Therapeutic Apheresis in Neurology

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Abstract

Therapeutic plasma exchange (TPE) remove harmful plasma constituents from patient's blood and replacing the extracted plasma with replacement solutions. The advantages of TPE with hollow fiber membranes are a complete separation of the corpuscular components from the plasma and due to increased blood flow rate higher efficacy. Therapeutic apheresis (TA) is used more and more throughout the world. The development of new, more sophisticated membranes and new adsorption technologies allow the most selective separation of plasma components. TA has been successfully introduced in a variety of autoantibody-mediated diseases. TA is the first- or second-line therapy in the treatment of neurological disorders. The updated information on immunology and molecular biology of different neurological diseases are discussed in relation to the rationale for apheresis therapy and its place in combination with other modern treatments. The different neurological diseases can be treated by various apheresis methods. Pathogenetical aspects are demonstrated in these diseases, in which they are clarified. TA has been shown to effectively remove the autoantibodies, immune complexes, inflammatory moderators, paraproteins, and other toxins from blood and lead to rapid clinical improvement. For the neurological diseases, which can be treated with TA, the guidelines of the Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) are cited.

Key words: therapeutic apheresis, therapeutic plasma exchange, immunoadsorption, human monoclonal antibodies, neurologic disorders

Introduction

Therapeutic apheresis summarizes different extracorporeal blood purification techniques that removes inflammatory mediators, antibodies and other toxic substances, which are pathogenic in various diseases and is used commonly in many autoimmune disorders [1]. Up to now, therapeutic apheresis has proved itself in a series of immunological, metabolic diseases, and intoxications. More selective plasma separation and immunoadsorption (IA) with immobilized monoclonal or polyclonal antibodies etc. have secured their place in clinical routine.

The introduction of hollow fiber modules in TA shows a complete separation of the corpuscular components from the plasma and due to increases blood flow rate and higher efficacy [2]. It is no advantage that TA using centrifuges has shorter treatment times such as TA using hollow fibers shown by Hafer et al. [3]. More important is to keep the blood levels with antibodies, and/or pathogenic substances on a very low level over long time during the treatment. In this situation the substances that should be eliminated could invade into the intravascular space and be eliminated by the membrane separators. Furthermore, cell damage – especially to thrombocytes – occurs less using membranes than centrifuges for cell separation. The adsorption technologies allow the most selective separation of plasma components without the use of any substitution solution [2]. Membrane techniques are simple and safe to apply and can be competitive to other plasma separation and treatment technologies [4]. The advantages of membranes plasma exchange include its simplicity to use with blood pumps and no observed white blood cell or platelet loss, compared with centrifuges.

As early as 1980, physicians adapted the single-needle technique to plasma spheresis and simplified the system in the process. They used a double head pump in combination with a hollow fiber module, a pressure balancing system, and a bi-lancing pump [5]. Over a period of more than 25 years, this system was used in more than 20.000 treatments. In addition, two level detectors were added to the system; therefore, the system could work on a semi-automatic principle [6].

The therapeutic plasma exchange equipment´s are, however, not perfect, because the filtered plasma fractions have to be discarded. Substitution solutions supplement with human albumin, plasma substitutes (e.g., gelatine solutions), or fresh frozen plasma (FFP) are used to replace the discarded fractions [2]. For several years, plasma perfusion methods such as IA or other selective plasma adsorption methods have been available without the use of a substitution solution.

TPE is the most frequent therapeutic apheresis procedure used to remove the plasma, together with its high-molecular-weight agents such as immune complexes, antibodies, complement components, cytokines, different toxins and cryoglobulins, as well as to return of the majority of cellular components and a substitution solution to the patients. TPE was explored in the treatment of a variety of indications from neurology, nephrology, hematology, endocrinology, cardiology, pulmology, dermatology, oncology, infectiology, and toxicology [2, 7].

There are only a few prospective controlled trials available that are of adequate statistical power to allow definitive conclusions to be reached regarding the therapeutic value of TA. This drawback reflects, in part, the relative rarity of most of the disorders under investigation. To compensate, many investigators have understandably grouped

heterogenous diseases together, often retrospectively, and used historical controls. The latter design is potentially hazardous, given that earlier diagnosis, recognition of milder cases, and improved general care over time may be lost as a benefit of TPE. For those neurological diseases for which the use of TA is used, the guidelines on the use of TA from the Apheresis Applications Committee (AAC) of the American Society for Apheresis (ASFA) are cited [8, 9]. Since the introduction of hollow fiber modules in TPE, this therapy method is mostly used in nephrology, as many of these membranes can be used with the currently available dialysis equipment.

