Journal of Neuroimmunology 332 (2019) 135–137

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short Communication

Anti-glutamic acid decarboxylase (GAD) positive cerebellar Ataxia with transitioning to progressive encephalomyelitis with rigidity and myoclonus (PERM), responsive to immunotherapy: A case report and review of literature

Noushin Jazebi*,[1], Shashika Rodrigo[1], Bhanu Gogia, Ahmad Shawagfeh

University of Texas Medical Branch, Department of Neurology, 301 University Blvd, Galveston, TX 77555, USA

A B S T R A C T

We present a case of a 65-year-old African American male, immunosuppressed on Tacrolimus, who initially presented with cerebellar ataxia and rapidly developed Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM) with positive anti-glutamic acid decarboxylase (GAD65) antibodies, no underlying malignancy, and normal neuroimaging. PERM is a rare spectrum of Stiff Person Syndrome (SPS), which is strongly associated with anti-GAD antibodies and characterized by flare-ups and remissions of encephalopathy, myelopathy and rigidity with myoclonus. PERM is diagnosed clinically and has been successfully treated with both Intravenous Immunoglobulin (IVIg) and plasmapheresis. Our patient was successfully treated with IVIg. On day 14 after starting IVIg treatment, his neurological symptoms started to improve and ultimately returned to baseline.

1. Introduction

Stiff Person Syndrome (SPS) is a disorder with fluctuating muscular rigidity and spasm (Moersch and Woltman, 1956). Principal signs and symptoms of SPS include spasms and stiffness, primarily of the back, hips and legs as well as signs of neurologic hyperexcitability, such as startle response and hyperekplexia. Though the etiology was initially unknown, the discovery of antiglutamic acid decarboxylase (GAD) antibodies indicates that SPS may be an autoimmune disorder. Since its discovery, many variants of SPS have been elucidated, including focal SPS, jerking SPS and paraneoplastic SPS (Meinck and Thompson, 2002).

Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM) is a subtype of SPS and can be distinguished by prominence of myoclonus and encephalopathy. The onset occurs gradually over a period of weeks, and the duration can be weeks to years. Unlike SPS, symptoms of rigidity and muscle stiffness may be preceded by ataxia, vertigo and dysarthria (Meinck and Thompson, 2002). PERM is a chronic disease strongly associated with anti-GAD antibodies and characterized by flare-ups and remissions (Meinck and Thompson, 2002). Glycine receptor antibodies and NMDA receptor antibodies have also been found in PERM (Meinck et al., 2001; Carvajal-Gonzalez et al., 2014). PERM is diagnosed clinically and has been successfully treated with both IVIg and plasmapheresis (Dalakas, 2005; Quintas et al., 2018).

Below, we describe here a case of PERM in an immunocompromised patient with history of two renal transplants and positive anti-GAD65 but negative paraneoplastic panels who achieved recovery from the symptoms two weeks after receiving intravenous immunoglobulins (IVIg).

2. Methods

We searched the PubMed and Medline database to look for articles with “Stiff person syndrome”, “PERM”, “anti-GAD Ab”, “Anti-glycine Ab”, “PERM and IVIg”, “cerebellar ataxia and PERM”.

3. Discussion

3.1. Case report

A 65 year old African-American male with past medical history of hypertension, atrial fibrillation, end stage renal disease (secondary to hypertension), status post two kidney transplants and chronic subdural hematoma who was initially admitted for dehydration and diarrhea, complicated with Acute Kidney Insufficiency (AKI). Relevant medications included Apixaban and Tacrolimus. Upon admission, patient's

* Corresponding author.
E-mail addresses: nojazebi@UTMB.EDU (N. Jazebi), shmrodri@UTMB.EDU (S. Rodrigo), bhgogia@UTMB.EDU (B. Gogia), aashawag@UTMB.EDU (A. Shawagfeh).

[1] Noushin and Shashika are sharing first authorship.

https://doi.org/10.1016/j.jneuroim.2019.04.003
Received 16 January 2019; Received in revised form 5 March 2019; Accepted 3 April 2019

mental status was at baseline. He was alert and oriented to person, place, date and situation and is able to perform his ADLs, with mild short memory deficit. Neurology service evaluated the patient for two-week history of hand tremor, abnormal movements, slowed mentation, weakness and poor balance. Within three days of admission, patient had acute change in mental status with cerebellar ataxia, infrequent non-rhythmic multifocal myoclonic appendicular and facial jerks, coarse intention tremor, unsteady standing and posture and increased muscle tone with rigidity. Pertinent negatives included intact deep tendon reflexes, flexor plantar response and intact cranial nerve and sensory exam. Within one week of admission, patient developed both spontaneous and provoked myoclonus with tactile stimulation. The toxic and metabolic work up was only significant for pre-renal pattern Acute Kidney Insufficiency (AKI), treated with hemodialysis. Patient remained with persistent encephalopathy after complete resolution of metabolic disarrangements.

