Therapeutic Plasmapheresis with Albumin Replacement in Alzheimer's Disease

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Contributor: Omar Cauli

Reducing the burden of beta-amyloid accumulation and toxic autoimmunity-related proteins, one of the recognized pathophysiological markers of chronic and common neurological disorders such as Alzheimer's disease (AD) and multiple sclerosis (MS), may be a valid alternative therapy to reduce their accumulation in the brain and thus reduce the progression of these disorders.

Keywords: plasmapheresis ; albumin ; auto-immunity ; dementia ; magnetic resonance imaging ; amyloid beta

1. Introduction

Neurological disorders are increasingly being recognized as major causes of death and disability worldwide. A recent worldwide epidemiological study found the burden of neurological disorders, measured in terms of the absolute number of disability-adjusted life-years (DALYs), i.e., the sum of years of life lost and years lived with disability by age and sex, has increased for most neurological disorders in the last decade [1]. Among common neurological disorders, Alzheimer's disease (AD) and multiple sclerosis (MS) are associated with high-morbidity levels and health costs [2][3]. To date, only symptomatic pharmacological treatments have been approved for the treatment of AD, including cholinesterase inhibitors and N-methyl-d-aspartate receptor antagonists, as the cornerstone of pharmacotherapy [4]. The amyloid beta (Aβ) peptide is the main protein component of the extracellular space found in senile plaque in the brain parenchyma, and is involved in memory dysfunction in AD [5][6]. Besides accumulation of Aβ peptide, other pathogenic hallmarks, such as neurofibrillary tangles, are responsible for the pathology of AD [7]. MS is a chronic-autoimmune disease of the central nervous system (CNS) which is most common in young female patients. Its pathophysiological hallmark is the destruction of the myelin sheath, with axonal degeneration and neuronal cell death. Furthermore, pharmacological treatment in MS is not curative, and is based on three goals: treatment of exacerbations, slowing the disease's progression with disease-modifying therapies (DMTs), and symptomatic therapies [8]. Disease-modifying drugs have mostly failed as treatments for the clinical form of progressive MS [9] and there is a particular need for new strategies to treat patients with this form of MS. Management of progressive MS, therefore, merely aims to minimize the symptoms, prevent exacerbations, and if possible, improve function. Therapies aimed at preventing the accumulation of toxic substances in the blood (Aβ or autoantibodies), or in the brain, may have therapeutic uses in AD and MS patients. Reducing amyloid deposits or reducing the amount of plaque in the brain are currently being investigated for AD treatment [10][11][12]. Promising results pinpoint the reduction of the concentration of toxic substances associated with AD physiopathology, such as the Aβ peptide in the brain [13]. Therapeutic plasma exchange apheresis (PP) is an extracorporeal blood purification technique designed to remove substances with a large molecular weight. The utility of this procedure includes the removal of antibodies, alloantibodies, immune complexes, monoclonal proteins, toxins and cytokines, and it involves the replenishment of a specific plasma factor containing 5% albumin. PP has been successfully used in several immune-mediated neurological disorders, including Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and myasthenia gravis [14][15][16][17][18]. Less common neurological diseases in which plasmapheresis has afforded beneficial effects are paraneoplastic polyneuropathies, neuromyelitis optica (also known as Devic's disease), motor neuron disease, polymyositis, and multifocal motor neuropathy [18]. PP can be a therapeutic strategy to remove or reduce the substances that are considered pathogenically responsible, e.g., Aβ peptides in AD from the blood, by changing their transportation through the blood-brain barrier, thereby limiting their accumulation in the brain. In the case of MS, eliminating pathogenic humoral factors from the blood [14], including suspected auto-antibodies directed against the myelin sheath, is needed in some patients with steroid refractory relapses [15], or in patients that develop neutralizing antibodies to interferon-beta (IFN-β), which are associated with reduced bioactivity and efficacy of IFN-β [19][20]. There is extensive literature related to the use of plasma exchange in relapsing and remitting multiple sclerosis, and its use as a temporary treatment of acute relapses in steroid-unresponsive MS patients has been recently reviewed [15][16]. In a therapeutic plasmapheresis (plasma exchange), a volume of circulating plasma is extracted to eliminate toxic compounds, and is usually substituted by a 5%

albumin solution, or occasionally by fresh frozen plasma (from donors) to replace the plasma volume removed, and thereby maintain the volemia [15][21][22].