Methods

TA includes the following methods, which are mentioned here [10]:

- Therapeutic plasma exchange (TPE) in which the whole blood is passed a hollow fiber module, which separates the plasma from the cellular components of blood. The plasma is removed and replaced with albumin-electrolyte and/or plasma solution and/or fresh frozen plasma.

- Immunoadsorption (IA), in which the plasma after separation from the blood is passed through a medical device with special binding to active component of the devices. The active components can be staphylococcal protein A, or other organic or synthetic adsorber,

which contains synthetic peptid-goat-antimouse, which works like a mini-receptor together with an epitop, and adsorber with covalently bound tryptophan.

- Whole blood adsorption (hemoperfusion, HP): lipoprotein apheresis is a selective method to remove low-density lipoproteins from the blood with the return of the remaining blood. The removal of LDL cholesterol based upon charge (dextran-sulfate or polyacrylate or precipitation at low pH, HELP), or IA with anti-Apo B-100 antibodies. In IA and HP, no substitution solution is necessary.

- In addition, other adsorption methods which are mentioned elsewhere [10].

Neurologic diseases

Neurological disorders constitute the largest group of indications for TA [11]. Severe central nervous system (CNS) involvement is associated with poor prognosis, and high mortality rate. High dose steroid and cyclophosphamide (oral or intravenous) are the first choice of drugs in the treatment; TA, intra-venous immune globulin (IVIG), thalidomide, intratechal treatment may be valuable in treatment resistant, and serious cases. Table 1 shows the most of the neurological diseases that have been treated with TPE with the categories and the recommendation grade (RG) of the AAC [8, 9].

Table 1: TA in pediatric diseases (neurological diseases)

Category I: accepted for TA as first-line therapy; **Category II:** accepted for TA as second-line therapy; **Category III:** not accepted for TA, decision should be individualized; **Category IV:** not accepted for TA, IMB approval is desirable if TA is undertaken (8, 9).

Neurological diseases	Apheresis Application Committee of ASFA, 2016, 2019 (8, 9)				
	Category	RG	TA modality	Replacement fluid	Exchange volume (TPV)
Acute inflammatory demyelinating polyneuropathy (AIDP)	I	1A	TPE	5% HA-	1-1.5 TPV
			IA, Peptide-GAM	n.s	
Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD)	I	1B			
Miller-Fisher syndrome (MFS)	III	2C	TPE	5% HA-	
Myasthenia gravis (moderate, severe)	I	1A			
Pre-thymectomy	I	1C			
Lambert-Eaton myasthenic syndrome	II	2C			
Multiple sclerosis (MS)					
- acute MS	II	1A,1B			
- chronic MS	III	1B			
- chronic progressive MS	III	2B	IA	n.s	
Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS);	I	1B	TPE	5 % HA-	
Sydenham´s corea (SC)	I	1B			
Phytanic acid storage disease (Refsum´s disease)	II	1C	Lipoprotein apheresis	n.s	
	II	2C			
Chronic focal encephalitis (Rasmussen encephalitis)	III	2C	TPE	5 % HA-	
	III	2C	IA	n.s	
Acute disseminated encephalitis (ADEM)	II	2C	TPE	5 % HA-	

Peptide-GAM®: synthetic peptide-goat-antimouse, Tryptophan: absorber with covalently bound tryptophan, %% HA-: 5% human albumin electrolyte solution, n.s: no substitution, TPV: total plasma volume.

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) (Guillain-Barré Syndrome, GBS)

AIDP is an auto aggressive disorder that develops subsequent to infectious diseases and because of other noxae [2]. It is an acute polyradiculitis, which mostly affects the distal and proximal muscles of the extremities, as well as the trunk muscles and can progress with severe ascending paralysis, ending in respiratory paralysis [12]. Most patients with AIDP have inflammatory, predominantly demyelinating polyneuropathy. This acute progressive disease, leading to rising paralysis, usually reaches its height within one to two weeks; 25 percent of all patients require artificial ventilation. AIDP occurs in one out of 50,000 persons each year in the industrial nations, regardless of gender or age [2].

