wessig C, Klein R, Schneidier MF, et al. Neuropathology and binding studies in anti-amphophysin-associated stiff-person syndrome. Neurology. 2003;61:195–8.

11. Shariatmadar S, Noto TA. Plasma exchange in stiff-man syndrome. Ther Apher. 2001;5(1):64–7.

12. Hayashi A, Nakamagoe K, Ohkoshi N, et al. Double filtration plasma exchange and immunoadsorption therapy in a case of stiff-man syndrome with negative anti-GAD antibody. J Med. 1999;30:321–7.

13. Hao W, Davis C, Hirsh IB, et al. Plasma exchange and immunosuppression in stiff-man syndrome with type 1 diabetes: a 2-year study. J Neurol. 1999;30:321–7.

14. Barker RA, Revesz T, Thom M, et al. Review of 23 patients affected by the stiff man syndrome: clinical subdivision into stiff trunk(man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. J Neurol Neurosurg Psychiatry. 1998;65:633–40.

15. Nakamagoe K, Okoshi N, Hayashi A, et al. Marked clinical improvement by plasmapheresis in a patient with stiff-man syndrome: a case with a negative anti-GAD antibody. Rinsho Shinkeigaku. 1995;35(8):897–900.

16. Brashear HR, Phillips LH 2nd. Autoantibodies to GABAergic and response to plasmapheresis in stiff-man syndrome. Neurology. 1991;41(10):1588–92.

17. Vicari AM, Folli F, Pozza G, et al. Plasmapheresis in the treatment of stiff-man syndrome. N Engl J Med. 1989;320(22):1499.

8.92 | Worksheet 92

Diseases: Systemic lupus erythematosus (SLE)

Procedure: PE, DFPP, IAPP

Purpose: Treatment of severe pathology and nephritis

Recommendation: Severe pathology, 2C; nephritis, 2B

Category: Severe pathology, II; nephritis, II

The number of references: RCT 3, CT 2, CS 11, CR 1

Description of the disease

SLE is a chronic inflammatory disease with autoantibody- and immune complex-mediated tissue damage. It mainly affects women of childbearing age, with a male-to-female correspondence of approximately 1:10. SLE presents with various clinical symptoms, including nonspecific fever, general malaise, weight loss, rashes, cytopenia, proteinuria, hematuria, decreased renal function, arthritis, and serous inflammation. Severe pathologies, such as severe nephritis, central nervous system lupus, diffuse alveolar hemorrhage (DAH), and vasculitis, have a poor prognosis.

Current management/treatment

High-dose steroid monotherapy has traditionally been used for SLE. However, the combined use of immunosuppressants (e.g., cyclophosphamide, tacrolimus, mycophenolate mofetil, azathioprine) has become common, with approved insurance coverage. The combined use of hydroxychloroquine, which is also covered by insurance, is actively conducted.

Rationale for apheresis

PE removes autoantibodies and cytokines, which play a major role in the pathogenesis of SLE, and thus is considered useful for controlling the disease. Its usefulness as a monotherapy compared to that of PE combined with steroid + cyclophosphamide treatment for severe SLE has been reported. There have also been case reports which showed that therapeutic PE was effective as a monotherapy or in combination with cyclophosphamide in SLE cases with DAH and central nervous system lupus.

Technical notes

PE, DFPP, and IAPP are selected depending on the presenting pathological conditions. The plasma processing volume is 1–1.5 TPV. Albumin or fresh frozen plasma is used for replacement solutions, and nafamostat mesylate or heparin is used for anticoagulation. Insurance coverage is limited to cases of rapidly progressive glomerulonephritis.

Duration and discontinuation/number of procedures

Implement daily or every other day for SLE or DAH, with the suspension of disease progression indicating treatment completion. Insured coverage is up to four times a month.

Implementing 3–6 sessions is common for central nervous system lupus encephalitis, with improvement of symptoms indicating treatment completion. Insured coverage is up to four times a month.

References

1. Bambauer R, Schwarze U, Schiel R. Cyclosporin A and therapeutic plasma exchange in the treatments of severe systemic lupus erythematosus. Artif Organs. 2000;24:852–6.

2. Canas C, Tobon GJ, Granados M, Fernandez L. Diffuse alveolar hemorrhage in Colombian patients with systemic lupus erythematosus. Clin Rheumatol. 2007;26:1947–9.

3. Claridge S, Das P, Dorling A, Robson MG. Plasmapheresis as rescue therapy for systemic lupus erythematosus-associated diffuse alveolar hemorrhage. BMJ Case Rep. 2011;2011: pii:bcr0220113893. https://doi.org/10.1136/bcr.02.2011.3893. Erratum in: BMJ Case Rep. 2012;2012. https://doi.org/10.1136/bcr.02.2011.3893.corrl. Robson, Michael [corrected to Robson, Michael G].

4. Danieli MG, Palmieri C, Salvi A, Refe MC, Strusi AS, Danieli G. Synchronized therapy and high-dose cyclophosphamide in proliferative lupus nephritis. J Clin Apher. 2002;17:72–7.

