PLASMA EXCHANGE IN THE TREATMENT OF RELAPSING MULTIPLE SCLEROSIS: CASE REPORT

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ABSTRACT

Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system characterized by multiple disseminated lesions. The pathogenesis of this disease is still insufficiently clarified, and the course of the disease is unpredictable. It happens that severe relapses do not respond to drug therapy and in such cases it is recommended therapeutic plasma exchange (TPE).

We present a young man with severe motor relapse, weakness of the left leg, pronounced tremor of the right arm, unstable gait and bilaterally reduction of vision. Brain magnetic resonance imaging showed a large number of chronic demyelinating lesions of the white mass, numerous were merged, with signs of brain reduction. The patient underwent five cycles of TPE, which were conducted every other day. Although TPE led to a disturbance of the hemostasis status and some biochemical parameters, the patient's response to the applied therapy was good. The improvement of the patient's condition was reflected through the return of vision and a moderate reduction in neurological deficit.

Despite the fact that therapeutic plasma exchange can cause some complications, it should be considered when drug therapy does not lead to improvement in these patients.

Keywords: *multiple sclerosis, relapse, therapeutic plasma exchange.*

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) characterized by multiple disseminated lesions. Despite many years of research, the exact pathogenesis of this disorder is still unknown, probably due to the complex interaction of several pathological mechanisms. The most accepted hypothesis is that a genetic predisposition combined with exposure to an unknown environment or an infectious trigger elicits an immune response that ultimately fails the central and / or peripheral immune system surveillance leading to autoimmunity (1). In a small number of patients, multiple sclerosis can present as a fulminant disease characterized by severe and frequent relapses, which are associated with significant morbidity and mortality. Therefore, it is important to identify patients early in the disease in order to be effectively treated with disease-modifying agents and improve outcomes (2-4). The gold standard treatment for MS relapses are corticosteroids. Their efficiency is the result of a multiple mechanism of action: decrease of oedema due to anti-inflammatory component; reduction of B-lymphocyte counts and their availability at the inflammatory lesions resulting in a decreased number of immunoglobulin (Ig) G synthesizing cells in the CNS. Often, severe relapses do not respond to the medicament therapy and in such cases several options have been studied and used, such as therapeutic plasma exchange (TPE) (5, 6).

TPE is a therapy in which plasma is separated from the blood cellular components ex vivo, discarded and replaced with an isosmotic fluid (commonly 5% albumin or frozen plasma) to maintain appropriate oncotic pressure in the patient. The goal of TPE is to remove autoantibodies, pathogenic molecules, immune complexes, toxins, high concentration lipoproteins, and pathological proteins (7). It has been suggested that the therapeutic mechanism of TPE in patients with MS is related to the removal of disease-causing agents such as antibodies and autoantibodies, immune complexes, and cytokines. TPE will not eliminate larger molecules such as IgM, but it might eliminate smaller size molecules such as IgG, complements, and cytokines, which is of great importance given that serum IgG class antibodies are considered to be important in the MS pathogenesis (8).

In this case report we present a young man with severe motor relapse, weakness of the left leg, pronounced tremor of the right arm, unstable gait and bilaterally reduction of vision who underwent TPE.

CASE REPORT

A 33-year-old man, with a previously confirmed diagnosis of multiple sclerosis, was hospitalized in Clinical Center Kragujevac, Demyelinating Diseases Department on 28.05.2021., due to severe motor relapse, weakness of the left leg, pronounced tremor of the right arm and unstable gait. The patient received the first cycle of therapy for MS, 9 months ago (September, 2020), (tbl. Mavenclad). The neurological examination showed that the patient was conscious, oriented, Lerhmitte's sign was negative and that there was no cranial disease. The upper extremities were neat quantity of muscle mass and tones, and the rough motor power of the right side was weakened. Muscle tendon reflexes were polykinetically and enhanced bilaterally. Abdominal cutaneous reflexes were extinguished bilaterally. The lower extremities were of increased tone, more on the left side, with free mobility up to 30 degrees for the left side and 45 degrees to right side. Babinski sign was positive bilaterally. Cerebellar tests were positive with gross intentional tremor and right dysmetry. Patient was able to control the sphincters and unable to walk without assistance. Expanded Disability Status Scale (EDSS) was 7.0.