2. Plasmapheresis Protocol

The PP was mostly performed using a commercial continuous flow cell separator with technology based on centrifugation or transmembrane filtration. A peripheral or central double lumen access was used, depending on the patient's individual characteristics. In each PP session, the total plasma volume of the patient was calculated, taking into account sex, body weight, height, and hematocrit. It required a volume of approximately 35–45 mL/kg, for a volume of 2500–3000 mL for a subject weighing 70 kg; the same volume of 5% serum albumin (60–100 mL/min) was generally administered as a replacement fluid (50 g of albumin per liter of plasma replaced), with a concentration of albumin similar to plasma. A variation of this protocol consisted of 60 mL/kg body weight of plasma exchanged for 3.5% albumin in normal saline containing 6.9 mEq Ca2+/L, 1.2 mEq Mg2+/L, and 4 mEq K+/L [19].

3. Effect of Plasmapheresis on Amyloid Beta Concentration in AD Patients

Two of the three manuscripts on PP in AD patients came from a single clinical trial [23][24]. While the average levels of Aβ40 and Aβ42 in plasma of AD patients did not show a clear behavior pattern associated with the PP procedure in the seven patients included in the pilot study [25], a clear decreasing pattern was observed over time in the 12-month follow-up study, which was more evident for the Aβ40 concentration [23]. The plasma levels of Aβ40 presented a saw-tooth pattern that ranged between, approximately, 100 and 300 pg/mL. Likewise, plasma Aβ42 levels also behaved with a similar saw-tooth pattern, both in the group treated with PE (ranging between 20 and 60 pg/mL) and in the control group. However, in the group treated with PP, the plasmatic levels of this peptide were statistically lower than in the control group after each treatment period, although during the follow-up period of the study, the levels of Aβ42, and the levels of Aβ40 returned to the control group levels. In the cerebrospinal fluid (CSF), while the average levels of Aβ40 and Aβ42 of the seven patients who underwent PP in the pilot study [25] declined during the PP period, this was followed by a gradual increase during the follow-up period, and returned to baseline levels six months after the start of the study. In contrast, in the follow-up study [23], the levels of both peptides during the treatment period remained stable and showed a slight increase in the case of Aβ42. On the other hand, while the mean values of Aβ42 in CSF between the baseline and the end of the treatment phase showed a tendency to increase in comparison with the average levels in the control group, no significant differences for Aβ40 were observed between the two groups of patients [23].

4. Effect of Plasmapheresis on Blood Immune Factors in Chronic Progressive MS Patients

In MS patients, PP was mainly tested in individuals with the chronic progressive form of the disease [19][26]. PP reduced the concentration of immunoglobulin IgG, IgA, and IgM immediately, and 7 days after PP. In addition, a decline in serum complement C3 and C4 levels was observed after PP [26]. In the PP clinical study of MS patients, immunosuppressive therapy was added during the PP protocol (mainly low doses of cyclophosphamide and other drugs) in order to minimize the rebound increase in antibodies and other proteins removed by PP. The MS patients' unresponsiveness to IFN therapy could be attributed to the synthesis of serum inhibitory factors to IFN and to lymphokine [19]. A restoration of responsiveness to IFN therapy in 21 out of 24 patients was demonstrated following PP and immunosuppressive therapy, which was accompanied by a normalization of circulating immune complexes and elevated CD4 lymphocyte counts. The concentration of CD8, human leukocyte antigen—DR isotype (HLA-DR) antigen-bearing cells, NK, serum IFN, and monocyte/macrophage cell populations also increased in the PP responders [19]. However, mixed results have been reported following PP, with no effects on human leukocyte antigen (HLA) typing, T-cell subsets, but enhancement of the suppressor-cell functional activity after PP [24]. A recent study confirmed the utility of PP in reducing the blood concentration of neutralizing antibodies to IFN-beta, and therefore restoring the biological activity of IFN-beta in 4 out of 6 MS patients [20]. Unfortunately, the effect on IFN was transient, and lasted for 1–2 months even during the ongoing PP sessions [20].