The pathophysiologic mechanism has not been established completely, but in many cases, an antecedent infection by campylobacter jejuni leads to the production of antibodies (abs) directed against certain epitopes of the bacterium that also destroy the myelin sheath of the peripheral nerve. This phenomenon has been described as molecular mimicry [13]. The spectrum of organisms responsible for infections can trigger GBS ranges from Eppstein-Barr virus to mycoplasma, herpes zoster, and mumps virus, borrelia to the HIV viruses (14). However, AIDP directly attacks the myelin sheath, resulting in segmental demyelination and remyelination.

In recent years, the triggering causes have been described as being:

1) Antibodies against peripheral nerves, in particular against myelin; 2) circulating immune complexes; 3) complement activation in the cerebrospinal fluid and in serum; 4) other inflammatory mediators and cytokines; and 5) a disorder in cell-related immunity [2, 15].

Electro-diagnostic study is the accepted standard for differentiating between axonal and myelin lesions in early-stage acute polyneuropathy. However, current electro-diagnostic criteria have some limitation in diagnosing axonal GBS [16]. The axonal type of GBS is pathophysiologically characterized not only by axonal degeneration, but also by reversible conduction failure. Antiganglioside antibody tests will facilitate a correct diagnosis. However, there are seronegative AIDP patients, too [17].

Spontaneous recovery normally occurs between the 2nd and 4th week of illness, and, in 75 percent of the patients, it can even occur after several months of illness. Due to remaining damage and relapses, lethality is between 5 and 25 percent after one year. The rationale for TA is based on the humeral and cellular immune dysfunction in this disease [18].

Intra-venous immunoglobulin (IVIG) has also been shown to be effective in the treatment of AIDP. In a recent large international randomized study of TPE, IVIG, and combined treatments in AIDP, all three modalities were effective (19). While no significant statistical differences were noted between the groups, TPE was noted to be better than IVIG, and the combination was better than either of the treatments alone [20, 21]

In recent years, researchers have applied a combination therapy of TPE or IA following by IgG (0.4g/kg BW for 5 days) [2]. Haupt et al. reported results which suggesting that such a combination treatment of AIDP may be superior to plasma exchange alone [22]. Accordingly, with TPE treatment in GBS, it was possible to reduce the costs by between 30 to 40

percent in America, due to the shorter periods of inpatient treatment and shorter duration of artificial respiration [2].

Various human monoclonal antibodies were introduced successfully in AIDP or refractory patients, however, further controlled studies are necessary [23, 24]

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Chronic inflammatory demyelinating polyradiculoneuropathy is an uncommon progressive or relapsing paralysing disease caused by inflammation of the peripheral nerves [8]. Neurologic symptoms are decreased sensation, diminished or absent reflexes, elevated cerebrospinal fluid level, and evidence of demyelination [9]. Cellular and humeral components of the immune system attack myelin on large peripheral nerve fibers in CIPD, leading to demyelination that manifests as weakness, numbers, paraesthesia, and sensory ataxia [25]. As the disease progresses, axonal loss occurs secondary to demyelination and is associated with a poor prognosis [25, 26]. CIDP is an acquired disorder of the peripheral nervous system has probably an autoimmune pathogenesis. The nature of the responsible auto-antigens is unclear in most patients. The frequency of such antibodies is significantly greater in CIDP patients than in normal control subjects [27].

Recent clinical trials have confirmed the short-term efficacy of IVIG, prednisone and TPE. In the absence of better evidence about long-term efficacy, corticosteroids or IVIG are usually favoured because of convenience. Benefit following introduction of azathioprine, cyclophosphamide, cyclosporine, other immunosuppressive agents, and interferon-β and –α and rituximab has been reported but randomized trials are needed to confirm these benefits [26, 27].

Hughes et al. recommended in 2006 that the principle treatments are [28]:

- intravenous immunoglobulin or corticosteroids should be considered in sensory and motor CIPD,

- IVIG should be considered as the initial treatment in pure motor CIDP,

- if IVIG and corticosteroids are ineffective TPE should be considered,

- if the response is inadequate or the maintenance doses of the initial treatment are high,

- combination treatments or adding an immunosuppressant or immunomodulatory drugs could be considered,

- Symptomatic treatment and multidisciplinary management should be considered.