5. Gaubitz M, Schneider KM. Immunoadsorption in systemic lupus erythematosus: different techniques and their current role in medical therapy. Ther Apher Dial. 2003;7:183–8.

6. Gaubitz M, Seidel M, Kummer S, Schotte H, Perniok A, Domschke W, Schneider M. Prospective randomized trial of two different immunoadsorbers in severe systemic lupus erythematosus. J Autoimmun. 1998;11:495–501.

7. Hanly JG, Hong C, Zayed E, Jones JV, Jones E. Immunomodulating effects of synchronized plasmapheresis and intravenous bolus cyclophosphamide in systemic lupus erythematosus. Lupus. 1995;4:457–63.

8. Sorensen H, Schneidewind-Mueller JM, Lange D, Kashiwagi N, Franz M, Yokoyama T, et al. Pilot clinical study of Adacolumn cytapheresis in patients with systemic lupus erythematosus. Rheumatol Int. 2006;26:409–15.

9. Hershko AY, Sceinman-Elazari A, Amar S, Naparstek Y. Extracorporeal immunoadsorption of antibodies against the VRT-101 laminin epitope in systemic lupus erythematosus: a feasibility evaluation study. Immunol Res. 2013;56:376–81.

10. Kronbichler A, Brezina B, Quintana LF, Jayne DR. Efficacy of plasma exchange and immunoadsorption in systemic lupus erythematosus and antiphospholipid syndrome: a systemic review. Autoimmun Rev. 2016;15:38–49.

11. Lewis EJ, Hunsicker LG, lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. N Engl J Med. 1992;326:1373–9.

12. Loo CY, Said M, Mohd R, Abdul Gafor AH, Saidin R, Halim NA, et al. Immunoadsorption and plasmapheresis are equally efficatious as adjunctive therapies for severe lupus nephritis. Transfus Apher Sci. 2010;43: 335–40.

13. Marmont du Haut Champ AM. Hematopoietic stem cell transplantation for systemic lupus erythematosus. Clin Dev Immunol. 2012;2012:380391.

14. Neuwelt CM. The role of plasmapheresis in the treatment of severe central nervous system neuropsychiatric systemic lupus erythematosus: different techniques and their current role in medical therapy. Ther Apher Dial. 2003;7:173–82.

15. Richter HI, Krumann J, Gorez G. Extracorporeal photopheresis in therapy-refractory disseminated discoid lupus erythematosus. Hautarzt. 1998;49:487–91.

16. Schroeder JO, Euler HH. Treatment combining plasmapheresis and pulse cyclophosphamide in severe systemic lupus erythematosus. Adv Exp Med Biol. 1989;260:203–13.

17. Stummvoll GH, Schmaldienst S, Smolen JS, Derfler K, Biesenbach P. Lupus nephritis: prolonged immunoadsorption(IAS) reduces proteinuria and stabilizes global disease activity. Nephrol Dial Transplant. 2012;27:618–26.

18. Wallace DJ, Goldfinger D, Pepkowitz SH, Fichman M, Metzger AL, Schroeder JO, Euler HH. Randomized controlled trial of pulse/synchronization cyclophosphamide/apheresis for proliferative lupus nephritis. J Clin Apher. 1998;13:163–6.

19. Wei N, Klippel JH, Huston DP, Hall RP, Lawley TJ, Balow JE, et al. Randomized trial of plasma exchange in mild systemic lupus erythematosus. Lancet. 1983;1: 17–22.

20. Li MX, Wang YD, Qiu Q, Wei RB, Gao YW, Zhang L, et al. Therapeutic effect of double-filtration plasmapheresis combined with methylprednisolone to treat diffuse proliferative lupus nephritis. J Clin Apher. 2016;31:375–80.

8.93 | Worksheet 93

Diseases: Thrombotic thrombocytopenic purpura (TTP)

Procedure: PE (FFP used as a replenishment solution)

Purpose: Removal of anti-ADAMTS13 antibody, replenishment of ADAMTS13

Recommendation: 1A

Category: I

The number of references: RCT 7, CT 5, CS 38, CR N/A

Description of the disease

The unusually large von Willebrand Factor multimer (ULVWFM), which is secreted from the vascular endothelium, is cleaved to its functional isoforms by a distintegrin-like metalloprotease with a thrombospondin Type 1 motif13, ADAMTS13, which allows for proper VWF mediated interactions with the platelets and promotes appropriate hemostatic functions.

However, when antibodies against ADAMTS13 are produced and ADAMTS13 activity decreases to below 10%, platelets then bind to the full length ULVWFM in the microvessels producing VWF platelets thrombosis. This results in damage to various organs, including the brain, in the form of both consumptive thrombocytopenia and ischemia.

Current management/treatment

PE (with FFP as the replacement solution) is implemented in conjunction with the use of corticosteroids to remove these antibodies and replenish ADAMTS13, which is especially deficient. Immunosuppression is enhanced if the ADAMTS13 antibodies do not sufficiently decrease. Rituximab, which is an anti-CD20 antibody, has also recently become available in Japan.

Rationale for apheresis

Before the function of ADAMTS13 within this system was clarified, RCTs showed that PE was more effective than plasma infusion. It is expected that PE with FFP eliminates VWF platelets thrombosis. by rapidly removing anti-ADAMTS13 antibodies and replenishing ADAMTS13.

