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Case Report

Primary Lateral Sclerosis/Stiff Person Syndrome with a Response to Intravenous Immunoglobulin

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Abstract

Background: This is a case of a patient initially diagnosed with Amyotrophic Lateral Sclerosis (ALS) whose clinical progression over a period of two years was more consistent with Primary Lateral Sclerosis with a positive response to Intravenous Immunoglobulin (IVIG).

Clinical Presentation: We discuss a 51 year old Caucasian male who presented with a predominance of upper motor neuron signs with minimal clinical evidence of lower motor neuron signs over two years. Over a period of three years the patient developed signs of axial stiffness with anti-GAD antibodies noted suspicious for Stiff-Person-Syndrome (SPS).

Conclusion: Associated conditions should be evaluated for in unusual or rare cases **to** allow for an alternative potentially reversible treatment. In our case, the patient with PLS, anti-GAD antibodies, and clinical features suggestive of SPS responded well to IVIG allowing a reduction in medication and an improved quality of life.

Keywords: Primary Lateral Sclerosis, Stiff Person Syndrome, Intravenous Immunoglobulin

Case Report

Introduction

Primary Lateral Sclerosis is a sister disease of ALS whose differences focus on the predominance of upper motor neuron findings with very little to no lower motor neuron findings. Our patient presented initially with spasticity predominately of the lower extremities with UMN findings of hyperreflexia in the patellar reflexes and an abnormal Babinski on the left. Eventually, the patient developed intermittent proximal spasms and increased spinal stiffness leading to decreased range of motion and mobility. At this time, the patient also had the presence of anti-Glutamic acid decarboxylase (GAD) antibodies which can be seen in 60% of patients with Stiff Person Syndrome [1]. Given these findings, patients may be treated with intravenous immunoglobulin (IVIg) 0.75 g/kg every three weeks. Our patient developed a significant clinical response with near elimination of severe multiple daily generalized spasms. Our patient still has evidence of increased muscle tone and spasticity but his quality of life has improved with decreased spasms, however, muscle pain, particularly in the posterior leg muscles, remains problematic. Though IVIg could cause a placebo effect, missing doses, due to a serum sickness-like disease, led to an increased return of the patient's symptoms.

Case

We report the case of a 50 year old white male who presented with increasing spastic activity, especially present in the lower limbs, with associated pain. There was a complaint of mild left lower extremity weakness but no other sites of lower motor neuron involvement. The patient experienced mild shortness of breath with exercise. He denied hoarseness, difficulty swallowing, or fasciculations. His total lung capacity was reduced with a normal carbon monoxide diffusing capacity, Associated similar decreases in the forced vital capacity and the forced expiratory volume in one second suggested of extrinsic restrictive disease. An initial EMG demonstrated normal nerve conduction studies with fasciculation potentials in 8 different muscle groups. Chronic re-innervation changes were seen in 5 muscle groups. Magnetic resonance imaging of the C-spine revealed some degenerative changes at C3-C4 without cord or nerve impingement. A sleep study showed moderate to severe sleep apnea; the patient was treated with bilevel positive airway pressure and supplemental oxygen at night. His current exam demonstrated normal vitals without orthostasis. His oxygen saturation was 94% on room air. Weight appeared normal with no evidence of cachexia or focal muscle atrophy/fasciculation. Cardiopulmonary and abdominal exams were benign. The neurologic exam demonstrated no cranial nerve defects. There was bilateral patellar hyperreflexia with mild lower extremity clonus. The Babinski was up-going on the left. Muscle strength was normal everywhere except for 4+ hip flexors in the left lower extremity. No other neurologic abnormalities were noted.