In the guidelines on the use of TA in clinical practice-evidence-based approach from the AAC of the ASFA, the AIDP and CIPD have the category I with the RG 1A or 1 [8, 9] (Table 1). The main etiology of AIDP is autoimmune antibody-mediated damage to the peripheral nerve myelin. Several controlled trials comparing TPE to supportive care alone indicate TPE treatment can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones [8]. The Cochrane Neuromuscular Disease Group review of TPE in AIDP found that TPE is most effective when initiated within 7 days of disease onset. In recent years IA has been increasingly recognized as an alternative to TPE for AIDP and CIPD [29].

Miller-Fisher syndrome (MFS) is characterized by the acute onset of ophthalmoplegia, ataxia, and areflexia. It is considered a variant form of Guillain-Barré syndrome. Because MFS is classified as a variant form of GBS and has a close association with the presence of the anti-GQ1b antibody, one would expect the efficacy of treatment with TPE or IVIG to have been proved. Anecdotal reports of the response of patients with MFS to TPE would be consistent with a pathogenic role for the anti-GQ1b antibody. However, there are some MFS patients without this antibody, and the ultimate proof that anti-GQ1b antibody mediates MFS has not been demonstrated [30].

MFS patients had deviated T-helper Type-1 (Th1) / T-helper Type-2 (Th2) polarization and plasmapheresis can shift Th2-dominant status to Th-1dominant status in patients with MFS. TPE may remove humoral factors including anti-GQ1b, and may induce a shift of the Th1/Th2 cytokine-producing cell balance in peripheral blood. Nowadays, there are case reports of GBS and MFS in Covid-19 patients and by the clinical suggestion of treating neurological complications with IVIG [31, 32].

In the guidelines of the AAC of the ASFA, the MFS has the category III and the RF 2C (Table 1) [8, 9]. Further controlled studies would be useful.

Myasthenia Gravis (MG)

MG is a disease caused by autoantibodies, which are directed against acetylcholine receptors of the skeletal muscles. The acetylcholine receptor antibodies (Ach-R-ab) belong to a heterogenous group of polyclonal abs, which are directed against various sections of the post-synaptic receptor molecule. Due to blockage of the receptors, normal nerve transmission from motor nerves to striated muscle is interrupted. This disease primarily affects the muscles of the eyes, oesophagus, and respiratory muscles, as well as the extremities.

Subgroups are patients with muscle-specific kinase (MuSK) and the low-density lipoprotein-related protein (LRP4) antibodies [33]. MuSK, a transmembrane tyrosine kinase, is expressed predominantly at the postsynaptic membrane of the neuromuscular junction (NMJ). MuSK binds LRP4 and transmits an agrin-mediated signal for the clustering of AChR [34]. MG with anti-MuSK antibodies corresponds to about of the MG patients. The LRP4 protein belongs to a family of proteins that has been recently identified as the receptor for the neural agrin that can activate MuSK [35].

The therapies are thymectomy and administration of cholinesterase-blocking substances (36). In cases with severe progression, immunosuppressives are also given to suppress autoantibody synthesis. TPE has been implemented with good results, especially in the case of severe, previously therapy-resistant progression [37]. The rapid elimination of autoantibodies achieved with TPE results in an improvement in clinical symptoms within hours to days. With the rapid improvement in the symptoms of their patients through TPE. Immunosuppressive drugs target autoantibody production but can take months to have an effect. IVIG and TPE have a more rapid effect than immunosuppressive therapy [38].

The rationale for TA is to remove circulating autoantibodies. In acute attacks, TPE is the first-line therapy (Table 1). The seropositve and seronegative patients respond to TPE. TPE is especially used in myasthenic crisis, perioperatively for thymectomy, or as an adjunct to other therapies to maintain optimal clinical status [8]. TPE works rapidly; clinical effect can be seen within 24 hours but may take a week. The benefits will likely subside in 2 – 4 weeks, if immunosuppressive therapies are not initiated to keep antibody levels from reforming. A combination of TPE and immunosuppressives seems to be successful but randomized trials are necessary.

Rituximab, eculizumab, and belimumab, human monoclonal antibodies (HMA), are used in studies of patients with refractory MG and showed good results, but further studies are necessary,too [39, 40].

Lambert-Eaten myasthenic syndrome (LEMS) is a rare, but reasonably well understood, antibody-mediated autoimmune disease that is caused by serum autoantibodies and results in muscle weakness and autonomic dysfunction [41]. Like MG, Lambert-Eaton syndrome is based on a disorder of the transmission of neuromuscular excitation. In these cases, no acetylcholine is released. LEMS is caused by an autoimmune attack against presynaptic voltage gated calcium cannels and is characterized by late onset of fatigue, skeletal muscle weakness, weight loss, automatic

dysfunction, and areflexia. It develops in the context of a malignant neoplasm, usually small cell lung carcinoma [42].

