Chuck C, Herman K, El Jamal S. Progressive Encephalomyelitis with Rigidity and Myoclonus Treated with Rituximab: Case Report and Review of the Literature. *Brown J Hosp Med*. 2022;1(2). doi:10.26300/cd20-cq84

Case Reports

Progressive Encephalomyelitis with Rigidity and Myoclonus Treated with Rituximab: Case Report and Review of the Literature

Carlin Chuck[1], Karl Herman, MD[2], Sleiman El Jamal, MD[3]

[1] Medicine, Warren Alpert Medical School at Brown University, [2] Division of Hospital Medicine, Department of Medicine, Warren Alpert Medical School at Brown University, [3] Neurology, Warren Alpert Medical School at Brown University

Keywords: Progressive Encephalomyelitis with Rigidity and Myoclonus, PERM, rituximab, stiff person syndrome, stiff person syndrome plus

https://doi.org/10.26300/cd20-cq84

Vol. 1, Issue 2, 2022

A woman in her 50s presented with hyper-religiosity, auditory hallucinations, episodes of staring associated with unresponsiveness and stiffening of her entire body. A broad workup excluded autoimmune encephalitis, sarcoidosis, and prion disease. She was diagnosed with PERM (progressive encephalomyelitis with rigidity and myoclonus) syndrome which was supported by elevated cerebrospinal fluid (CSF) autoantibodies against glutamic acid decarboxylase (GAD) glutamic acid decarboxylase. She responded to treatment with corticosteroids and weekly rituximab therapy over four weeks. PERM is an autoimmune condition which is a rare variant of stiff person syndrome involving rigidity, dysautonomia and encephalopathy. PERM requires the clinician to have a high index of clinical suspicion to recognize and treat.

INTRODUCTION

Stiff person syndrome is a rare neurological condition characterized by muscular rigidity and painful muscle spasms. Spasticity accompanied by mental status changes and dysautonomia invokes the possibility of PERM (progressive encephalomyelitis with rigidity and myoclonus) syndrome. This rare autoimmune condition is often acute in presentation and may be life-threatening but is also considered curable. PERM is considered a subset of stiff person syndrome and is associated with various serological findings. Prognosis and treatment are not well-established for this rare disorder.

CASE PRESENTATION

A 59-year-old woman with a history of remote lower cervical spinal cord injury resulting in paraplegia and complete heart block with insertion of cardiac pacemaker presented to hospital with a complaint of altered mentation, unusual behaviors and hallucinations. The patient begun to experience spells of inattention and staring 3 days prior to presentation. The patient's family members described the spells as events when the patient becomes inattentive, withdrawn and is unable to carry on conversation, answering only in single words or head nods. The episodes had a duration of 2-3 minutes initially but on the day of presentation the patient experienced an episode that lasted 2-3 hours. It was associated with stiffening of the whole body, closed eyelids, and minimal responsiveness at which point the patient was transferred to hospital for evaluation. The patient was not noted to have tongue biting, tonic-clonic movements, or eye-rolling.

The patient was also found to be praying frequently, greatly exceeding her usual amount of time in this activity. The patient was noted to have fatigue, low oral intake, lethargy and mild headache over the preceding few days. No fever, chills, night sweats, cough, chest pain, abdominal pain, nausea, vomiting, diarrhea were reported. No focal weakness, numbness, difficulty with vision, or language was reported. The patient's medical history included coronary artery disease, chronic systolic heart failure, hypothyroidism, and hypertension. Surgical history included placement of automatic implantable cardiac defibrillator, and suprapubic tube placement. The patient had no known use of tobacco products, alcohol, recreational drugs and marijuana. The patient's sister reported a personal history of rheumatoid arthritis.

On examination the temperature was 97.8 °F, heart rate 69 beats per minute, respiratory rate 16 breaths per minute, blood pressure of 140/61 mmHg, and pulse oximetry of 96% on ambient air. The patient was somnolent but arousable. Neurological examination revealed an awake patient with extraocular muscles intact, pupils which were round, equal and reactive to light. Face was symmetric and speech was non-dysarthric. She was able to identify herself and the place of examination. She was found to be softly muttering, repeating statements of a religious nature and was not able to carry on with conversation, appearing to be in a trance-like state. She was able to hold both arms against gravity, and move both legs in the plane of the bed. Diffuse hyperreflexia (4+) was found with a positive Hoffman's sign and bilateral ankle clonus.