Labs including a CBC and CMP were normal. The urinalysis was normal except for trace proteinuria. Testing for the human immunodeficiency virus (HIV) and syphilis were negative. A total testosterone was 3.4 nmol/L with a normal luteinizing hormone suggesting secondary hypogonadism. An MRI of the brain/pituitary was normal with no dysfunction of the other pituitary axis's chemically. A 25-Hydroxyvitamin D level was mildly low at 6.2 nmol/L. A hemoglobin A1C was 0.06 as a proportion of total hemoglobin. A serum protein electrophoresis demonstrated two small monoclonal spikes with evidence of an elevated serum kappa gammopathy (21.1 mg/dl) and normal levels of immunoglobulins. Urinary protein studies were normal. A bone marrow demonstrated a normocelluar marrow with no increased plasma cells. Iron stores were deficient with normal ferritin and serum iron levels. An erythrocyte sedimentation rate was mildly elevated at 20 mm/h. Subsequently, a quadriceps and sural nerve biopsy was obtained which suggested neuro-immune involvement of the muscle with angulated atrophic fibers and group atrophy. A normal sural nerve was consistent with the normal nerve conduction studies. An anti-myelin-associated glycoprotein was negative. Antibodies for anti-Glutamic Acid Decarboxalase (anti-GAD) were positive. A lumbar puncture was normal without signs of multiple sclerosis or elevation in cerebrospinal protein levels. Paraneoplastic antibodies Anti-Yo and Anti-Hu were negative along with normal computed tomographries of the chest and abdomen.

The patient was treated with injectable depotestosterone, oral Vitamin D, and intravenous iron (low stores were thought secondary to a longstanding bleeding colon polyp removed at age 43). Celiac sprue autoantibodies were negative. Muscle strength along with lung volume indices improved. Over a two year period, the patient had persistent, yet stable, upper motor nerve findings with no progression of the mild lower motor nerve findings. A repeat electromyogram demonstrated no abnormal features. Given the possible diagnosis of primary lateral sclerosis evolving into SPS, increased monoclonal light chains, and muscle biopsy results, a decision was made to utilize intravenous immune globulin (IVIG) 2 days every 3 weeks, and follow his clinical status. Following the second round of IVIG, the patient was able to decrease the use of pain and anti-spasmodic medications by 30%. However, during the third infusion, he developed a fever of 40.8 C^0 with ultimate blood cultures from his port growing a Bacillus species requiring port removal and two weeks of antibiotics. During this time, the patient felt his neurological symptoms relapsed with no improvement during the third infusion while on intravenous antibiotics. The patient had just received his first round of every three weeks trial, with noted improvement through reduction of medications. These

medications included oxymorphone extended release every eight hours, oxycodone for breakthrough pain, and diazepam in the evening.

Discussion

Primary lateral sclerosis (PLS) is a rare condition typically seen as 1-4% of cases in large Amyotrophic Lateral Sclerosis (ALS) clinics [2]. Typically, the main feature of differentiation between ALS and PLS is the predominance of upper motor neuron symptoms over time limited to lower motor neuron symptoms. Monitoring over time is a key diagnostic feature as there is typical ALS, upper motor neuron dominant ALS, and PLS. Particularly with UMN predominate ALS patients, acquired EMG evidence of denervation occurred in a median of 3.2 years after symptom onset with clinical LMN signs appearing within 6 months. EMG evidence in this sub-group was consistent with acute denervation (fibrillation potentials, positive sharp waves, or both) [3]. As seen in our case, there were predominant UMN findings in the lower extremities without progression over time with limited development of any lower motor neuron signs. Since there is no single diagnostic test, monitoring over time in a multidisciplinary clinic is essential to management. Of course, this assumes that a thorough evaluation for other causes has been completed to review other possibilities. In our case, while there was some mild initial EMG findings, those resolved over a two year timeframe. In addition, our patientalso demonstrated mild fronto-temporal dysfunction in the memory disorder clinic's testing. Though cognition was initially thought to be normal, subsequent studies have suggested frontal lobe dysfunction without frank dementia may be seen in 10-20% of ALS patients [4]. In diagnostic categories, clinically pure PLS is described as evident UMN signs, no focal atrophy of fasciculations, and no evidence of denervation on EMG at > 4 years from symptom onset. Age onset after age 40 and secondary conditions are excluded by laboratory and neuroimaging [4]. Since our patient is on year 3 from his initial symptom onset, it appears that he meets these criteria to date.