The rationale is similar to that in myasthenia gravis; that is, patient strength should be improved by the removal of the pathogenic antibody to the voltage-gated calcium channel. In most cases, patients are treated long-term with a combination of corticosteroids and immunosuppressive therapy has failed has TPE been attempted (Table 1) [43]. There are only case series, which have suggested some benefit by TPE. Further controlled studies must show the effectiveness.

Multiple Sclerosis (MS)

Multiple sclerosis is a replasing, remitting chronic demyelinating disease of the CNS and is the most common cause of neurologic disability in young adults [44]. Worldwide, there are more than one million afflicted with the disease. Alone in Germany, there are affected 120,000 to 140,000 patients with MS, and in the United States, there are more than 300,000 patients. MS is also diagnosed in children and adolescents. Estimates suggest that 8,000-10,000 children (up to 18 years old) in the USA have MS, and another 10,000-15,000 have experienced at least one symptom suggestive of MS.

The definition of MS as an autoimmune disease is based on the following characteristics [20]:

– HLA association and genetic predisposition: T cell subset and cytokine correlation with disease activity,

– clinical responses to immunosuppression and immune activators,

– analogies with experimental autoimmune encephalomyelitis,

– cerebrospinal fluid oligoclonal IgG bands,

– CNS pathology using immunocytochemistry techniques,

– evidence of intrathecal synthesis of tumor necrosis factor beta in MS, and the level of TNF alpha in cerebro-spinal fluid may correlate with the severity and progression of disease and reflect histologic disease activity in MS,

– increased levels of gamma interferon correlate with the disease worsening.

MS is an autoimmune disease the pathogenesis is not clearly understood. TPE may be benefit MS patients by removing an antibody, such as antimyelin antibody, or by modulating immune response. There have been four immunopathologic patterns of demyelination in early MS lesions. The characteristics of demyelination for each pattern are [8]: T cell/macrophage-associated, antibody/complement-associated, distal oligodendrogliopathy, and oligodendrocyte degeneration.

B-cells act as antigen-presenting cells to activate T-cells and produce pro-inflammatory ((interleukin-6, interferon-γ, and tumor necrosis factor), and anti-inflammatory cytokines (interleukin-10) that regulate the immune process. These cells are also the source of mature plasma cells that secrete antibodies. Based on accumulation evidence, B cells participate in the pathogenesis of the disease through this multifunctional mechanism [45, 46]

The rationale for treating MS patients with plasma exchange derives from the presence of these circulating antimyelin antibodies, non-antibody demyelinating factors, aquaporin-4-specific serum autoantibodies, and neuroelectric blocking factors [47]. TPE removes antibodies and other humoral factors from the circulation safely and effectively. TPE has also been shown to increase the number and percentage of suppressor T cells and decrease the helper T cells in MS patients, thus effectively decreasing the ratio of elevated helper/inducer to suppressor/cytotoxic cell [48]. This point is important, because T cells play a pivotal role in the pathogenesis

of MS [2]. TPE and IA, too, showed high efficacy and good tolerability [49]. Children should be treated with corticosteroids. If corticosteroids alone do not bring enough improvement, other treatments, including IVIG, Interferon ß 1a, and TPE, are available to treat-to-treat MS attacks. For drug removal in MS with natalizumab who develop progressive multifocal leukoencephalopathy (PML), TPE may also be used. PML is a severe opportunistic brain infection caused by virus, which is a known complication of natalizumab therapy [8].

In the guidelines of the AAC of the ASFA has acute attack of MS the category II and the RG 1A, 1B, the chronic MS and the chronic progressive MS the category III and the RG 1B respectively 2B (Table 1) [8, 9].