What used to be a survival rate of around 10% prior to the implementation of PE has been improved to over 80%. However, PE using FFP for anti-ADAMTS13 antibody-producing cells can induce antibody production, often referred to as inhibitor boosting, so immunosuppressive therapy is essential.

Technical notes

Conduct combined therapy with immunosuppressants and corticosteroids. Enhance immunosuppression centered on rituximab if inhibitor boosting occurs. Platelet transfusion is contraindicated as a general rule. Be aware that relapse is very common. There are many case reports.

Duration and discontinuation/number of procedures

Continue implementing PE with FFP using a per session processing volume of 1–1.5 times the circulating plasma volume once a day until 2 days after the platelet count reaches 150 000/μl or more. Ensure that corticosteroids are used concomitantly.

Consider the possibility of inhibitor boosting when platelet counts, LDH, and so on, which were once improving, reverse and worsen, and act accordingly.

References

1. Matsumoto M, Fujimura Y, Wada H, Kokame K, Miyakawa Y, Ueda Y, et al. Diagnostic and treatment guidelines for thrombotic thrombocytopenic purpura (TTP) 2017 in Japan. Int J Hematol. 2017;106:3–15.

2. Scully M, Cataland S, Coppo P, de la Rubia J, Friedman KD, Kremer Hovinga J, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost. 2017 Feb;15:312–22.

3. Miyakawa Y, Imada K, Ichinohe T, et al. Efficacy and safety of rituximab in Japanese patients with acquired thrombotic thrombocytopenic purpura refractory to conventional therapy. Int J Hematol. 2016;104:228–35.

4. Isonishi A, Bennett CL, Plaimauer B, et al. Poor responder to plasma exchange therapy in acquired thrombotic thrombocytopenic purpura is associated with ADAMTS13 inhibitor boosting: visualization of an ADAMTS13 inhibitor complex and its proteolytic clearance from plasma. Transfusion. 2015;55:2321–30.

5. Scully M, Hunt BS, Liesner R, Rose P, Peyvandi F, Machin S. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158:323–35.

6. Scully M, McDonald V, Cavenagh J, Hunt B, Longair I, Cohen H, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood. 2011;118:1746–53.

7. Moake JL. Thrombotic microangiopathies. N Engl J Med. 2002;347:589–600.

8. Soejima K, Mimura N, Hirashima M, Maeda H, Hamamoto T, Nakagaki T, et al. A novel human metalloprotease synthesized in the liver and secreted into the blood: possibly, the von Willebrand factor-cleaving protease? J Biochem. 2001;130:475–80.

9. Furlan M, Robles R, Galubusera M, Remuzzi G, Kyrle PA, Brenner B, et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. N Engl J Med. 1998;339:1578–84.

10. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med. 1991;325:393–7.

8.94 | Worksheet 94

Diseases: Tumefactive demyelinating disease
Procedure: PE
Purpose: Improving clinical symptoms
Recommendation: 2C
Category: III
The number of references: RCT 0, CT 0, CS 0, CR 4

Description of the disease

Tumefactive demyelinating disease (TDD) is a general term for central inflammatory demyelinating diseases presenting with tumefactive demyelinating lesions (TDLs) measuring ≥2 cm, edema, and mass effects and frequently shows a ring-shaped contrast effect on brain magnetic resonance imaging (MRI). It has been reported under various terms such as Marburg disease, fulminant multiple sclerosis (MS), and tumefactive MS. The MRI characteristics of a TDL include (1) mass effects, (2) edema, (3) hypointense findings around the lesion in T2-weighted images, (4) peripheral diffusion restrictions as the lesion boundary on diffusion-weighted imaging, (5) ring-shaped or open ring-shaped contrast effects, and (6) contrast findings of dilated veins. Pathological findings of TDLs are characterized by demyelination, reactive gliosis, Creutzfeldt-Peters cells, macrophages that phagocytose the myelin sheath, lymphocyte infiltration, and relatively retained axons. Diagnosis requires differentiation from acute disseminated encephalomyelitis, brain tumors, brain abscesses, and neuroneutrophil diseases.

Current management/treatment

Treatment for TDD includes steroid therapy, plasmapheresis, and interferon β (IFN-β). Treatment normally follows MS guidelines, and after steroid pulse therapy has been implemented during the active disease period, PE is implemented for steroid-resistant cases. There are no randomized control trials (RCTs) only analyzing TDD, but many studies have shown the therapeutic effects of PE in steroid-resistant cases. Recent studies have reported treatment with rituxan.

Rationale for apheresis

Inflammatory demyelinating changes are seen during the active phase; therefore, PE is performed for removing inflammatory cytokines, complements, immune complexes, and other molecules and improving the Th1/Th2 balance in the blood.

Technical notes

After steroid pulse therapy is admninistered during the active disease period according to the MS guidelines, PE is perfomed in steroid-resistant cases. There are no RCTs only analyzing TDD, but many studies have shown the therapeutic effects of PE in steroid-resistant cases.

Duration and discontinuation/number of procedures

Perform PE 2–3 times a week at an interval of ≥1 day during the active disease period.