The differential diagnosis is broad and includes hereditary (HSP) and infectious forms of spastic paraplegias. HSP usually presents in adolescence. No evidence of these conditions were noted in our patient. Given the patient has had significant C-spine and concussive trauma and such causation has been reported in the literature particularly in ALS. A cervical myelopathy or global or gyral atrophy was not evident on neuroimaging studies. Autopsy findings in a few patients with PLS demonstrated degeneration and loss of motor neurons in the precentral gyrus and degeneration of the corticospinal tracts without motor neuron loss or gliosis in the brainstem or spinal cord [4-6]. While reports of associated diseases are uncommon with PLS, there have been cases associated with breast cancer and HIV. There was one case of advanced PLS associated with an IgM paraproteinemia that ultimately required treatment for multiple myeloma which had no effect on the patient's advanced symptoms of PLS [7]. Though, like our case, there was a paraproteinemia it is certainly likely to be more commonly present than that described in the literature. The presence of Anti-GAD antibodies is more suggestive of Stiff-Person Syndrome since our patient had the development of axial findings.

In one study reviewing progression of PLS, 50 patients were classified into 3 groups based on their location of symptoms at the time of presentation: ascending (PLS-A), multifocal (PLS-M) and sporadic paraparesis (PLS-SP). At a follow-up of 7 years, with mean disease duration of 14 years, 47 patients continued to fulfill PLS criteria [2]. Their conclusion was that PLS progression does not occur steadily, but does have periods of decline upon spreading to a new region. PLS-A patients had a more predicable progression to additional body regions but subsequent stabilization was rapid in PLS-A and PLS-M subtypes. The conclusions were that PLS progression is slow and progression to ALS is rare, particularly after 4 years of stability without LMN symptoms.

On a potentially similar spectrum our patient likely also has Stiff Person Syndrome with his increasing axial rigidity and presence of anti-GAD autoantibodies. Our patient had the main finding of global muscle stiffness with episodic spasms and the presence of Anti-GAD antibodies [8]. Other cases of SPS have been associated with pituitary deficiency syndromes [9]. However, our patient's pituitary dysfunction has been isolated to the Luteinizing Hormone aspect and has not broadened further to date. Therefore, our patient likely has features of SPS and PLS based on criteria with many of the same symptomatic treatments available.

Treatment of PLS is typically symptomatic. Medications include anti-depressants for likely associated depression/pain and anti-spasmodics for spastic activity. Assistive devices can be utilized as needed for safety particularly with gait. The use of other treatments in the literature is sporadic and typically ineffective. The use of intravenous immunoglobulin (IVIG) in our case is controversial for PLS but not for SPS. Guidelines were released in 2007 on the use of IVIG in neurologic conditions. Recommendations for use was made for 14 conditions: acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, dematomyositis, diabetic neuropathy, Gullain Barre syndrome, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, multiple sclerosis, myasthenia gravis, opsoclonus-myoclonus, pediatric autoimmune neuro-psychiatric disorders associated with streptococcal infections, polmyositis, Rasmussen's encephalitis and stiff person syndrome [10]. There are no recommendations for ALS or PLS. In our case, the IVIG was initiated based on the muscle biopsy findings in association with the kappa gammopathy. Of course, the significance of those findings are unknown and

there are no specific criteria that might be more indicative of a clinical response to IVIG in PLS.

Our patient had good prognostic factors with minimal to no LMN symptoms or bulbar involvement and stability of his UMN findings over a period of three years to date. There have been minimal side effects, mainly fatigue, after the infusions. The cost is roughly 15 thousand dollars per round and he is entering a planned treatment protocol of two days of IVIG every 3 weeks. However, even after 3 treatments he has been able to significantly decrease (~30%) his medications for neuropathic pain and spasticity. Whether there is a placebo effect or this is the result of IVIG remains to be determined by monitoring his response over time. On one occasion, during the holidays, infusion therapy was extended to four weeks causing a re-exacerbation of symptoms in the last week before therapy resumed. Since Kappa gammopathy patients are at risk of progression to multiple myeloma, he needs to be monitored closely with quantitative immunoglobulins and serum/urine electrophoresis every 6 months with a repeat bone marrow biopsy if there is any concern.

In summary, we present a case of PLS/SPS with positive Anti-GAD antibodies and a muscle biopsy suggestive of a neuro-immune process. The patient was treated with several ongoing courses of IVIG resulting in less neuropathic pain and a significant decrease in daily spasms, allowing for a decrease in medication and improved quality of life. Whether this clinical response is progressive or persistent remains to be determined by monitoring his clinical status over time.

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