Patient initially received plasmapheresis (day 10 after admission) for 5 days. Patient remained with encephalopathy, severe axial and appendicular rigidity and stiffness. Because of no initial improvement, on week 5 after admission, patient was begun on a course of intravenous immunoglobulin (IVIg) at 0.4 g/kg/dose. On day 14 after completing the first course IVIg treatment, patient showed marked improvement in mental status, stiffness, spasticity and respiratory drive two weeks after. Pertinent laboratory findings included positive serum anti-GAD antibodies beginning on day 5 of hospitalization (titer: 1:250), negative cerebrospinal fluid (CSF) and plasma paraneoplastic panel (including anti-amphiphysin antibodies), negative anti-NDMA antibodies, negative anti-ganglioside antibodies, as well as absent oligoclonal band and normal IgG index. Anti Glycine Antibody (Ab) could not be obtained. Lumbar Puncture showed CSF values within normal range (Protein: 42 mg/L, Glucose: 82 mmol/L, White Blood Cells: 2 per mm^3), negative CSF cultures and a negative meningitis/encephalitis panel. Meningitis/Encephalitis Panel included *Escherichia coli* K1, Haemophilus influenza, *Listeria monocytogenes*, Neisseria meningitis (encapsulated), *Streptococcus agalactiae*, *Streptococcus pneumoniae*, Cytomegalovirus, Enterovirus, Herpes simplex virus 1 and 2, Human herpesvirus 6, Human parechovirus, Varicella zoster virus, and Cryptococcus neoformans/gattii. The patient had CT scans of the abdomen, head and thorax which all came back negative. Three brain MRIs during his hospital stay showed stable subacute subdural hematoma and no acute abnormalities. Complete work up excluded the presence of malignancy. Pertinent metabolic findings included Creatinine: 4.86 mg/dL, Urea Nitrogen: 436 mg/dL, TSH: 1.29 mIU/L, T4, and Vitamin B12: 888 pg/mL. Multiple Electroencephalograms (EEG) showed mild diffuse slowing, excess fast activity suggestive of medication effect and irregular heart and rhythm. No triphasic waves were seen. Patient also had consistently low Tacrolimus titers.

3.2. Case discussion

The case described in section 3.1 presented with cerebellar ataxia, infrequent non-rhythmic multifocal myoclonic appendicular and facial jerks, coarse intention tremor, unsteady standing and posture and increased muscle tone with rigidity and was diagnosed with PERM after Anti-GAD Ab. Toxic and metabolic etiology of acute encephalopathy were ruled out through extensive work ups. The etiology of anti-GAD positive SPS or PERM can be either paraneoplastic or autoimmune (Meinck and Thompson, 2002). Patient had positive anti-GAD antibodies beginning on day 5 of hospitalization. EMG could not be performed because family did not consent. In our patient, the paraneoplastic panel of the CSF and plasma came back negative. In addition, the patient's negative whole body CT scans confirmed the absence of underlying malignancy, which could cause paraneoplastic disease. Besides, there was no clinical evidence of malignancy over the one-year course of follow up surveillance. Acute Encephalitis (AE) presenting with anti-GAD65 antibodies is often non-paraneoplastic and shows better immune responsiveness than paraneoplastic AE (Shin et al., 2017).