The monoclonal antibody rituximab showed efficacy in the treatment of MS, although ocrelizumab, a humanized anti-CD20 antibody, showed beneficial effects on relapsing MS and partial effects on primary MS [50]. Other new anti-CD20 antibodies have been introduced in the treatment of MS: ofatumumab, and ublituximab, a new glycoengineered, chimeric anti-human CD20 (51). However, further studies are necessary to see a benefit for patients with MS.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS); Sydenham´s chorea (SC)

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and Sydenham´s chorea is post infectious neuropsychiatric disorders. Both have neuropsychiatric symptoms, which typically follow Group-A beta-hemolytic streptococcus (GABHS) infection. Streptococcal antigens induce antineural antibodies by an abnormal immune response if this pathogenesis is postulated [8]. GABHS infection has been associated with childhood-onset neuropsychiatric. The onsets of PANDAS are acute and dramatic which present with emotional/mood lability, attention deficit, deterioration of handwriting, separation anxiety, tactile/sensory defensiveness, enuresis, cognitive deficits, and motor hyperactivity [52].

SC is the main common acquired chorea of childhood. The major clinical manifestations are chorea, hypotonia, and emotional lability. The duration of SC is several months with a recurrence rate of about 20 percent [8]. The mean ages of onset for PANDAS and SC are 6.8 years and 8.4 years old, respectively. SC is diagnosed exclusively by clinical presentations and a history of rheumatic fever. Choreatic movements are rapid, and affect the face, trunk, and extremities. PANDAS are temporally associated with GABHS; it is not associated with rheumatic fever. Laboratory tests show elevated or increasing streptococcal antibody titers, but an elevated titer does not necessarily indicate a recent streptococcal infection. The presence of streptococcal infection in PANDAS is associated with at least two episodes of neuropsychiatric symptoms as well as negative throat culture or stable titers during times of remission.

The treatments for PANDAS include antibiotics and cognitive behavioral therapy. Severe form of SC is treated with diazepam, valproic acid, carbamazepine, or haloperidol [8]. If these fail, corticosteroids may be tried. While children with SC require long-term penicillin prophylaxis to reduce the risk of rheumatic carditis, the efficacy of penicillin prohylaxis in preventing symptom exacerbations in children with PANDAS remains doubtful. In severe symptomatic or refractory patients with PANDAS or SC, IVIG (1 g/kg/day for 2 days) or TPE has been shown to reduce symptom severity or shorten the course. TPE is indicated in severe extreme cases after the conservative therapy have been exhausted; or as first line therapy in situations of life threatening functional impairment [53]. The frequency is daily or every other day for five or six procedures over 7 to 14 days. There are no data on any benefit of repeated treatment. In the guidelines on the use of TPE from the AAC of the ASFA PANDAS or SC have the category I with RG 1B (8, 9) (Table 1).

TA should be reserved for treatment of children and adolescents who are severely affected by PANDAS. In such patients, it appears to be safe, well-tolerated, and beneficial treatment option [54]. Bien et al reported in 2020, besides the first-line interventions of steroids, IVIG, and TA as second-line treatments cyclophosphamide or rituximab [55].

Phytanic Acid Storage Disease (Refsum´s Disease)

Refsum´s disease, also called heredopathia atactica polyneuritiformis, is a rare recessive autosomal inherited metabolic disease, based on an isolated lack of the enzyme, which results in phytanic acid (PA) being stored in the body and causing corresponding symptoms [56]. The clinical symptoms include retinitis pigmentosa, anosmia, deafness, chronic sensory-motor neuropathy, ataxia and the accumulation of PA in blood and body tissues [57, 58]. Removal of the phytanic acid through TPE and a phytanic acid-reduced diet can achieve a significant improvement in the disease [59]. Dietary restriction is the first and important therapy step in Refsum disease. The average daily intake of phytanic acid is 50 – 100 mg/day, and ideally, this should be reduced to 10 – 20 mg/day. PA is almost exclusively of exogenous origin and levels of PA > 800 µmol/L is not uncommon. Poorly metabolized PA, pristanic acid (PrA), and picolenic acid (PiA) accumulate in fatty issues, myelitis sheaths, heart, kidneys and retina, leading to retinitis pigmentosa, peripheral dissociative polyneuropathy, cerebellar ataxia ("sailors walk"), renal, cardiac and liver impairment 65 percent of plasma PA and PrA is localized within VLDL, LDL, HDL lipoprotein particles. Dietary restriction of PA is mostly not sufficient to prevent acute attacks and stabilize the progressive course [59]. Clinical improvement is given achieved when the phytanic acid is reduced to below 500 mg/l by TPE. Latest experience with black cumin oil (nigella sativa) in a dose of 3 g/day shows a support and regression of some malnutrition effects in PA restricted dietary and a supportive effects to membrane differential filtration [60].