5. Clinical Effects Observed after Plasmapheresis in AD and Chronic Progressive MS Patients

This outcome was analyzed by changes in neuropsychological examination, including cognitive, behavioral, neurological, and functional measures. In AD patients, PP showed a tendency towards cognitive stabilization six months after the end of PE sessions, as assessed by the mini-mental state examination (MMSE) and the Alzheimer's disease Assessment

Scale–Cognitive Subscale (ADAS-Cog) [25]. This beneficial effect was confirmed in a subsequent randomized clinical trial (RCT) [23]. In addition, the RCT patients treated with PP showed a significant improvement in language functions compared to the control group, as assessed by the Boston nomenclature test and semantic verbal fluency; this improvement persisted after PP was discontinued. The control group scored better than the PP-treated group in behavioral (based on the neuropsychiatric inventory, NPI) and functional (Alzheimer's Disease Cooperative Study - Activities of Daily Living, ADCS-ADL) measures [23]. However, the statistical differences were diminished during the observational phase. A possible explanation for this is that PE has a negative impact on activities of daily living during the intensive treatment phases, but it returns to baseline levels once the treatment is complete. Similarly, patients in the control group had better NPI scores than the group treated with PE, although the treated group showed greater improvement than the control group at the end of the observational phase. This indicates that PP can trigger psychiatric symptoms in AD patients, which are either related to the fact that the patients have to live with a catheter inserted in the chest, experience discomfort caused by metabolic alterations related to PE, or both. Indeed, around 50% of the patients in the treated group developed psychiatric symptoms, especially anxiety. In the case of MS, the RCTs by Khatri et al. [24] and [26] showed an improvement of one or more steps on the Kurtzke DSS scale (the gold standard for MS clinical evaluation) in around 60% of the study sample, whereas the improvement in the control group (sham PP) was around 27% of the study sample. The other patients remained stable, and one worsened in the PP group. Importantly, the consistent and objective neurological improvement did not appear until after 10 weeks of PP therapy, and the PP group continued to improve over time until the twentieth week. In the study by Medenica et al. [19], 21 out 24 patients (87.5%) improved by 2 to 4 steps on the Kurtzke DSS, and stabilization and the duration of these beneficial effects ranged between 2 and 8 years. However, in the study by Hauser et al. [27] fewer than 30% of MS patients clinically improved following PP. The beneficial effects of PP are greater in patients with the cerebral form of MS (compared to cerebellar and spinal clinical presentation of MS) [26], and in those with a shorter total duration of the disease [27][26].

6. Effects on Brain Alterations Induced by Plasmapheresis

Two studies have evaluated the functional and structural brain changes associated with brain Aβ mobilization and cognitive improvement observed in patients treated with PP [25][28]. Neuroimaging analysis showed a significant increase in brain perfusion in both the frontal and temporal areas six months after treatment [25]. As for brain structural changes, a progressive increase in the volume of the hippocampus was observed, although it did not reach a significant p value. On the contrary, the results of a longitudinal study conducted by Cuberas-Borrós et al. [28] showed a reduced total brain and hippocampus volume, in both patients treated with PP and in controls, as expected in the progression of AD. Likewise, the overall analysis of cerebral perfusion with statistical parametric mapping showed a marked stabilization or an absence of progression of perfusion in the PP-treatment group. In MS patients, no changes in the number and dimension of MS lesions were observed in the CNS by magnetic resonance imaging (MRI) [19] or by computerized tomography of the brain [24]. A reduction was observed in some lesions in some patients, but this effect was attributed to a regression of the surrounding lesion edema rather than a decline in the number of brain plaques [19].

