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Plasmapheresis for the Progressive Encephalitis with Rigidity and Myoclonus (PERM) Variant of Stiff Person Syndrome and Anti-Glycine Receptor Antibodies

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Abstract

We present a case report of a female in her fifties with the progressive encephalomyelitis with rigidity and myoclonus variant of stiff person syndrome. She had anti-glycine receptor antibodies rather than the more common anti-glutamic acid decarboxylase antibodies. She did not have any malignancies or other autoimmune conditions. She presented 1 year after a subdural hematoma with ongoing complications with a 3-week history of worsening tremors and altered mental status. She was treated with immunosuppression, intravenous immunoglobulin, and plasmapheresis. She showed minimal improvement after intravenous immunoglobulin but did not show improvement after plasmapheresis.

Introduction

Stiff person syndrome (SPS) is an autoimmune and neurologic condition that is characterized by muscle rigidity and spasms and most commonly with a positive anti-glutamic acid decarboxylase antibody titer [1]. The pathophysiology is not fully understood, but the association with auto-antibodies points to a probable autoimmune pathology [1].

The progressive encephalomyelitis with rigidity and myoclonus (PERM) variant is known to present more acutely and progress more quickly compared to classic stiff person syndrome [1]. The PERM variant is commonly associated with anti-glutamic acid decarboxylase, glycine receptor (glyR), and DPPX antibodies [2]. It has clinical features of SPS with additional brainstem and autonomous nerve involvement [1]. PERM is associated with tumors in 20% of cases as well as other autoimmune conditions [2].

Common therapies for SPS and PERM are GABAergic and immunosuppressant therapy [3]. While many patients with SPS can live with symptom management, the prognosis can be variable between patients, and the PERM variant is known to be especially life threatening [4]. Although there are scattered case reports of using therapeutic plasmapheresis or therapeutic plasma exchange (TPE) as adjunctive treatment for stiff person syndrome along with immunomodulatory medications, there are no randomized controlled trials on the effectiveness of TPE for SPS or the PERM variant [5].

Case Presentation

The patient was a female in her fifties with a history of subdural hematoma 1 year prior to presentation that was complicated by cerebral edema that required decompressive craniotomy and placement of a ventriculoperitoneal shunt. She had no history of autoimmune disease. She was living at an acute rehab facility after a hospital discharge for repeat infections of her cranioplasty site and presented with new onset tremors, visual hallucinations, and altered mental status. Symptoms started 3 weeks prior to presentation.

Her physical exam was notable for a coarse tremor in all four extremities with her right side more affected than her left. Ocular movements were largely normal with limited right eye adduction noted. She was hyperreflexic bilaterally in both upper and lower extremities.

Given her significant tremors, she was intubated and sedated in order to obtain an MRI. MRI showed intracranial hypotension for which her VP shunt was adjusted without signs of improvement. EEG was not notable for seizure activity, but she was started on levetiracetam due to her history of epilepsy. Further lab testing revealed a positive anti-glyR antibody titer raising concern for the progressive encephalomyelitis with rigidity and myoclonus variant of stiff person syndrome.

She was immediately started on Diazepam, Tizanidine, Gabapentin and Amantadine for symptomatic treatment. Despite these, she had worsening dysphagia and communication abilities. She was treated with a 5-day course of intravenous immunoglobulin (IVIG) followed by a 5-day course of Methylprednisolone 1g IV. She showed some response to IVIG treatment. Her immunosuppressant medication was not continued due to ongoing infection of her cranioplasty site for which she was receiving broad-spectrum antibiotic treatment with vancomycin and cefepime. There was also a concern for opportunistic infection.

Due to refractory symptoms despite high dose steroids and IVIG, she had her first TPE 4 weeks after diagnosis. She was given a total of 5 plasma exchange therapies on a Monday, Wednesday, Friday schedule. Each one was a 1-plasma volume exchange via centrifugal apheresis with 5% albumin as the replacement fluid. She did not have a significant improvement after 5 TPE treatments.

Throughout her hospital stay she had difficulty speaking and dysphagia that required speech therapy services and remained on tube feeds post-discharge to acute rehab facility. She survived for 5 months after the time of TPE. Some highlights from her clinical course are listed in Table 1.