References

1. Keegan M, Pneda AA, McClelland RL, et al. Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology. 2002;58:143–6.

2. Weinshenker BG. Therapeutic plasma exchange for acute inflammatory demyelinating syndromes of the central nervous system. J Clin Apher.1999;14:144–8.

3. Paus S, Promse A, Schmidt S, et al. Treatment of steroid-unresponsive tumefactive demyelinating disease with plasma exchange. Neurology. 2003;61:1022.

4. Ikeda KM, Lee DH, Fraser A, et al. Plasma exchange in a patient with tumefactive, corticosteroid-resistant multiple sclerosis. Int J MS Care. 2015;17:231–5.

8.95 | Worksheet 95

Diseases: Ulcerative colitis

Procedure: GMA, LCAP

Purpose: Adsorb and remove leukocytes such as abnormally activated granulocytes and monocytes

Recommendation: 1B

Category: II

The number of references: RCT 13, CT 110, CS 38, CR 30

Description of the disease

Ulcerative colitis is a diffuse, nonspecific inflammation of the large intestine, primarily affecting the mucous membranes and forming erosions and ulcers. Epsiodes of relapse and remission are often repeated during the course of this disease. It is common in adults under the age of 30, but found also in children, and in those over the age of 50. Causes are unknown, and thought to involve both immunopathological mechanisms and psychological factors. The main symptoms are bloody stools and diarrhea, the degree of which depend on the extent and severity of the lesions. Other symptoms frequently include abdominal pain and fever. Ulcerative colitis is, furthermore, often accompanied by extraintestinal complications such as arthritis, iritis, pancreatitis, and cutaneous symptoms (e.g., erythema nodosum, pyoderma gangrenosum).

Current management/treatment

As a general rule, 5-ASA preparations should be used for mild and moderate cases, and corticosteroids should be used for ineffective or severe cases. Immunomodulators are used for steroid-dependent cases, with tacrolimus, anti-TNFα receptor antagonists (infliximab, adalimumab, golimumab) or cytapheresis for steroid-resistant or dependent cases. Remission is maintained by using 5-ASA preparations, but immunomodulatory drugs should also be considered in steroid-dependent cases. When using anti-TNFα receptor antagonists in order to introduce remission, the same drugs are often used to maintain remission as well. Physician-led clinical trials are currently underway with regards to the usefulness of maintenance therapy for cytapheresis.

Rationale for apheresis

Apheresis is used, under insurance coverage, in Japan for moderate to severe ulcerative colitis. The effectiveness of GMA has not been confirmed in blinded RCTs in the West using sham-controlled clinical trials. However, Zhu et al. conducted a meta-analysis on the effects of apheresis in inducing remission in moderate to severe ulcerative colitis, and reported that it had further favorable results in terms of safety and steroid reduction effects. In Japan, Yoshino et al. compared apheresis with corticosteroids and showed that the former was effective in initiating clinical remission (odds ratio of 2.23; 95% confidence interval: 1.38–3.60). The authors reported that apheresis was associated with a lower rate of adverse events and was safer than corticosteroids (odds ratio of 0.24; 95% confidence interval: 0.15–0.37). As for the number of implementations, an RCT (open trial) revealed improvements in the early stage remission introduction effect, and remission rate, with the twice-a-week method (54% vs. 71%). There are, however, few reports on the effects of apheresis in maintaining remission in UC. A multicenter joint trial is, however, currently underway, comparing the cumulative 1-year nonrecurrence rate, by means of an experimental twice-a-month group and a continued conventional treatment control group.

Technical notes

Usually conducted once a week, but effects are higher when conducted twice a week for cases with stronger symptoms. Treatment should be changed for cases that worsen during treatment or cases where treatment was deemed ineffective. Should be combined from a relatively early stage in severe cases, with determination of effectiveness made at an early stage as well. This treatment should be conducted at a specialized facility.

As a general rule, GMA and LCAP circulation should be conducted with flow rates of 30 ml/min and 30–50 ml/min, respectively. Apheresis should be conducted over a 60-min treatment period.

Duration and discontinuation/number of procedures

The limit is 10 times per series, and 11 times for fulminant patients. There is no limit to the interval periods between each implementation, and therapy should not be limited to apheresis in severe/fulminant cases when positive effects are not obtained during the initial treatment period. Tacrolimus, infliximab, adalimumab, golimumab, or surgery should be considered in these cases. Seek to maintain remission with 5-ASA preparations or immunosuppressants, after introducing remission.

References

1. Sands BE, et al. A randomized, double-blind, sham-controlled study of granulocyte/monocyte apheresisfor active ulcerative colitis. Gastroenterology. 2008;135:400–9.

2. Zhu M, et al. The efficacy and safety of selective leukocytapheresis in the treatment of ulcerative colitis: a meta-analysis. Int J Colorectal Dis. 2011;26:999–1007.

3. Yoshino T, et al. Efficacy and safety of granulocyte and monocyte adsorption apheresis for ulcerative colitis: a meta-analysis. Dig Liver Dis. 2014;46:219–26.