7. Safety and Adverse Effects

In terms of safety and tolerability, only a single study [23] monitored the adverse effects (AE) that patients experienced during the study period. These authors observed a higher incidence of AE, related to treatment or study procedures or otherwise, in the group that received PP than in the control group (94.7% in plasmapheresis-treated patients versus 70.0% in controls). However, they found no significant differences in the severity of AE (15.8% versus 10.0%). In both groups, the most frequent AE were infections (55.6% versus 28.6%) and psychiatric disorders (50.0% versus 35.7%). The only fatal AE (myocardial infarction) occurred in the group treated with PP, when the patient died two days after undergoing a PP session. However, the researchers believed they were unlikely to be related to the treatment or study procedures. In patients with MS, vascular access was a problem in 18 (out of 26) patients, but was always relieved by a simple technique involving femoral vein catheterization. Eleven of 26 patients [26], or some patients [19], experienced transient hypotension, corrected by rapid infusion of normal saline and 5% albumin solution [19][26]. Two bedridden patients had deep vein thrombosis requiring anticoagulation, but this was probably due to being bedridden rather than PP, per se [26]. One of the six patients switched to centrifugal PP due to an excessive itchy rash (which was resistant to dexamethasone and clemastine treatment). One patient had urticaria, which completely regressed after antihistamine treatment. One patient (out of 6) had appendicitis that was probably unrelated to PP [20].

References

1. Feigin, V.L.; Nichols, E.; Alam, T. Global, regional, and national burden of neurological disorders, 1990–2016: A systematic analysis for the Global Burden of Disease Study. Lancet Neurol. 2016, 18, 459–480.
2. Ernstsson, O.; Gyllensten, H.; Alexanderson, K.; Tinghög, P.; Friberg, E.; Norlund, A. Cost of Illness of Multiple Sclerosis-A Systematic Review. PLoS ONE 2016, 11, e0159129.
3. Maresova, P.; Mohelska, H.; Dolejs, J.; Kuca, K. Socio-economic Aspects of Alzheimer's Disease. Curr. Alzheimer Res. 2015, 12, 903–911.
4. Parsons, C.G.; Danysz, W.; Dekundy, A.; Pulte, I. Memantine and cholinesterase inhibitors: Complementary mechanisms in the treatment of Alzheimer's disease. Neurotox. Res. 2013, 24, 358–369.
5. Hardy, J.A.; Higgins, G.A. Alzheimer's disease: The amyloid cascade hypothesis. Science 1992, 256, 184–185.
6. O'Brien, R.J.; Wong, P.C. Amyloid precursor protein processing and Alzheimer's disease. Annu. Rev. Neurosci. 2011, 34, 185–204.
7. Singh, S.K.; Srivastav, S.; Yadav, A.K.; Srikrishna, S.; Perry, G. Overview of Alzheimer's Disease and Some Therapeutic Approaches Targeting Aβ by Using Several Synthetic and Herbal Compounds. Oxid. Med. Cell. Longev. 2016, 2016, 7361613.
8. Hart, F.M.; Bainbridge, J. Current and emerging treatment of multiple sclerosis. Am. J. Manag. Care 2016, 22, 159–170.
9. Feinstein, A.; Freeman, J.; Lo, A.C. Treatment of progressive multiple sclerosis: What works, what does not, and what is needed. Lancet Neurol. 2015, 14, 194–207.
10. Giacobini, E.; Gold, G. Alzheimer disease therapy—moving from amyloid-β to tau. Nat. Rev. Neurol. 2013, 9, 677–686.
11. Sevigny, J.; Chiao, P.; Bussière, T.; Weinreb, P.H.; Williams, L.; Maier, M.; Dunstan, R.; Salloway, S.; Chen, T.; Ling, Y.; et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2016, 537, 50–56.
12. Sikanyika, N.L.; Parkington, H.C.; Smith, A.I.; Kuruppu, S. Powering Amyloid Beta Degrading Enzymes: A Possible Therapy for Alzheimer's Disease. Neurochem. Res. 2019, 44, 1289.
13. Murphy, M.P.; LeVine, H. Alzheimer's disease and the amyloid-beta peptide. J. Alzheimers Dis. 2010, 19, 311–323.
14. Khatri, B.O. Therapeutic plasma exchange for worsening multiple sclerosis: Does it work? Expert Rev. Clin. Immunol. 2009, 5, 491–493.
15. Padmanabhan, A.; Connelly-Smith, L.; Aqui, N.; Balogun, R.A.; Klingel, R.; Meyer, E.; Pham, H.P.; Schneiderman, J.; Witt, V.; Wu, Y.; 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.
16. Rolfes, L.; Pfeuffer, S.; Ruck, T.; Melzer, N.; Pawlitzki, M.; Heming, M.; Brand, M.; Wiendl, H.; Meuth, S.G. Therapeutic Apheresis in Acute Relapsing Multiple Sclerosis: Current Evidence and Unmet Needs-A Systematic Review. J. Clin. Med. 2019, 8, 1623.
17. McKhann, G.; Drachman, D.; Folstein, M.; Katzman, R.; Price, D.; Stadlan, E.M. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984, 34, 939–944.
18. Gafoor, V.A.; Jose, J.; Saifudheen, K.; Musthafa, M. Plasmapheresis in neurological disorders: Experience from a tertiary care hospital in South India. Ann. Indian Acad. Neurol. 2015, 18, 15–19.
19. Faissner, S.; Nikolayczik, J.; Chan, A.; Hellwig, K.; Gold, R.; Yoon, M.S.; Haghikia, A. Plasmapheresis and immunoadsorption in patients with steroid refractory multiple sclerosis relapses. J. Neurol. 2016, 263, 1092.
20. Medenica, R.D.; Mukerjee, S.; Huschart, T.; Corbitt, W. Interferon inhibitor factor predicting success of plasmapheresis in patients with multiple sclerosis. J. Clin. Apher. 1994, 9, 216–221.
21. Schröder, A.; Linker, R.A.; Gold, R. Plasmapheresis for neurological disorders. Expert Rev. Neurother. 2009, 9, 1331–1339.
22. Oji, S.; Nomura, K. Immunoadsorption in neurological disorders. Transfus. Apher. 2017, 56, 671–676.
23. Cuberas-Borrós, G.; Roca, I.; Boada, M.; Tárraga, L.; Hernández, I.; Buendia, M.; Pujadas, F. Longitudinal Neuroimaging Analysis in Mild-Moderate Alzheimer's Disease Patients Treated with Plasma Exchange with 5% Human Albumin. J. Alzheimers Dis. 2018, 61, 321–332.