Laboratory evaluation revealed normal complete blood counts, chemistry analysis, renal function and blood glucose. Hemoglobin A1C was 6.3%. Cerebrospinal fluid analysis revealed 6 leukocytes per high powered field (93% lymphocytes) and protein level of 225 mg/dL, with a negative gram stain as well as bacterial, fungal, and viral cultures. Computed tomography (CT) of the brain with intravenous contrast angiography and chest, abdomen, and pelvis were

unremarkable. An autoimmune encephalitis panel including anti-neuronal antibody, anti-NR1, anti-NMDA, and others tested through the Mayo Clinic Encephalopthy-Autoimmune evaluation panel (ENC1) were negative. Prion disease assessed through RT-QuiC testing, 14-3-3 protein testing and serum thyroid peroxidase antibodies were negative. Ebstein-Barr and cytomegalovirus plasma PCR testing was negative. Electroencephalography revealed diffuse slowing with background rhythms up to 7 Hz.

The patient was treated for presumed catatonia with intravenous lorazepam but did not respond. She was empirically treated with IV methylprednisolone and immunoglobulin for autoimmune encephalitis but continued to have confusion and rigidity. Fever occurred without evidence of infection and did not respond to empiric antibiotic therapy. Lumbar puncture was repeated and stiff-person variant syndrome with progressive encephalomyelitis with rigidity and myoclonus was placed on the differential. Serum anti-glutamic acid decarboxylase antibody titers (150 IU/mL) were found to be elevated on two separate occasions. Treatment was initiated with IV methylprednisolone and rituximab over a period of 4 weeks. The patient began to gradually improve, as manifested by improving encephalopathy and diminished episodes of muscular rigidity with a return to her baseline level of function.

DISCUSSION

We report a case of PERM treated with rituximab with good effect, the second case in the literature of PERM treated with rituximab and the first with substantial treatment response. PERM is a rare autoimmune disorder sometimes also called stiff person syndrome plus, thought to occur due to autoantibody formation against glutamic acid decarboxylase (GAD) and glycine receptor (GlyR), which are thought to disrupt and reduce presynaptic GABA(gamma-aminobutyric acid)-ergic inhibition mediated through amphiphysin, an intracellular synaptic protein which mediates GABA synaptic release.[1] Previous postmortem studies have also demonstrated a T-lymphocyte infiltration of the central nervous system suggestive of additional cell-mediated autoimmunity.[2]

PERM is characterized by painful muscle spasms, often involving the neck, trunk, or limbs.[3] Patients may also present with an excessive startle and oculomotor dysfunction. Less frequently, patients may present with cognitive disturbances or seizures.[4] Patients often present in adulthood, though pediatric cases of PERM have also been described.[5] The role of hyper-religiosity in our patients presentation is unclear and has not previously been described in encephalopathy related to PERM. A minority of patients with PERM have other pre-existing autoimmune conditions at, and rarely did patients present with abnormal MRI brain findings. However, about 20% of patients presenting with PERM did have a tumor (thymoma, Hodgkin's lymphoma, lung and breast cancer) noted after further workup.[6]

Testing is most often done through serum and CSF for the GAD-65 or GlyR antibodies, though other antibodies including DPPX (dipeptidyl-peptidase-like protein 6) have also been implicated.[7,8] In prior literature review, 70% of prior PERM cases presented with GlyR-Ab-positive, 14% presented with GAD, DPPX, or anti-amphiphysin antibodies, while 16% presented with either untested or no autoimmunity antibody identified.[4]

