The Role of Therapeutic Plasma Exchange in Treatment of Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy

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ABSTRACT

KEY IDEAS

- Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a recently identified inflammatory central nervous system (CNS) disorder marked by GFAP-IgG autoantibodies.
- Therapeutic plasma exchange (TPE) removes pathogenic autoantibodies, cytokines, and immune complexes, thereby targeting the disease's core immunopathology.
- TPE is a rational and potentially lifesaving therapy in autoimmune GFAP astrocytopathy, especially in refractory or life-threatening cases.

KEYWORDS: Autoimmune GFAP Astrocytopathy; Plasma Exchange; Plasmapheresis

INTRODUCTION

Autoimmune GFAP astrocytopathy is a rare, recently recognized autoimmune inflammatory disease of the central nervous system with presumably less than a thousand cases reported to date.[1] It is characterized by the presence of GFAP-IgG autoantibodies,[2,3] and it typically manifests as an antibody-mediated meningoencephalomyelitis, with patients often presenting with acute meningeal irritation and encephalitic symptoms such as fever, headache, ataxia, psychosis, dyskinesia, dementia, seizures and altered consciousness, and sometimes myelitis or optic neuritis.[4–6] Nevertheless, a subset of patients may only present with some or a few of the aforementioned symptoms, thereby eluding early detection.[6] Although the exact pathophysiology is unknown, autoimmune GFAP astrocytopathy appears driven by both T-cell and B-cell immune mechanisms as well as cytokines.[7,8] Pathological analyses have found abundant CD138+ plasma cells in CNS lesions with intrathecal antibody synthesis—GFAP-IgG titers are often higher in cerebrospinal fluid (CSF) than serum[9]—and elevated inflammatory mediators in the CSF. In particular, patients show significantly increased levels of proinflammatory cytokines (IL-1β, IL-6, IL-17) and activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome in CSF—involved in the release of IL-1β and IL-18 from the cells—correlating with disease severity and antibody titers.[10] These findings hypothesize that pathogenic autoantibodies and downstream neuroinflammatory cascades immune-cell recruitment with subsequent cytokine release and eventual astrocytic injury are central to autoimmune GFAP astrocytopathy's pathogenesis. Due to the rarity and only recent recognition of the disease, there is an absence of solid evidence such as controlled studies or randomized trials. The purpose of this brief review is to critically evaluate the emerging evidence supporting TPE in refractory autoimmune GFAP astrocytopathy, offering clinical insights and guidance for neurologists managing this condition.

UTILITY OF THERAPEUTIC PLASMA EXCHANGE IN AUTOIMMUNE GFAP ASTROCYTOPATHY

Given this immune-driven pathology, TPE has emerged as a logical acute treatment modality in severe autoimmune GFAP astrocytopathy. TPE can rapidly eliminate autoantibodies, cytokines, chemokines, immune complexes, and complement components that contribute to ongoing CNS injury.[5] By reducing this inflammatory burden and modulating immune-cell trafficking, plasma exchange directly addresses the disease's mechanism, attenuating the immune attack on astrocytes.[5] Clinically, high-dose corticosteroids remain first-line therapy as the majority (approximately 70–80%) of patients show a dramatic and rapid response to the treatment.[5] However, a significant subset experience relapses or inadequate response, especially those with high CSF antibody load or extensive CNS lesions.[9] In such refractory or fulminant cases, plasma exchange has been shown to improve outcomes.

CLINICAL EVIDENCE FOR THERAPEUTIC PLASMA EXCHANGE IN AUTOIMMUNE GFAP ASTROCYTOPATHY

Case reports describe patients who failed to improve with steroids and IVIG yet had dramatic recovery after TPE. In a case reported by Du et al,[5] two patients with autoimmune GFAP astrocytopathy and life-threatening brainstem involvement with respiratory failure were successfully weaned off ventilatory support only after plasma exchange therapy was instituted.[5] Likewise, immunoadsorption, a selective form of

plasma exchange that specifically removes IgG, has reversed severe steroid-resistant autoimmune GFAP astrocytopathy in at least one case described by Qin et al,[3] underscoring the pivotal role of pathogenic antibodies in this disease. Ip et al[11] described a patient who developed autoimmune GFAP astrocytopathy-associated meningoencephalomyelitis, acute bilateral sensorineuronal deafness, tetraplegia, bulbar palsy and respiratory failure. The patient was treated with steroids and IVIG that resulted in partial recovery. Later, she had a course of TPE followed by rituximab and she showed marked recovery of her disease. Gklinos et al[12] reported a severe case that did not respond to steroid treatment and underwent five cycles of TPE that resulted in clinical improvement. Yang et al[13] presented a patient who failed to respond to steroids and IVIG but improved after TPE. Taken together, these insights suggest that timely TPE can be a critical therapeutic option in the management of autoimmune GFAP astrocytopathy—presumably by acutely removing the immune elements driving the astrocytic inflammation, TPE targets the presumed core pathophysiology and may improve neurologic outcomes when conventional immunotherapies are insufficient.

PRACTICAL CLINICAL CONSIDERATIONS AND LIMITATIONS

Despite recognition of TPE as a valuable intervention in autoimmune GFAP astrocytopathy, several challenges limit its widespread integration into clinical practice. Due to the rarity of the condition, current evidence is largely derived from isolated case reports, which, although informative, lack the power to guide definitive recommendations. Additionally, the optimal timing, number of exchange sessions, and integration of TPE with other immunotherapies (e.g., corticosteroids, IVIG, rituximab) remain uncertain. Moreover, the risks of procedure-related complications and cost effectiveness in this context have not been systematically evaluated. Although TPE is promising, clinicians must balance potential benefits against procedural risks, including infections, bleeding, vascular access complications, and resource demands. Early initiation may be most beneficial in rapidly progressive disease or severe clinical presentations with high antibody loads, although this hypothesis warrants validation.

FUTURE DIRECTIONS AND RESEARCH NEEDS

Future research should include prospective, multicenter studies to validate TPE efficacy systematically, identify reliable biomarkers of therapeutic response, and determine optimal protocols for integrating TPE with adjunctive immunotherapies.

CONCLUSION

Autoimmune GFAP astrocytopathy is a challenging neuroinflammatory disorder driven by autoantibodies and immune activation. While corticosteroids are the currently considered mainstay of therapy, a subset of patients with severe or refractory disease may benefit from TPE. By removing circulating autoantibodies and proinflammatory mediators, TPE directly addresses the immunopathological mechanisms underlying astrocytic injury. Accumulating case-based evidence supports its use in steroid-resistant or fulminant presentations, including life-threatening brainstem involvement. TPE should be considered in the treatment of autoimmune GFAP astrocytopathy, especially in refractory cases.

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Disclosures

Conflict of interest statement: The author declares no conflicts of interest.

Financial disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

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