Diagnosis

Before the TPE was started, additional diagnostic procedures and examinations were performed (complete blood count-CBC, biochemical analyzes, electrolytes, hemostasis status, blood group and RhD factor, virology). Serology was negative for CMV, VZV, EBV, EBNA, HBsAg, HCV, HIV, Rubella, Morbilli, MUMPS. Ophthalmologic examination showed a bilaterally reduction of vision and rotatory nystagmus. X-ray of the lungs showed normal findings. Cardiac examinations showed that the patient was stable with normal findings. Patient was Covid-19 negative, confirmed by both, antigen and polymerase chain reaction (PCR) test. Biochemical analyzes showed low value of vitamin D. Hemoglobin was lower then normal, vitamin B12 was normal and transferrin saturation was increased. Thyroid stimulating hormone (TSH) and free thyroxine (FT4) were normal and anti-TPA antibodies were increased. Coagulation parameters, prothrombin time (PTs), and aPTT were prolonged. Other blood, urine, and stool parameters were normal. Autoantibodies were also determined (ANA, pANCA, cANCA, Cardiolipin IgG, Cardiolipin IgM, dsDNA, AMA, RF_A, IgA, IgG, IgM, C3, C4, ASO).

MRI of endocranium was conducted: native T1W sagittal, transverse PDW, FLAIR (Fluid attenuated inversion recovery), DWI/ADC (Diffusion weighted imaging/apparent diffusion coefficient map), T2W coronal, as well as postcontrast T1W transverse and coronal endocranial tomograms were made (**Figure 1**).

Supratentorial bilateral frontariotooccital and bilateral temporal, dominant paraventricular, a large number of T1W hypointense, PDW/T2W/FLAIR hyperintensive demyelinating lesions of the white mass and a large number of "Dowsons fingers" type are noticed. The largest was located right paratrigonally 18x11 mm (anteroposterior-laterolateral). A large number of lesions of the juxtacortical frontopanriotoccipital bilateral were also observed. Lesions of the same MRI characteristics were present on both sides of the thalamus. A large number of lesions were merged paraventically and juxtacortically. No signs of diffusion restriction were observed in the observed plaques, there was no post-contrast enhancement of signal intensity, nor MRI signs of activity.

Infratentorial intraascular bilateral cerebellar, bilateral in the upper and lower peduncles of the cerebellum, it was noticed a large number of demyelinating lesions, as well as one lesion in the pons on the left 7 mm and in the right crus cerebri 5 mm. There was no postcontrast signal intensity enhancement in these lesions. A consequent reduction in the gray but especially white mass of the brain was observed. The laterolateralni diameter of the third cerebral ventricle was 12 mm. The corpus callosum was of preserved morphology but significantly reduced in size. There were no signs of diffusion restriction. The ventricular system was symmetrical, consequently dilated, without pathological content. There was no movement of the mediosagittal line. Sella turcica wass oval in shape and normal diameter. No organic pathological changes were observed in the angulus pontocerebelaris neither internal auditory canals. The foramen magnum was free. Mastoid cells of bilateral paranasal cavity were without pathological content. Conclusion is next: infratentorial and supratentorial bilaterally, a large number of chronic demyelinating lesions of the white mass, numerous were merged, with signs of brain reduction. No signs of MRI activity were observed in the described lesions.

Treatment

On 01.06.2021., patient was prepared for TPE. Under conditions of asepsis and local anesthesia, the patient was fitted with a dialysis central venous catheter (CVC) in the right jugular vein. Satisfactory flow was achieved on all three branches. The catheter branches were heparized. X-rays showed that the position of the catheter was satisfactory, hemidiaphragms were clearly contoured and in the lung parenchyma were not observed consolidation. The cycles of TPE were conducted every other day, five TPE in total (**Figure 2**), with start on 01.06.2021. All 5 cycles of TPE have elapsed without problems. **Table 1** shows the values of the monitored parameters during TPE.

In days between the two TPEs, CBC, biochemical analyzes, electrolytes and hemostasis status were monitored, followed by volume compensation and electrolyte correction. With each following TPE coagulation parameters – PTs and international normalized ratio (INR) were more prolonged and fibrinogen was lower. The percentage of granulocytes was increasing while the percentage of lymphocytes was getting lower, hemoglobin, iron, total proteins, alkaline phosphatase, magnesium, phosphorus, globulins, urea were decreased. C-reactive protein (CRP) was increased. Proteins and hemoglobin (blood) were present in the urine. After the fourth TPE, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) jumped sharply and drastically, values for both were three times higher than the normal upper limit.