After diagnosis, immunosuppressive therapy is the mainstay of therapy. Of note, GlyR-negative individuals may be associated with better response to immunotherapy than GlyR-positive individuals, with prior studies finding a slightly higher rate of good neurologic outcome after treatment.[9] Corticosteroids are the most commonly used immunosuppressive, with the majority of documented cases treated first with corticosteroids followed by other immunosuppressive agents and strategies including immunoglobulin, cyclophosphamide, and plasmapheresis. Of note, one prior case documented using steroids, immunoglobulin, and rituximab for GlyR-positive PERM; however, this patient did not show significant improvement with this combination of immunotherapy.[10] The mechanism of action of rituximab in this condition may be attributable to the targeting CD20+ B cells which produce GAD or GlyR autoantibodies.[10] After symptom resolution, relapse of PERM symptoms has been described in the literature, most commonly in patients who had relapse while under no maintenance immunotherapy or decreased dosage of their immunotherapy.[4]

PERM is a rare autoimmune-mediated neurologic disorder which requires a high clinical suspicion to accurately diagnose. While significant advances have been made in understanding its autoimmune pathophysiology, further research is needed to determine what therapeutic regimens and duration best lead to symptom resolution. This report demonstrates the efficacy of using rituximab as a treatment modality for this rare variant of stiff person syndrome.

CONFLICTS OF INTEREST

The author report no conflicts of interest in relation to this work.

CORRESPONDING AUTHOR

Karl Herman, MD
Assistant Professor of Medicine, Clinician Educator
Warren Alpert Medical School at Brown University
Division of Hospital Medicine, Department of Medicine
The Miriam Hospital, 164 Summit Avenue, Providence, RI 02906
Tel: 401-793-2104
Email: kherman@lifespan.org

Submitted: May 13, 2022 EDT, Accepted: May 27, 2022 EDT

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-NC-4.0). View this license's legal deed at https://creativecommons.org/licenses/by-nc/4.0 and legal code at https://creativecommons.org/licenses/by-nc/4.0/legalcode for more information.

REFERENCES

1. Geis C, Weishaupt A, Hallermann S, et al. Stiff person syndrome-associated autoantibodies to amphiphysin mediate reduced GABAergic inhibition. *Brain*. 2010;133(11):3166-3180. doi:10.1093/brain/awq253

2. Turner MR, Irani SR, Leite MI, Nithi K, Vincent A, Ansorge O. Progressive encephalomyelitis with rigidity and myoclonus: glycine and NMDA receptor antibodies. *Neurology*. 2011;77(5):439-443. doi:10.1212/wnl.0b013e318227b176

3. Whiteley AM, Swash M, Urich H. Progressive encephalomyelitis with rigidity. *Brain*. 1976;99(1):27-42. doi:10.1093/brain/99.1.27

4. Chang A, Lin KY, Chuang KJ, et al. Progressive encephalomyelitis with rigidity: A Taiwanese case and review of literature. *Clin Neurol Neurosurg*. 2021;208:106807. doi:10.1016/j.clineuro.2021.106807

5. Damásio J, Leite MI, Coutinho E, et al. Progressive Encephalomyelitis With Rigidity and Myoclonus: The First Pediatric Case With Glycine Receptor Antibodies. *JAMA Neurol*. 2013;70(4):498-501. doi:10.1001/jamaneurol.2013.1872

6. Su Y, Cui L, Zhu M, Liang Y, Zhang Y. Progressive Encephalomyelitis With Rigidity and Myoclonus With Thymoma: A Case Report and Literature Review. *Front Neurol*. 2020;11:1017. doi:10.3389/fneur.2020.01017

7. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. *Neurology*. 2008;71(16):1291-1292. doi:10.1212/01.wnl.0000327606.50322.f0

8. Balint B, Jarius S, Nagel S, et al. Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. *Neurology*. 2014;82(17):1521-1528. doi:10.1212/wnl.0000000000000372

9. Crisp SJ, Balint B, Vincent A. Redefining progressive encephalomyelitis with rigidity and myoclonus after the discovery of antibodies to glycine receptors. *Curr Opin Neurol*. 2017;30(3):310-316. doi:10.1097/wco.0000000000000450

10. Gluck L, Hernandez AL, Wesley SF, Fulbright RK, Longbrake EE, Stathopoulos P. Therapeutic considerations in a case of progressive encephalomyelitis with rigidity and myoclonus. *J Neurol Sci*. 2020;416:116993. doi:10.1016/j.jns.2020.116993