4. Liu Z, et al. The efficacy and safety of selective granulocyte and monocyte apheresis for inflammatory bowel disease: a meta-analysis. Eur J Intern Med. 2016;36:e26–7.

5. Sakuraba A, et al. An open-label prospective randomized multicenter study shows very rapid remission of ulcerative colitis by intensive granulocyte and monocyte adsorptive apheresis as compared with routine weekly treatment. Am J Gastroenterol. 2009;104:2990.

6. Dignass AU, et al. Clinical trial: five or ten cycles of granulocyte-monocyte apheresis show equivalent efficacy and safety in ulcerative colitis. Aliment Pharmacol Ther. 2010;31:1286–95.

7. Domènech E, et al. Addition of granulocyte/monocyte apheresis to oral prednisone for steroid-dependent ulcerative colitis: a randomized multicentre clinical trial. J Crohns Colitis. 2018;12:687–94.

8. Fukunaga K, et al. Adsorptive granulocyte/monocyte apheresis for the maintenance of remission in patients with ulcerative colitis: a prospective randomized, double blind, sham-controlled clinical trial. Gut Liver. 2012;6:427–33.

9. Sakuraba A, et al. Intermittent granulocyte and monocyte apheresis versus mercaptopurine for maintaining remission of ulcerative colitis: a pilot study. Ther Apher Dial. 2012;16:213–8.

8.96 | Worksheet 96

Diseases: Drug poisoning

Procedure: Plasma filtration with dialysis (PDF)

Purpose: Removal of nephrotoxic, albumin-binding, and nonalbumin-binding toxic substances

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 2, CR 4

Description of the disease

- Poisoning symptoms caused by excessive drug intake or administration.
- Organ disorders such as renal failure and liver failure caused by toxic substances.

Current management/treatment

(1) Direct hemoperfusion (DHP), (2) Plasma exchange (PE), (3) Continuous hemodiafiltration (CHDF)

Rationale for apheresis

- Substances with a molecular weight within the removal spectrum, smaller distribution volume, and lower protein binding rate are generally more likely to be removed. However, substances with a high protein binding rate cannot be removed with hemodialysis. Therefore, albumin-binding substances cannot be removed. PDF therapy can also be conducted to remove toxic substances.
- In PDF using EC-4A membrane, the drug may be more efficiently removed when selective PE (SePE) is performed. A 180-min experimental system using EC-4A in the PE with dialysis method, which is PDF therapy specialized for dialysis, rather than filtration dialysis, showed that lithium could be removed as efficiently as in SePE, and that phenobarbital could be removed as efficiently as DHP-1. In other words, the effect was obtained which combined the advantages of both SePE and dihydropyrimidinase-1.
- In one study, combined use of conventional PE and hemodiafiltration for 7 days was successfully used to treat acute liver failure brought on by a deliberate overdose of acetaminophen.
- Three to twelve sessions of PDF and 1–11 of CHDF led to recovery in two cases of Chinese herbal medicine poisoning and one case of alcoholic hepatitis, respectively.
- Improvements in verapamil poisoning were reported after one session of albumin dialysis.

Technical notes

- A modality must be selected based on the molecular weight, distribution volume, and protein-binding rate of the pathogenic substance. Clinicians must select a modality that allows albumin-binding substance removal (PED/PDF, PE [conventional or SePE using EC-4A]) in cases of substances with a high protein binding rate. PED using EC-4A is especially recommended when the causative agent is unknown or if multiple substances were taken.
- Replacement with albumin solution may be conducted if coagulation factor supplementation is not required.
- You must consult the ethics committee of each facility to ensure the utmost medical safety in procedures such as D port connection.

Duration and discontinuation/number of procedures

- The number of implementations and completion depend on severity, but the effects should be judged after around 10 sessions, as in cases of acute liver failure.

References

1. Son R, Tsuruoka A, Ishimura K, et al. A case of severe alcoholic hepatitis performed with PDF (plasma filtration with dialysis). J Jpn Soc Intensive Care Med. 2018;25(S):O33–3. [in Japanese].

2. Nakae H. Blood purification for drug intoxication. Jpn J Clin Dial. 2010;26:1365–70. [in Japanese].

3. Okamoto M, Yanagitani A, Tanaka K, et al. A case of acute liver failure by acetaminophen overdose. J Tottori Med Assoc. 2007;35:115–20. [in Japanese].

4. Nakada T, Hirasawa H. Acute blood purification for toxic epidermal necrosis (TEN). Iyaku-no-mon 2004;44:349–55. [in Japanese].

5. Yoshioka T, Mori T, Kondo H, et al. Plasma diafiltration (PDF) in patients with fulminant liver failure. Jpn J Intensive Care Med. 2003;27:S179–81. [in Japanese].

6. Nakae H. Blood purification for intoxication. Contrib Nephrol. 2010;166:93–9.

7. Nakae H, Hattori T, Igarashi T, et al. Removal of toxic substances by a selective membrane plasma separator. Ther Apher Dial. 2014;18:265–71.

8. Nakae H, Hosoi N, Tomida K, et al. A preliminary study on selective plasma exchange with dialysis. Jpn J Apher. 2017;36:41–6. [in Japanese].