In the guidelines of the AAC of the ASFA the Refsum´s disease has the category II with the RG 2C (8, 9) (Table 1). TPE can reduce the elevated plasma levels of PA. This can avoid acute attacks or exacerbation of the disease as well as for maintenance therapy. The normal plasma PA level in humans is < 33 µmol/L. Symptomatic levels of Refsum´s disease range from 700 to 8,000µmol/L. PA is also bound to plasma lipoproteins and triglycerides therefore lipoprotein apheresis has been used to successfully treat these patients [8].

The approaches to therapeutic apheresis for Refsum´s disease vary; a typical course consists of 1-2 plasma exchange treatments per week for several weeks to months [8]. In some cases maintenance TPE continue with decreasing frequency over subsequent weeks to months. Therapeutic strategy is ultimately determined by monitoring the patient´s PA level, clinical signs and symptoms, and the need to control or prevent exacerbations of the disease [61]. To date, no cure exists for Refsum´s disease, but phytanate levels in patients can be reduced by TPE and a strict diet [62, 63].

Chronic focal encephalitis (Rasmussen Disease)

The Rasmussen disease, is chronic focal encephalitis, and characterized by intractable focal seizures and slowly progressive neurological deterioration [8]. Onset is typically in childhood, mean age 6.8 ± 5.1 years, but a similar syndrome has been described in adults, too. The etiology of this disease is unknown, but antecedent infection with Eppstein-Barr virus, herpes simplex, enterovirus, or cytomegalovirus has been implicated. Cytomegalo-virus genome has been found in resected cortical tissue of three adult patients with Rasmussen´s encephalitis. Cerebrospinal fluid analysis in most cases is normal. Mild lymphocytic pleocytosis and elevated protein may be found. The important symptom of Rasmussen´s encephalitis is epilepsy uncontrollable with anticonvulsant drugs, progressive hemiparesis, and progressive unilateral

cerebral atrophy. There is progressive loss of function in the affected cerebral hemisphere [8].

Anticonvulsants are necessary but are not always effective in controlling the disease nor do they stop its progression. Subtotal, functional complete hemispherectomy can markedly reduce seizure activity in a majority of patients but results in permanent contralateral hemiplegia corticosteroids and IVIG given for up to two years in a tapering schedule to diminish epilepsia and other symptoms [8].

Patients with Rasmussen encephalitis and antibodies against neural molecules, and autoantibodies can be produced in the CNS after cytotoxic T cell-mediated neuronal damage [9]. The Rasmussen encephalitis has the category III with RG 2C in the AAC of the ASFA and the rationale for therapeutic apheresis is as follows:

Neuropsychological assessment may be helpful in evaluating patients with slowly progressive disease to determine wether TPE is effective in postponing surgical therapy. An initial course of TPE may be followed by 2 days of IVIG 1 g/kg/day. Monthly IA of 1.5 – 2 TPV per treatment has been reported effective in one patient [8]. Confirmation of anti-GluR3 antibodies may support the use of TA in patients with Rasmussen᾽s encephalitis. The frequency of TPE is every other day. After initial 5 – 6 TPE over 10 – 12 days, subsequent courses of TPE (with or without IVIG) may be performed at 2 – 3 month intervals as empirically needed. Immunosuppressive medications may increase the interval between courses.

In the AAC of the ASFA Rasmussen encephalitis has the category III and the RG 2C for the treatment with TPE and IA, assigned on paucity of data (Table 1). Until to date, there is no definitive consensus on treatment, with proposed strategies ranging from acute chronic immunotherapy to hemispherectomy [64].

Acute disseminated encephalomyopathy (ADEM)

ADEM is an acute inflammatory monophasic demyelinating disease that effects the brain and spinal cord, which typically occurs after a febrile (often presumed to be viral) prodrome or vaccination [8]. Typical presentation for the multifocal neurological deficits is ataxia, weakness, dysarthria, and dysphagia accompanied by change in mental status. Most commonly, it is a monophasic illness that lasts from 2 to 4 weeks. Children and young adults are most affected. The differentiation of ADEM from the first attack of multiple sclerosis has prognostic and therapeutic implications. The features of ADEM, which can help to distinguish it from MS, are florid polysymptomatic presentation, lack of oligoclonal band in CSF, predominance of MRI lesions in the subcortical region with relative sparing of the periventricular area, and complete or partial resolution of MRI lesions during convalescence.