Discussion

Diagnosis

She was diagnosed with the PERM variant of SPS based on her physical exam and a positive anti-glyR antibody titer. MRI showed intracranial hypotension that did not resolve after adjusting her shunt settings. Lumbar puncture found elevated RBCs (196) in spinal fluid and a nucleated cell count of 13. Glutamic acid decarboxylase antibody titer was undetectable, EEG was not notable for seizure activity, and PET scan did not show any lesions suspicious of malignancy or a paraneoplastic syndrome. This patient's condition could be attributed to an autoimmune cause considering her PET scan did not suggest a neoplastic etiology, her MRI was nearly normal, and she had positive autoantibodies towards the glycine receptor.

Treatment

Treatment for PERM is not well-established, and different patients have been noted to respond to different therapies. Part of this discrepancy could be due to the fact that the pathophysiology of PERM is not well known and could be variable between patients. According to Ortiz et al., there are two main modalities for treating SPS or PERM: GABAergic treatment and immunotherapy [3].

GABAergic therapies include benzodiazepines, and the most commonly accepted one for this syndrome is diazepam. In addition, anti-seizure medications such as levetiracetam and pregabalin have also been used. If symptoms persist despite these therapies, then adding on baclofen for further muscle relaxant effects and starting immunotherapy with IVIG is suggested. Plasmapheresis is rarely offered as a third-line therapy [3].

Our patient was immediately started on diazepam and levetiracetam. Once positive antibodies were found positive in her blood sample, she was started on mycophenolate motefil. The rationale behind GABAergic treatment in patients with SPS is that 85% of patients have anti-glutamic acid decarboxylase antibodies, which is an essential neurotransmitter in the manufacturing of GABA. By treating patients with medications that increase GABA function, it should theoretically compensate for the antibodies. However, our patient did not have anti-glutamic acid decarboxylase antibodies and did not show significant improvement with diazepam and levetiracetam. Her persistent symptoms despite GABAergic treatment could have been due to the absence of anti-glutamic acid decarboxylase antibodies.

Due to her persistent symptoms of stiffness, altered mental status, and worsening dysphagia, she received 5 days of IVIG followed by 5 TPEs over 9 days. Multiple case reports have suggested that IVIG may be beneficial for patients with PERM [4]. Rituximab was considered but not administered because of her ongoing infection of her cranioplasty site and unclear evidence of its effectiveness in this disease.

The American Society for Apheresis (ASFA) routinely publishes recommendations on the use of TPE in many disease entities. Per the ASFA guidelines, using therapeutic plasma exchange for stiff person syndrome is given a category III recommendation, which suggests that the role and efficacy of TPE in SPS is unclear [5].

The lack of certainty in the benefit of TPE in treating SPS could be due to the paucity of data and mixed results [6]. Jazebi et al. presented a case of a 65-year-old male with a history of ESRD that was admitted for cerebellar symptoms but later diagnosed with PERM [7]. He was treated with TPE for 5 days followed by IVIG and showed significant improvement in his condition. However, the role of TPE in his recovery was unclear as the combination of the two treatments might have resulted in the improvement of symptoms [7].

Hutchinson et al. described a case of a 54-year-old male with PERM that was treated with IVIG, cyclophosphamide, and TPE [8]. However, 14 months after treatment, his condition relapsed, and he needed repeat treatment. After that second treatment series, he achieved remission [8]. DeBlauwe et al. and Borellini et. al both published case reports of patients with malignancy associated anti-glyR+ PERM who responded well to TPE as well as tumor removal and chemotherapy to treat their underlying malignancies [2, 9].

Pagano et. al and Albahra et. al reviewed multiple cases of anti-glutamic acid decarboxylase-positive SPS cases that were treated with TPE [6, 10]. Both reviews reported that TPE seemed to be associated with at least minimal improvement for most patients. Similar case reports were not available for patients with anti-glyR+ PERM.

The sparse data about effective treatments and the incomplete understanding of the pathophysiology of this disease makes it a difficult disease for clinicians to treat. We share our experience with a patient with the PERM variant of stiff person syndrome who was treated adjunctively with TPE in addition to immunosuppressant therapy and IVIG. This patient showed some clinical improvement with IVIG treatments but did not show significant clinical improvement after TPE.

Hospital Day	Treatment
Day 1	Levetiracetam, Diazepam, Tizanidine, Gabapentin and Amantadine continued throughout hospital stay
Day 5	Started on mycophenolate motefil
Day 14-18	5-day course of IVIG
Day 19-23	5-day course of Methylprednisolone
Day 24-28	5-day course of PLEX
Day 28-discharge	IVIG
Discharge	Discontinued IVIG. Discharged to acute rehab facility on Levitiracetam, Diazepam, Tizanidine, Gabapentin, and Amantadine

Table 1: Treatments by hospital day

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