9. Nakae H. A case of severe verapamil poisoning treated with molecular adsorbent recirculating system (MARS®). Jpn J Occup Med Trauma. 2004;52:321–6. [in Japanese].

8.97 | Worksheet 97

Diseases: Liver failure

Procedure: Plasma filtration with dialysis (PDF)

Purpose: Removal of nephrotoxic and albumin-binding substances

Recommendation: 1C

Category: II

The number of references: RCT 0, CT 3, CS 14, CR 6

Description of the disease

Acute liver failure is a syndrome that can cause hepatic coma and bleeding due to extensive hepatocellular necrosis. Liver transplantation is the last resort when the liver does not regenerate, with intensive care centered on blood purification. According to Japanese diagnostic criteria, acute liver failure is identified when a liver with normal hepatic reserve is impaired, and where a prothrombin time of ≤40% or an INR value of ≥1.5 is present within 8 weeks of onset; a hepatic encephalopathy degree of I or below is defined as non-coma type, while a degree of II or higher is coma type; a time period of less than 10 days from initial onset to encephalopathy degree II is acute type, while longer periods of time are subacute type. The survival rates of the acute and subacute types are 43.7% and 27.2%, respectively.

Current management/treatment

The most reliable treatment worldwide is liver transplantation. Living-donor liver transplantation accounts for a majority of transplantations in Japan because there is a serious shortage of donors in the country. Intensive medical care is the preferred treatment for adults. The main components of intensive medical care are plasma exchange (PE) and blood purification therapies (e.g., hemodiafiltration, continuous hemodiafiltration [CHDF], on-line hemodiafiltration), as well as steroid pulse therapy and its tapering.

Rationale for apheresis

- PDF reduces inflammatory mediators (TNF-α, IL-6, IL-18), cystatin C, and bilirubin. Prospective studies reported a MELD score of 20–29 and a 90-day survival rate of 70%. The treatment was also effective as a bridge to transplantation.
- Adiponectin decreased after normal implementation of PE but increased with PDF.
- This treatment is effective and safe even in pediatric cases.
- Continuous and gradual administration of fresh frozen plasma from replenishment lines (continuous PDF) has also been implemented. This approach is safe, with a survival rate of 90% for acute liver failure.

Technical notes

- It is preferable to use a general CHDF circuit or blood purification device only. Installing an additional new infusion pump to make a replenishing line is not recommended because the water balance cannot be precisely controlled and may be disrupted by deviations in pump braking.
- When water removal is required due to renal failure, normal CHDF can be used.
- You must consult the ethics committee of each facility to ensure the utmost medical safety in procedures such as D port connection.

Duration and discontinuation/number of procedures

PDF exhibits therapeutic effects when implemented 4–10 times. Continuous PDF has been conducted 1–10 times.

References

1. Nakae H. Hemolysis hardly ocuurs in selective plasma exchange. Jpn J Apher. 2016;35:1. [in Japanese].

2. Takeda K, Todo A, Nakano K, et al. A case of acute liver failure treated with plasma filtration with dialysis (PDF).J Osaka Soc Dial Ther. 2017;35:37–42. [in Japanese].

3. Misumi T. Plasma filtration with dialysis (PDF) for fulminant hepatitis patients before liver transplantation. Jpn J Apher. 2017;36:180–3. [in Japanese].

4. Yamamoto H, Nakae H, Uji Y, et al. Plasma adiponectin levels in acute liver failure patients treated with plasma filtration with dialysis and plasma exchange. Ther Apher Dial. 2015;19:349–54.

5. Hirayama C, Kamizato K, Fuchigami T, et al. Effect and utility of plasma filtration with dialysis for artificial liver support: a case report.Jpn J Apher. 2016;35:42–7. [in Japanese].

6. Nakae H, Igarashi T, Tajimi K, et al. Selective plasma exchange with dialysis in patients with acute liver failure. Ther Apher Dial. 2012;16:467–71.

7. Nakae H, Eguchi Y, Yoshioka T, et al. Plasma diafiltration therapy in patients with postoperative liver failure. Ther Apher Dial. 2011;15:406–10.

8. Tamura Y, Kuroda K, Ochiai Y, et al. A case of subacute fluminant hepatitis performed with PDF. J Hokkaido Assoc Clin Eng Technol. 2010;20:139–41. [in Japanese].

9. Tsujimoto I, Toriyabe Y, Tandai T, et al. The study of continuous plasma filtration with dialysis (PDF). Med J Kensei Hosp. 2010;33:15–6. [in Japanese].

10. Nakae H, Igarashi T, Tajimi K, et al. A case report of pediatric fulminant hepatitis treated with plasma diafiltration. Ther Apher Dial. 2008;12:329–32.

11. Yoshioka T, Eguchi Y, Saotome T, et al. Multicenter study of plasma dia-filtration (PDF) -selective plasma filtration with dialysis. Jpn J Intensive Care Med. 2008:32:S93–6. [in Japanese].

12. Yoshioka T, Mori T, Kondo H, et al. Plasma diafiltration (PDF) in patients with fulminant liver failure. Jpn J Intensive Care Med. 2003;27:S179–81. [in Japanese].