The patient reacted favorably to TPE, which was noticed during the first TPE when his vision began to improve. There was also a moderate reduction in neurological deficit. During the hospitalization, the patient received antibiotic therapy due to fever, to which he responded favorably. At the patient's discharge he was conscious, oriented, Lerhmitte's sign was negative and that there was no cranial disease. The upper extremities were eutonic and eutrophic. In Wartenberg without sinking and without pronation. MRI was more active bilaterally and polykinetic. The lower extremities were of increased tone, spastic type, more on the left side. Weakness of fixation of the right leg when performing the Mingazzini probe, the left leg sinks. Babinski sign was positive bilaterally. Cerebellar tests were positive with gross intentional tremor and right dysmetry. Patient was able to control the sphincters and able to walk with assistance. On discharge from hospital EDSS was 6.0.

Figure 1. MRI findings of endocranium: (A) native T1W sagittal, (B) transverse PDW, (C) FLAIR, (D) T2W coronal, (E) precontrast T1W transverse, (F) postcontrast T1W transverse, (G) T1W coronal endocranial tomograms.

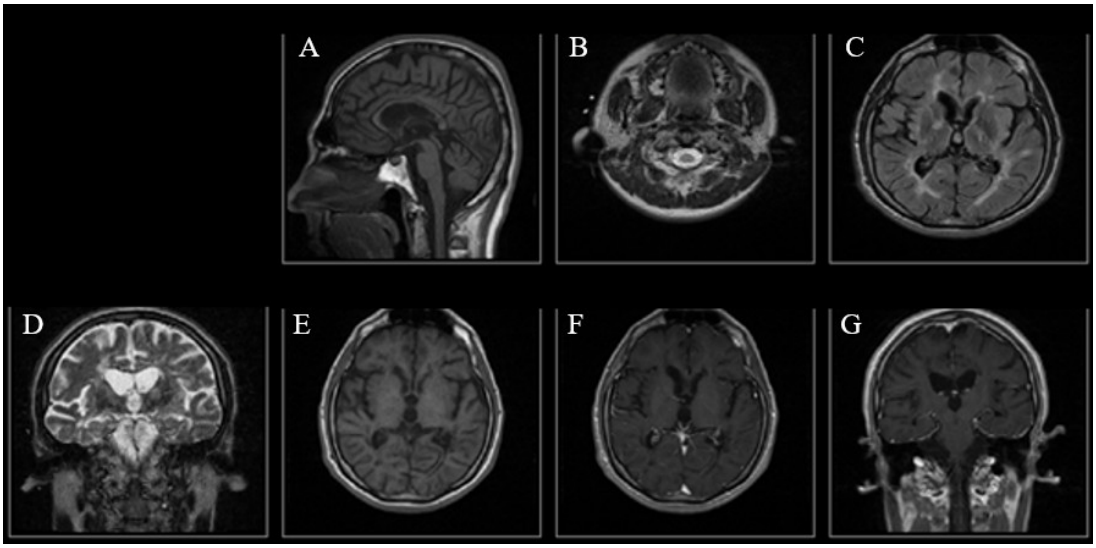


Figure 2. *Removed* plasma after every TPE.

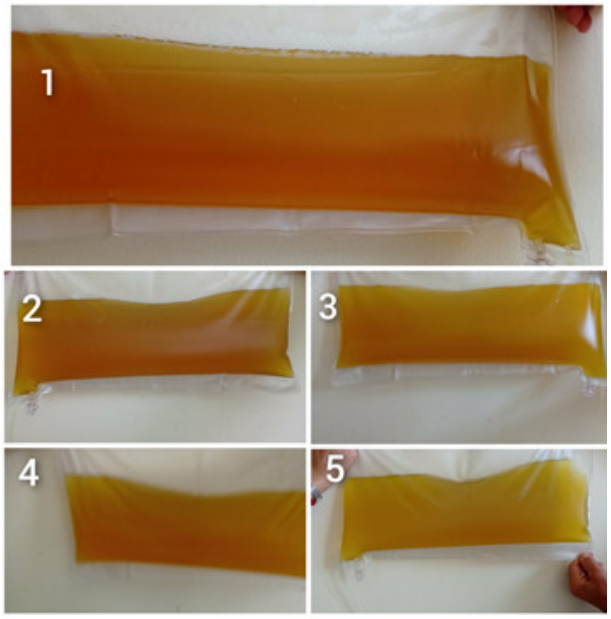


Table 1. Parameters monitored during therapeutic plasma exchange

Volume of (ml)	Days of TPE				
	I	II	III	IV	V
Removed plasma	3625	3316	3513	3471	3678
Substituted 5% albumin	3022	2751	2972	2927	3086
Processed blood	7009	6384	6114	6117	6726
Anticoagulant-citrate-dextrose	501	456	380	393	483