MRI of the brain without contrast was repeated three times during the patient's hospital stay and revealed no significant findings, including cerebellar abnormality. Lack of any neoplastic causes indicate that the etiology of PERM in this patient was likely autoimmune, though confirmation with additional PET scan was unavailable. Our patient's presentation was unique in that he initially came in with symptoms consistent with cerebellar ataxia two weeks prior to hospital admission, including unsteady standing and posture and coarse intention tremor. Studies have shown that anti-GAD antibodies are also present in patients with cerebellar ataxia, suggesting a possible autoimmune origin (Honnorat et al., 2001; Ishida et al., 2007). Ishida et al. proposed two possible mechanisms for this phenomenon: indirect damage of Purkinje cells by suppressed inhibition of synaptic currents by anti-GAD antibody or direct damage on Purkinje cells caused by surrounding white blood cells (Honnorat et al., 2001). About 2 weeks into his hospital stay, his symptoms were more suggestive of PERM, due to onset of spasticity, encephalopathy and severe axial and appendicular rigidity. As far as we know, this sequence of presentation of cerebellar ataxia followed by PERM has not been cited in the literature before. The patient had markedly elevated titers of anti-GAD antibodies in the serum. Serum Anti-GAD65 titer from day 3 was > 250 IU/mL, signifying a positive result. CSF Anti- GAD65 titer from day 29 was < 5.0 IU/mL, indicating absence of antibody in CSF. Meinck et al. studied presence of GAD antibodies in 13 patients with SPS, 9 patients with PERM, 279 patients with other neurological diseases and compared these to 100 control patients. They found that the GAD65 antibody was present in 80% of patients with SMS and PERM, 5% in patients with other neurological diseases and 1% of patients in control group showed presence of anti-GAD antibodies (Meinck et al., 2001). In addition to anti-GAD antibodies, glycine receptor antibodies have also been identified in patients with PERM. In one patient with PERM, both anti-glycine and anti-GAD antibodies were found in the serum and CSF, and titer amount correlated with severity of disease (Ishida et al., 2007). In another study, of 45 patients with anti-glycine antibodies, 33 patients had PERM. Of these 33 patients, only 3 patients had positive anti-GAD antibodies, which suggests that obtaining anti-glycine antibodies is valuable in patients presenting with signs of PERM (Carvajal-Gonzalez et al., 2014). Anti-glycine antibodies are directed against cell-surface antigens and patients with these antibodies are more responsive to immunotherapy, compared with those with anti-GAD65 or anti-amphiphysin antibodies (Shin et al., 2017).

We were not able to measure anti-glycine antibody titers in our patient due to limited availability but realize this could be a valuable marker of disease progression. NMDA receptor antibodies have also been associated with PERM. Turner et al. reported a case of PERM associated with both glycine receptor and NMDA receptor antibodies, which they posit may have contributed to progressive disease and sudden death (Turner et al., 2011).

Our patient also had a notable response to intravenous immunoglobulins (IVIg). On day 10 to 15 of hospital stay, patient received plasmapheresis for 5 days, which did not result in immediate improvement. Patient began course of IVIg at 0.4 g/kg/dose about 5 weeks after admission, which resulted in marked improvement in mental status, stiffness, spasticity and respiratory drive, starting exactly on day 14 after administration. Our patient required maintenance IVIg treatment and was planned for monthly infusion. It is difficult to discern if the patient's recovery was a result of sole effect of IVIg versus combination of IVIg and late effect of Plasmapheresis.

In a study of 16 GAD-antibody positive patients with SPS, patients were randomly assigned to receive either IVIg or placebo for 3 months. After this period, there was a washout followed by crossing to the alternate therapy for 3 more months. Researchers found that stiffness score in patients assigned to IVIg therapy declined significantly throughout the 3 month trial but returned after switching to placebo

treatment (Dalakas, 2005). In addition to immunotherapy, symptomatic treatment can be achieved with diazepam and intrathecal baclofen (Meinck and Thompson, 2002). In a case report of PERM possibly caused by brucellosis, rituximab resulted in improvement of symptoms and a decrease in glycine receptor antibody titers for months after onset of disease (Magira et al., 2016). However, a subsequent randomized trial of rituximab on 24 patients with SPS revealed no significant change in stiffness index at 6 months (Dalakas et al., 2017). Another case report documented a patient with PERM that was glycine receptor antibody- positive and GAD antibody negative, who recovered completely after thymectomy (Afanasiev et al., 2016). Thus, more research is needed on treatment modality and duration most effective for patients with PERM.

Also note, this patient was on the immunosuppressant tacrolimus due to having two kidney transplants in the past. Patient had serum tacrolimus titers taken almost every day during hospital stay and all were within normal range. Also patient has been one Tacrolimus for many years and his current presentation is not likely to be related to his immunosuppressed status. A case of subacute cerebellar ataxia was documented in a patient with a kidney transplant following administration of Tacrolimus, which was resolved after discontinuation of the drug (Kaleyias et al., 2006). Although this etiology is unlikely in our patient due to his consistently low tacrolimus titers, and lack of temporal relationship, possible toxicity should be suspected in patients who present with cerebellar ataxia soon after tacrolimus administration.

In conclusion, our case describes PERM with positive anti-GAD65 antibodies, which initially presented with cerebellar ataxia and transitioned to PERM within two weeks. This case highlights the importance of making diagnosis through testing serum and CSF for anti-glycine, anti-NMDA and anti-GAD antibodies, since this is a treatable condition. In addition, our case is unique due to the patient's marked response to IVIg, starting 14 days after administration. Though the delayed effect of plasmapheresis could not be excluded.

The limitations of our study included unavailability of anti-glycine antibody test, not performing an Electromyogram per patient's family wish and inability to get PET scan in inpatient setting.

Sources of funding

None.

Conflicts of interest

None.

Role of fundingsource

No funding source was needed.

Ethics Committee approval:

No ethics committee approval was needed.

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