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Short Communication

FIRST EXPERIENCE AND THE EFFECTIVENESS OF IMMUNOMODULATING TREATMENT IN INFLAMMATORY DEMYELINATING CNS DISEASES: ANALYSIS OF NINE PATIENTS

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Therapeutic plasma exchange (TPE) is used in many neurological disorders to remove immunoglobulin and other immunologically active substances. We observed patients that were admitted in Rīga East Clinical University Hospital "Gaiļezers", Clinic of Neurology and Neurosurgery, Multiple Sclerosis Unit, and were diagnosed with relapsing remitting multiple sclerosis (MS), according to McDonald criteria 2010 (five patients), Neuromyelitis optica (NMO) spectrum disorders (three patients) and one with NMO, according to Wingerchuk 2006 criteria. All relapses were confirmed according to clinical criteria. Visual acuity was assessed by an ophthalmologist, and neurological status by a neurologist. All patients received at least 1 cycle of 1000 mg methylprednisolone intravenous for five to seven days. The expanded disability status scale score in the MS patient group was in range 4.0–9.0 before TPE and 3.5–6.5 range after TPE. Best improvement was observed in the MS group: mean symptom reduction of 20%. Patients with NMO spectrum disorder had an EDSS score of 8.0–8.5 range on admission and 6.5–8.0 range after TPE. After one month, one patient in the NMO spectrum disorder group had good response to TPE and EDSS was 3.5, two patients had only slight improvement (EDSS scores 8.0 and 7.5). Condition of patients with NMO did not improve even after a month.

Key words: *therapeutic plasma exchange, multiple sclerosis, neuromyelitis optica.*

Therapeutic plasma exchange (TPE) has been used to remove immunoglobulin and other immunologically active substances, such as complements or cytokines (Hughes *et al.,* 2007). TPE can thereby be used in many neurological disorders where the main pathological substrate is autoimmune aetiology, such as Guillain-Barrè syndrome, Myasthenia Gravis and others. However, the benefit of plasma exchange in CNS demyelinating diseases such as multiple sclerosis (MS) and Neuromyelitis optica (NMO), is still debated, mainly due to lack of randomised control trials.

Multiple sclerosis is a multifocal inflammatory disease of the CNS, characterised by chronic inflammation, demyelination, axonal damage, and subsequent gliosis. Current concepts of its pathogenesis assume that in genetically susceptible individuals, potentially self-reactive T cells are activated in the immune system, home onto the CNS, and may initiate tissue damage via release of inflammatory cytokines, stimulation of B cells and macrophages, and activation of the complement system. Antibodies against myelin basic protein and myelin oligodendrocyte glycoprotein have been detected in subgroups of patients with MS. These antibodies may mediate injury by complement fixation or linking with innate immune effector cells such as macrophages (Lassmann *et al.,* 2007). Patients with MS may benefit from TPE by removing autoantibodies, such as antimyelin antibody, or modulating immune response in acute severe attacks of MS in patients who fail initial treatment

with high-dose steroids. However, no major therapeutic effect of TPE can be expected once antibodies have been deposited *in situ* in CNS lesions (Weinshenker *et al.,* 1999; Szczepiorkowski *et al.,* 2010).

Neuromyelitis optica is a severe idiopathic inflammatory demyelinating disease that selectively affects optic nerves and spinal cord, typically spares the brain, and generally follows a relapsing course. In the majority of cases, pathogenesis of NMO is associated with NMO–IgG, which binds to aquaporin-4 (a water channel) on astrocyte foot processes at the blood-brain barrier. Histopathology of NMO includes deposition of IgG and complement in the perivascular space with a granulocyte and eosinophil infiltrate, and hyalinisation of vascular walls (Lennon *et al.,* 2004). Within five years, 50% of patients lose functional vision in at least one eye or are unable to walk independently. Early and accurate diagnosis is important, since NMO carries a poorer prognosis than MS and the generally accepted treatment approaches differ (Wingerchuk *et al.,* 2006). Approximately 80% of patients with NMO have a relapsing course, which has a poor prognosis: 50% of patients become legally blind or wheelchair bound and 30% die from respiratory failure within five years. NMO worsens by incomplete recovery with each acute attack. Acute attacks are managed by 1 cycle of 1000 mg intravenous methylprednisolone for 5 to 7 days and, if this fails to resolve symptoms, TPE is added. TPE removes the pathologic antibody, immune complexes, and inflammatory mediators. Relapses are commonly resistant to steroids, and TPE can be helpful in recovery from acute attack, but does not prevent further relapses.