Corticosteroids are the first-line therapy, which hasten recovery and result in clinical improvement in up to 60 percent of patients. IVIG is for patients who do not respond to corticosteroids [8]. TPE is used and has a clearly defined role in other neurological conditions that are presumed to be immunologically mediated. TPE removes presumed offending antibodies as well as through immunomodulation. The category II for TPE with the RG 2C after the AAC of the ASFA is assigned on paucity of data (Table 1). The frequency is every other day between 3 to 6 treatments. After Moussa et al. TPE appears to be of benefit for children with severe ADEM and warrants early consideration [65].

Other Neurological Diseases

Brashear et al. found autoantibodies to GABAergic neurons in the **Stiff-Man syndrome** that were removed by TPE, and the patient improved [66]. Other neurological diseases, such as cryoglobulinemic polyneuropathy, central nervous system systemic lupus, acquired neuromyotonia, polymyositis/dermatomyositis, polyneuropathy in

paraproteinemia, neuropathy by hyperlipidemia, and encephalopathy in metabolic/hematologic diseases such as thyrotoxicosis, hepatic coma, and M. Moschcowitz are diseases that involve more organ systems and are mentioned elsewhere. Extensive blood and plasma exchange for the treatment of the coagulopathy have been successfully implemented in children with meningococcemia [67]. Other TA methods like immunoadsorption or lymphocytapheresis have been applied in ataxic neuropathy and idiopathic hypertrophic cranial pachymeningitis, Fabry disease, acute transverse myelitis and subacute sclerotic panencephalitis with success [68, 69]. In the neurological diseases mentioned above, TA can be regarded as a support therapy to the current treatment strategies.

Conclusion

TA, besides corticosteroids, IVIG, and immunosuppressive drugs, has been established as first-line therapy in a large number of neurological diseases. The various methods of TA are safe and effective procedures. Especially immune-mediated neurological diseases that without treatment can lead to significant disability and in a limited number of patients to death [70]. However, a specific therapy for an individual patient is dictated by several factors, including patient comorbidity and the practice environment. An improved understanding of antibody responses and genetic backgrounds in immune-mediated neurological disorders may offer new opportunities for target interventions.

Especially in pediatric patients, guidelines have been written for implementation [71-73]. Not only are physical issues important do physical problems play an important role, but also technical ones such as the apparatus required, and, above all, vascular access. TPE in children requires selected modifications due to the child᾽s smaller size, blood volume, and development age. Special considerations must be given to instrumentation, volume calculations, access, and complications, as well as to the psychosocial aspects of child development [74, 75].

In adults, an adequate blood flow of about 50 to 100 ml/ml for TA is required. This can be achieved via large-bore catheters in the internal or subclavian vein, or via peripheral large veins (1, 2). The substitution medium considerations for replacement fluids are a 5 % human albumin-electrolyte solution, fresh frozen plasma, or plasma substitutes (e.g., gelatine solutions) The patients must be monitored during and between TPE sessions. Particular attention must be paid to circulation, consciousness, coagulation status, and blood count. If a large lumen catheter is in place in a central vein, sterile procedures must be adhered to, to prevent catheter infection and sepsis. TA methods can be safely delivered with moderate complications and side effects by the medical and staff working in hemodialysis departments.

The indications for TA, calculations for the ordering of blood products, and several important and practical details to consider, must be discussed, thus preventing delays in starting the apheresis procedure. In the experience of Wright et al. TPE appears to be benefit during the acute phase of illness with organ-specific disease [75].

The use of TA is regarded to be an extreme therapeutic measure especially in children. However, when the need for such treatment is undebatable, TA must be done. A well-trained and experienced team can overcome the technical difficulties in order to complete the procedure without complications. The most frequently observed adverse effects are vascular relative access insufficiency (2%), and mild hypotension (2%) [75].

Newer therapy modalities such the human monoclonal antibodies rituximab, eculizumab, belimumab, or others showed clinically improvement in severe and refractory immune-mediated neurological disorders [41]. Further controlled multicentre studies must show the effectivity of these human monoclonal antibodies in immune mediated disorders.

However, for all mentioned diseases the quotient relevant for cost – effectivity assessment (cost of treatment – cost saved): (improvement in life quality) must be discusses and calculated exactly by all involment persons. After Malchesky, every effort should be made to delay the progression of chronic diseases. TA is clearly an important tool treatment of many complex conditions now and in future [76].

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