13. Mori T, EguchiY, Shimizu T, et al. A case of acute hepatic insufficiency treated with novel plasmapheresis plasma diafiltration for bridge use until liver transplantation. Ther Apher. 2002;6:463–6.

14. Eguchi Y, Yoshioka T. Plasma filtration with dialysis (PDF). Jpn J Apher. 2016;35:309–12. [in Japanese].

15. Eguchi Y. Plasma dia-filtration for severe sepsis. Contrib Nephrol. 2010;166:142–9.

16. Nakae H, Igarashi T, Tajimi K, et al. A case report of hepatorenal syndrome treated with plasma diafiltration (selective plasma filtration with dialysis). Ther Apher Dial. 2007;11:391–5.

17. Nakae H, Eguchi Y, Saotome T, et al. Multicenter study of plasma diafiltration in patients with acute liver failure. Ther Apher Dial. 2010;14:444–50.

18. Hayashi H, Takamura H, Taniguchi T, et al. A case of living donor liver transplant recipient treated with novel blood purification “plasma diafiltration”. Int Surg. 2013;98:428–31.

19. Komura T, Taniguchi T, Sakai Y, et al. Efficacy of continuous plasma diafiltration therapy in critical patients with acute liver failure. J Gastroenterol Hepatol. 2014;29:782–6.

20. Nakae H, Furuya T, Satoh K, et al. Continuous plasma exchange with dialysis in patients with acute liver failure. J Jpn Soc Blood Purif Crit Care. 2018;9:39–43.

8.98 | Worksheet 98

Diseases: Sepsis

Procedure: PDF

Purpose: Removal of nephrotoxic substances and albumin-binding substances

Recommendation: 2B

Category: III

The number of references: RCT 0, CT 1, CS 1, CR 2

Description of the disease

Sepsis is defined as "a condition in which an infectious disease causes serious organ damage." It is a pathological condition in which the biological response to invasion (i.e., infection) is unregulated, leading to life-threatening organ damage (a pathological condition in which overproduced cytokines are secreted into the blood, resulting in hypercytokinemia; prolonged exacerbation results in shock and organ failure due to dysregulation of tissue oxygen metabolism and direct disorders of immunological mediators).

Septic shock is a component of sepsis and is defined as "a condition in which acute circulatory insufficiency causes severe cell damage and metabolic disorders which potentially increase mortality."

Current management/treatment

Insurance covers up to two uses of PMX-DHP. CHDF using the PMMA or ANST69 membrane is also implemented for sepsis itself.

Rationale for apheresis

- It has been reported in an in vitro PDF model that removal of cytokines suppresses albumin loss. Experimental models with pigs showed PDF significantly reduces TNF-α and HMGB-1, retains the barrier mechanism of the small intestinal mucosa, and reduction of lymphocyte apoptosis.
- It has been clinically reported that the SOFA score improved with PDF. It has also been reported that IL-18 significantly decreased.

Technical notes

- Use of a general CHDF circuit or blood purification device only is desirable. Installing a new infusion pump in addition to this to make a replenishing line is not recommended because the water balance cannot be precisely controlled and may be disrupted due to deviations in pump braking.
- Cases where water removal is required due to renal failure can be set up in the same way as normal CHDF.
- Taking measures through the ethics committee of each facility in terms of medical safety (e.g., D port connection) is considered sound.

Duration and discontinuation/number of procedures

PMX-DHP can be implemented up to two times under insured medical treatment. PDF is not covered by insurance, but experience has shown that implementation of 2–8 sessions results in improved SOFA score, improved hemodynamics, increased PaO_2/FiO_2 ratio, increased urine volume, and reduced inflammatory response.

References

1. Eguchi Y. Plasma dia-filtration for severe sepsis. Contrib Nephrol. 2010;166:142–9.

2. Saotome T, Sasaki T, Hamamoto T, et al. A case of sepsis successfully treated with cytokine apharesis using plasma dia-filtration (Evacure EC-2A). Jpn J Intensive Care Med. 2006;30:S151. [in Japanese].

3. Oka H, Yoshioka T, Ishihara H, et al. Plasmapheresis using membrane plasma separator Evacure EC-2A for septic hyperbilirubinemia. Jpn J Intensive Care Med. 2002;26:S117–8. [in Japanese].

4. Tabata T, Endo Y, Tani T. Endotoxin removal with an apheresis. Jpn J Surg Metab Nutr. 2005;39:225–33. [in Japanese].

5. Li MX, Liu JF, Lu JD, et al. Plasma diafiltration ameliorating gut mucosal barrier dysfunction and improving survival in porcine sepsis models. Intensive Care Med Exp. 2016;4:31.

6. Li M, Xue J, Liu J, Kuang D, et al. Efficacy of cytokine removal by plasma diafiltration using a selective plasma separator: in vitro sepsis model. Ther Apher Dial. 2011;15:98–108.

7. Shimizu M, Nakayama Y, Taniguchi T. Successful treatment of enterohemorrhagic *Escherichia coli* O111-induced acute encephalopathy and hemolytic-uremic syndrome with plasma diafiltration. Ther Apher Dial. 2014;18:516–8.