According to the existing recommendations, TPE is approved for use in NMO after a course of systemic steroids and in case of MS only if initial therapy has no effect.

Present-day TPE is a continuous flow procedure where elimination follows a linear passive process. For example, a single exchange of 1 (approximately 3 l for a 70-kg patient), 1.5 and 2 plasma volumes removes 63%, 78%, and 86% of all solutes in plasma, respectively.

Under normal circumstances, TPE removes 40–60 ml of plasma/kg over 2–3 hours. Typically, blood components are separated by either plasma filtration, which allows the removal of all plasma components (i.e., except red blood cells), or online centrifugation, which allows selective removal of cell types depending on their respective specific gravity (e.g., red blood cells or white blood cells). Replacement fluids are dictated by the clinical scenario and they include colloids (e.g., 4–5% albumin), crystalloid/colloid combination, or plasma (FFP, thawed plasma, or cryo-poor plasma) (Ibrahim and Balogun, 2012).

The examined patients were admitted in the Rīga East Clinical University Clinical Hospital "Gaiļezers", Clinic of Neurology and Neurosurgery, Multiple Sclerosis Unit, between 1 of January 2011 and 1 July 2014.

We recruited: five patients diagnosed with relapsing remitting MS, according to McDonald criteria 2010, three patients with NMO spectrum disorders and one with NMO, according to Wingerchuk criteria 2006. All patients had more than one episode of relapse. Objective neurological status and visual acuity were assessed before, on the second day after the last TPE course and one month later. Disability status was verified using the EDSS scale and muscle strength was evaluated using the Medical Research Council scale (MRC). All relapses were confirmed according to clinical criteria. Relapse was clinically confirmed if the patient had any suspicion to optic neuritis and episode of neurologic symptoms characteristic of the disease, without any suspicion of infection, and that lasted for more than 24 hours.

Optic neuritis was confirmed by an ophthalmologist using direct ophthalmoscopy. Patients with isolated myelitis or optic neuritis were tested for aquaporin 4 (AQP 4) antibodies in the blood using the Immunofluorescence/EIROIMMUN test**.**

All patients received at least 1 cycle of high dose intravenous methylprednisolone 1000 mg for 5 to 7 days. TPE was performed if visual acuity and neurological symptoms had not recovered by 50% and the time after relapse onset was 3–8 weeks (mean 5.7 weeks).

Informed consent was obtained from all patients who were included in the study. In most cases, patients were treated with five cycles of TPE after placing a central venozus catheter in a jugular- or subclavian vein. Approximately 2 l of plasma were exchanged with 500.0 ml Haes and 1 l human albumin 5% using a Cobe spectra device with continuous flow. Total blood and plasma volumes were calculated by using standard equations. Blood tests and electrocardiography (ECG) were made daily and after the last TPE procedure. TPE was given every other day for most of the patients.

Mean age in the MS group was 29.2 (19–38); mean age in NMO group was 50 (43–63). The examined group consisted of four men and five women. All patients from the NMO group were treatment-naive, three patients from MS group received IFN β1b s/c for 6 to 23 weeks (mean 13.3 weeks).

On admission all patients had severe neurological dysfunction: five patients had paraparesis, sensory deficit and urinal retention, two patients had tetraparesis, two patients had paresis in only one limb, and one patient had optic neuritis. The expanded disability status scale (EDSS) had range from 4.0 to 9.0.

All patients received five TPE procedures, one in two days. In the NMO spectrum disorders group, a slight change in symptoms was seen only after the fifth TPE procedure and was related with increase of muscle strength. In the relapsing remitting MS patient group, the first changes in the neurological status were observed after the second TPE procedure, but two patients had changes in their neurological

status only after the fifth TPE procedure. Unfortunately, there was no benefit from TPE for one patient with NMO.

The expanded disability status scale score in the relapsing remitting MS patient group was in the range 4.0–9.0 before TPE and 3.5–6.5 after TPE. Patients 1 and 2 showed neurological symptom reduction by 20%, patients 3 and 5 had symptom reduction by 13.34% and 12.5%, respectively, and the best results were for patient 4 who showed symptom reduction by 36.36% after TPE. Patients with NMO spectrum disorder had and EDSS score in the range 8–8.5 on admission and 6.5–8.0 range after TPE. The best result was for patient 7 (symptom reduction by 18.75%); patients 6 and 8 had only a slight reduction in their symptoms (6% and 6.25%, respectively).