24. Boada, M.; Anaya, F.; Ortiz, P.; Olazarán, J.; Shua-Haim, J.R.; Obisesan, T.O.; Lafuente, A. Efficacy and Safety of Plasma Exchange with 5% Albumin to Modify Cerebrospinal Fluid and Plasma Amyloid-β Concentrations and Cognition Outcomes in Alzheimer's Disease Patients: A Multicenter, Randomized, Controlled Clinical Trial. J. Alzheimers Dis. 2017, 56, 129–143.
25. Munn, Z.; Tufanaru, C.; Aromataris, E. JBI's systematic reviews: Data extraction and synthesis. Am. J. Nurs. 2014, 114, 49–54.
26. Khatri, B.O.; Koethe, S.M.; McQuillen, M.P. Plasmapheresis with Immunosuppressive Drug Therapy in Progressive Multiple Sclerosis: A Pilot Study. Arch. Neurol. 1984, 41, 734–738.
27. Boada, M.; Ortiz, P.; Anaya, F.; Hernández, I.; Muñoz, J.; Núñez, L.; Olazarán, J.; Roca, I.; Cuberas, G.; Tárraga, L.; et al. Amyloid-targeted therapeutics in Alzheimer's disease: Use of human albumin in plasma exchange as a novel approach for Abeta mobilization. Drug News Perspect. 2009, 22, 325–339.
28. Hauser, S.L.; Dawson, D.M.; Lehrich, J.R.; Beal, M.F.; Kevy, S.V.; Weiner, H.L. Immunosuppression and plasmapheresis in chronic progressive multiple sclerosis. Design of a clinical trial. Arch. Neurol. 1983, 40, 687–690.