8.99 | Worksheet 99

Diseases: Severe acute pancreatitis

Procedure: Plasma filtration with dialysis (PDF)

Purpose: Removal of nephrotoxic and albumin-binding substances

Recommendation: 2C

Category: III

The number of references: RCT 0, CT 0, CS 1, CR 1

Description of the disease

Acute pancreatitis is an acute inflammation of the pancreas caused by disruption of pancreatic function. Causes include alcohol, gallstones, and hypertriglyceridemia (separately described). Severe acute pancreatitis (SAP) affects adjacent organs and induces abdominal compartment syndrome (ACS). Overproduction of humoral factors such as inflammatory cytokines cause vascular hyperpermeability and distant organ damage, necessitating systemic management in the intensive care unit and resulting in high mortality and complication rates. Necrotic areas often develop into walled-off pancreatic necrosis (WON), with secondary pancreatic infections affecting prognosis.

Current management/treatment

Continuous hemodiafiltration (CHDF) is covered by insurance for severe acute pancreatitis (SAP), and up to eight sessions of CHDF per series can be written into the costs.

Rationale for apheresis

The IL-6 clearance rate of PDF for SAP is 10.1 ml/min, and the blood urea nitrogen (BUN) is approximately 20, which can prevent multiple organ failure (MOF) and save lives.

The EC-4A membrane, which has large pores, is used to remove chemical mediators and thus improve pathological condition.

In SAP, clinicians should consider PDF with dialysis, with a 48-h single course.

Technical notes

It is preferable to use a general CHDF circuit or blood purification device only. Installing an additional new infusion pump to make a replenishing line is not recommended because the water balance cannot be precisely controlled and may be disrupted by deviations in pump braking. When water removal is required due to renal failure, normal CHDF can be used.

Blood preparations are used to treat SAP; therefore, the indications for CHDF are currently limited to cases with decreased protein synthesis. Therefore, albumin solution should be used instead of fresh frozen plasma in cases where no decreases in coagulation factor are observed.

You must consult the ethics committee of each facility to ensure the utmost medical safety in procedures such as D port connection.

Duration and discontinuation/number of procedures

It has been reported that C-reactive protein and lactate dehydrogenase rapidly decreased with three 8-h courses. Clinicians should evaluate the situation in response to improvements in patient condition, and the number of implementations should be gradually decreased or stopped when improvement occurs. Specifically, they may suspend treatment for about half a day, conduct follow-up observations, and reintroduce treatment in cases of re-exacerbation.

References

1. Nakae H. Plasmapheresis in patients with severe acute pancreatitis. Jpn J Apher. 2016;35:26–31. [in Japanese].

2. Nakae H, Endo S, Inoue Y, et al. Cytokine networks in patients with acute pancreatitis. Crit Care Shock. 2001;4:206–10.

3. Nakae H, Endo S, Inoue Y, et al. Matrix metalloproteinase-1 and cytokines in patients with acute pancreatitis. Pancreas. 2003;26:134–8.

4. Furuya T, Eto T, Ishii T, et al. PDF (plasma diafiltration) for severe acute pancreatitis. J Abdom Emerg Med. 2013;33:s396. [in Japanese].

5. Noguchi A, Tsuchida S, Takahashi I, et al. A case of acute pancreatitis associated with intractable ulcerative colitis treated with acute blood purification (PDF). Jpn J Pediatr Gastroenterol Hepatol Nutr. 2008;22; s68. [in Japanese].

6. Saotome T, Eguchi Y. Plasma dia-filtration (PDF) for severe acute pancreatitis. Iyaku-no-mon. 2007;47:492–6. [in Japanese].

7. Saotome T, Eguchi Y. A novel plasmapheresis plasma dia-filtration (PDF) as cytokine apheresis for severe acute pancreatitis. J Bilary Tract Pancreas. 2006;27:45–50. [in Japanese].

8. Nakae H. Blood purification for intoxication. Contrib Nephrol. 2010;166:93–9.

9. Nakae H, Hosoi N, Tomida K, et al. A preliminary study on selective plasma exchange with dialysis. Jpn J Apher. 2017;36:41–6. [in Japanese].

10. Furuya T. PDF (plasma filtration with dialysis) for acute pancreatitis. Jpn J Apher. 2017;36:171–4. [in Japanese].

CONFLICT OF INTEREST

A declaration of COI in accordance with the regulations of the Japanese Society for Apheresis has been submitted and is being managed by the Secretariat of the Japanese Society for Apheresis. At the time of the assumption of office, the following criteria were used to obtain declarations that there was no COI that would affect the development of the guideline for each committee member, committee member's spouse, first-degree relative, or person with whom the committee member shared income or property for the past 3 years retroactive to the previous year. In addition, the details of COI were published on the website of the Japanese Society for Apheresis.

REFERENCE

1. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis: the eighth special issue. J Clin Apher. 2019;34:171–354.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Abe T, Matsuo H, Abe R, Abe S, Asada H, Ashida A, et al. The Japanese Society for Apheresis clinical practice guideline for therapeutic apheresis. Ther Apher Dial. 2021;25:728–876. https://doi.org/10.1111/1744-9987.13749