We evaluated symptoms one month after TPE. The effect remained generally stable in the MS group, but patients 1 and 5 showed further symptom reduction: EDSS 5.5 and 3.0 after 1 month (improvement by 26.67% and 25% in comparison to results on admission).

The best response to TPE was by one patient in the NMO spectrum disorder group, who had an EDSS score of 3.5 after 1 month (reduction by 56.25%). The other two patients in the NMO spectrum disorder group showed no further improvement and their status remained stable 1 month after TPE. Unfortunately, even after a month, one patient with NMO had no improvement. (Summary of results is shown in Table 1)

No serious adverse events occurred in our cohort. We observed hypoproteinemia and in these cases TPE was interrupted for aday.

Neurological diseases are the most common indications treated by TPE (Kaya *et al.,* 2013). European guidelines on management of acute relapses of multiple sclerosis suggest beneficial effect of TPE in cases when patients are refractory to treatment with high-dose methylprednisolone (Sellebjerg *et al.,* 2011). The American Academy of Neurology guidelines recommend the use of TPE for adjunctive treatment of exacerbations in relapsing forms of MS, and that TPE can be considered in treatment of fulminant CNS demyelinating diseases that fail to respond to high-dose corticosteroid treatment (Cortese *et al.,* 2011). The use of TPE in NMO and NMO spectrum disorders is also recommended if initial therapy with corticosteroids fails to improve any symptoms (Sellner *et al.,* 2010).

Basic TPE application is recommended at a rate of five times daily or every other day; exchanging 1–1.5 times total plasma volume per session, in patients with neurological disease (Yilmaz *et al.,* 2011; Kes *et al.,* 2012). Five plasma exchange sessions are usually prescribed and believed to be sufficient to achieve antibody removal. The rate of extravas-

Table 1

SUMMARY OF RESULTS

No	Initials	Age (years)	Sex (m/f)	Group	Neurological deficiency on admission	EDSS on admission	Number of TPE before improvement	Improvement of symptoms	EDSS after TPE	EDSS 1 month after TPE
1.	I.V.	38	F	MS	Nystagmus, lower extremity paraparesis, muscle strength dx 1, sin 2	7.5	4	Muscle strength dx 3, sin 4	6.0	5.5
2.	L.Z.	25	F	MS	Nystagmus, dyplopia, asymmetric tetraparesis, muscle strength dx 2, sin 3	7.5	5	Muscle strength dx 3, sin 4	6.0	6.0
3.	L.F.	32	M	MS	Internuclear oftalmoplegy, tetraparesis, muscle strength lower extremity 3	7.5	3	Muscle strength 4	6.5	6.5
4.	L.A.	19	M	MS	Horizontal nystagmus, right leg paresis, muscle strength 4	5.5	5	Muscle strength 5, ataxia	3.5	3.5
5.	A.S.	32	M	MS	Lowered visual fields, optic neuritis sin, facial paresis dx, hemiparesis sin	4.0	2	Normal visual fields, muscle strength 5	3.5	3.0
6.	L.S.	64	F	NMO spectrum disorder	Lower extremity paraparesis, muscle strength lower extremity 2, bowel dysfunction	8.5	5	Muscle strength dx 2, sin 4	8.0	8.0
7.	K.P.	43	F	NMO spectrum disorder	Lower extremity paraparesis, muscle strength lower extremity 3, bowel dysfunction	8.0	5	Muscle strength dx 5, sin 3	6.5	3.5
8.	D.R.	43	F	NMO spectrum disorder	Lower extremity paraparesis, muscle strength lower extremity 1-0, urinary dysfunction	8.0	5	Muscle strength 1	7.5	7.5
9.	J.S.	30	M	NMO	Blindness, lower extremity paraparesis, muscle strength lower extremity 1-0, urinary dysfunction	9.0	5	No improvement	9.0	9.0

cular to intravascular equilibration is approximately one to two percent per hour, and five separate exchanges over seven to ten days are required to remove 90% of the total initial body immunoglobulin levels (Keller *et al.,* 1978).

Predictors of good response to TPE include sex, age, type of symptom, EDSS and the time of starting TPE after relapse onset. Unfortunately, our study has some limitation: small number of patients, delay in diagnostics, and fee for testing AQP4.