DISCUSION

The majority of the published studies have in common the inclusion of patients with MS experiencing with aggressive diseases and severe relapses (9). The demographic characteristics in most published studies are as follows, about 76% population is female gender and even 85% of proportion have relapsing-remitting subtype of MS with median EDSS of 2.25. Since EDSS highly relies on motor function disability, the increase in median EDSS during relapse was related to the type of symptoms experienced by the patients, mainly motor. In most cases, MRI of the brain in those patients showed gadolinium enhancing lesions. Even considering the patients without MS previously diagnosed, the relapse that led to TPE was very severe (with median EDSS during relapse of 3.5), and patients did not have an adequately response to corticosteroids. In all the cases, TPE was used as a second-line treatment after corticosteroids, in order to improve recovery and avoid residual deficits (5). Some patients respond promptly to TPE, while other do not respond at all. To explain this dichotomy, some authors propose that biological factors such as MS immunopathology heterogeneity between patients could contribute to differences in TPE response (10).

According to studies previously described the mean number of TPE sessions in those patients was about 7.39 sessions every other day (9-12). On the other hand, good results were also achieved with 3–5 sessions of TPE, acording to study that *Bennetto et al* conducted, which is also confirmed in our case report (13). Some studies have highlighted some predictors of good response after TPE such as male sex, retained reflexes and early initiation of TPE (10-12), which certainly contributed to the good recovery of our patient, whose EDSS was 7 at the beginning of TPE and 6 at the end of TPE. Common adverse effects described include anaemia, rash and symptomatic hypotension. Toward data from previous studies, minority of patients experienced some side effects related to TPE, most of them easily manageable. According to one study, placement of central intravenous catheter was necessary in 44.1% of the patients (10). Heparin associated thrombocytopenia and bacteraemia due to infection of their central venous line were also described (9-11). Fortunately, our patient had only mild complications such as disturbance of some coagulation and biochemical parameters.

CONCLUSION

In presented patient, TPE was clearly associated with improvement in clinical outcome. Data from this case report pointed out that, despite the fact that TPE can cause some complications, it should be considered when drug therapy does not lead to improvement, which did not endanger his health.

REFERENCE

1. Elsbernd PM, Carter JL. Using Monoclonal Antibody Therapies for Multiple Sclerosis: A Review. Biologics 2021; 15: 255-63.
2. Fernando KTM, James M. Early predictors of rapidly evolving multiple sclerosis: A case report. J Neuroimmunol 2017; 307: 42-6.
3. Nicholas R, Rashid W. Multiple sclerosis. BMJ Clin Evid 2012; 2012: 1202.
4. Markowitz CE. Multiple sclerosis update. Am J Manag Care 2013; 19(16 Suppl): s294-300.
5. Correia I, Ribeiro JJ, Isidoro L, Batista S, Nunes C, Macário C, Borges C, Tomaz J, Sousa L. Plasma exchange in severe acute relapses of multiple sclerosis - Results from a Portuguese cohort. Mult Scler Relat Disord 2018; 19: 148-52.
6. Rostami AM. Plasmapheresis in acute attacks of multiple sclerosis: the cons. J Clin Apher 1991; 6(4): 205-6.
7. Chegini A, Moghadami M, Maghary AH. Therapeutic Plasma Exchange in Tehran Between 2011 and 2014. Ther Apher Dial 2020; 24(2): 230-4.
8. Mimori M, Sato T, Omoto S, Sakai K, Mitsumura H, Iguchi Y. Selective plasma exchange for multiple sclerosis with optic neuritis. Neurol Clin Pract 2020; 10(4): e38-e40.
9. Weinshenker BG. Therapeutic plasma exchange for acute inflammatory demyelinating syndromes of the central nervous system. J Clin Apher 1999; 14(3): 144-8.
10. Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinshenker BG. Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology 2002; 58(1): 143-6.
11. Llufriu S, Castillo J, Blanco Y, Ramió-Torrentà L, Río J, Vallès M, et al. Plasma exchange for acute attacks of CNS demyelination: Predictors of improvement at 6 months. Neurology 2009; 73(12): 949-53.
12. Ehler J, Koball S, Sauer M, Mitzner S, Hickstein H, Benecke R, et al. Response to Therapeutic Plasma Exchange as a Rescue Treatment in Clinically Isolated Syndromes and Acute Worsening of Multiple Sclerosis: A Retrospective Analysis of 90 Patients. PLoS One 2015; 10(8): e0134583.
13. Bennetto L, Totham A, Healy P, Massey E, Scolding N. Plasma exchange in episodes of severe inflammatory demyelination of the central nervous system. A report of six cases. J Neurol 2004; 251(12): 1515-21.

CONFLICT OF INTEREST

Authors report no conflict of interest.