There is some evidence from case series that TPE is effective for acute relapse treatment in NMO patients who do not respond satisfactorily to high dose intravenous methylprednisolone (Keegan *et al.,* 2002; Watanabe *et al.,* 2007; Miyamoto *et al.,* 2009; Yoshida *et al.,* 2010). Moreover, clinical response seems to be related to the early initiation of treatment and it may be observed quickly once TPE sessions are started (Watanabe *et al.,* 2007).

Other case series that studied the effectiveness of TPE for patients with MS and optic neuritis also showed benefit of TPE for most patients (Weinshenker *et al.,* 1999; Keegan *et al.,* 2002; Ruprecht *et al.,* 2004). However, recommendations state that TPE should be approved for relapse remitting MS patients (Cortese *et al.,* 2011).

Our study is the first in Latvia that shows TPE effect on demyelinating diseases.

Unfortunately, due to lack of studies that included subgroups of patients with demyelinating diseases, it is not possible to determine if TPE is more or less effective in patients with different demyelinating diseases. Analysis of studies showed that NMO relapse is best resolved by treatment with intravenous methylprednisolone, followed by a TPE course, and that EDSS should be evaluated at 1, 6 and 12 months.

There are many studies that showed changes of AQP4 and oligoclonal bands titre after TPE (Yoshida *et al.,* 2010; Munemoto *et al.,* 2011), which was not analysed in the present study as the oligoclonal band test was not made for all patients.

In the future, to improve practical and scientific use of TPE in cases of demyelinating diseases, we recommend to measure AQP4 level at 6 and 12 months and to evaluate EDSS more often than in the present study.

There are a number of side effects of TPE — hypotension, hypocalcaemia, infection, embolism, bleeding. We did not observe any side effects mainly due to the small number of patients.

TPE is a safe and efficient add-on therapy in CNS demyelinating diseases.

Further prospective research is necessary to establish the role of TPE. Our study is limited by lack of a control group and the low number of patients, and more patients are needed for further studies. It would be a great advantage to estimate AQP4 and OCB titres after TPE.

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IMŪNMODULĒJOŠĀS TERAPIJAS EFEKTIVITĀTE CENTRĀLĀS NERVU SISTĒMAS IEKAISĪGU SASLIMŠANU GADĪJUMOS: DEVIŅU PACIENTU ANALĪZE

Terapeitiska plazmas apmaiņa (TPA) tiek lietota noteiktu neiroloģisku saslimšanu gadījumos ar mērķi no organisma izvadīt imūnglobulīnus un citas imunoloģiski aktīvas substances. Pētījumā tika ietverti un izvērtēti pacienti, kas ārstējās Rīgas Austrumu klīniskajā universitātes slimnīcā "Gaiļezers" Neiroloģijas un neiroķirurģijas klīnikā, multiplās sklerozes vienībā ar diagnozēm: multiplo sklerozi (MS), recivējoši remitējošu norisi (balstoties uz 2010. gadā izstrādātajiem *McDonald* kritērijiem (pieci pacienti)), optiskā neiromielīta spektra saslimšanu (trīs pacienti) un optisku neiromielītu (viens pacients). Visi slimības saasinājumi tika apstiprināti, balstoties uz atbilstošiem klīniskajiem kritērijiem. Pacientu redzes traucējumus izvērtēja oftalmologs, savukārt neiroloģisko stāvokli — neirologs. Visi pacienti terapijas ietvaros 5–7 dienas saņēma metilprednizonu 1000 mg intravenozi sistēmu veidā. Invaliditātes izvērtēšanas skalas (IIS) punktu skaits MS grupā bija 4,0–9,0 un 3,5–6,5 pēc TPA. Pacientiem ar optiskā neiromielīta spektra slimību IIS punktu skaits bija 8,0–8,5 diapazonā stacionēšanas laikā un 6,5–8,0 diapazonā pēc TPA. Vienam pacientam ar NMO spektra slimību bija labs rezultāts pēc TPA, IIS punktu skaits bija 3,5, bet pārējiem diviem bija tikai minimāls uzlabojums līdz 7,5. Optiska neiromielīta pacientam pēc TPA, izvērtējot klīniskos simptomus saasinājuma sākumā un pēc 1 mēneša, uzlabojumu nenovēroja.