

Therapeutic Plasma Exchange in an Uncommon Disease: Stiff-Person Syndrome: Case Report

Sıra Dışı Bir Hastalıkta Terapötik Plazma Değişimi: Stiff-Person Sendromu

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ABSTRACT Stiff-Person syndrome (SPS) is a rare and disabling disorder characterized by continuous motor unit activity causing severe rigidity and episodic spasms in axial and limb muscles. It deteriorates the quality of life and causes a serious burden in the patient's life. It is frequently associated with other autoimmune diseases such as diabetes mellitus. Treatment with intravenous immunoglobulin, anti-anxiety drugs, muscle relaxants, anti-convulsants will improve symptoms, but will not cure the disorder. Therapeutic plasma exchange is an alternative treatment for the patients resistant to other treatment options. Here, we report a patient with SPS treated in intensive care unit and underwent therapeutic plasma exchange.

Key Words: Stiff-Person syndrome; autoimmune diseases of the nervous system; plasmapheresis

ÖZET Stiff-Person sendromu (SPS) aksiyal ve ekstremitelerde kaslarında ciddi rijidite ve ataklar halinde spazmlara neden olan devamlı motor ünite aktivitesi ile karakterize nadir görülen ve sakat bırakan bir hastalıktır. Yaşam kalitesini kötüleştirir ve hastanın yaşamında ciddi yüke neden olur. Sıklıkla diabetes mellitus gibi diğer otoimmün hastalıklarla birlikte görülür. İntravenöz immünoglobulin, anti-anksiyetikler, kas gevşeticiler, antikonvülzanlarla tedavi semptomları düzeltir fakat hastalığı tedavi etmez. Terapötik plazma değişimi diğer tedavilere dirençli hastalar için alternatif bir tedavidir. Burada yoğun bakım ünitesinde tedavi edilen ve terapötik plazma değişimi yapılan bir hastayı sunuyoruz.

Anahtar Kelimeler: Stiff-Person sendromu; sinir sisteminin otoimmün hastalıkları; plazmaferez

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Stiff-Person syndrome (SPS) is a rare progressive neurological disorder characterized by constant painful contractions and spasms of voluntary muscles, particularly the muscles of the back and upper legs.^{1,2} The nature of the syndrome is considered to be autoimmune, with positive glutamic acid decarboxylase (anti-GAD) antibodies in most patients. These antibodies exert an influence over gamma-aminobutyric acid (GABAergic) transmission.³⁻⁵ The disease deteriorates the quality of life and causes a serious burden in the patient's life. SPS is a rare but treatable disorder that should be considered when patients present with stiffness and pain in the lower back and upper legs.

In recent years, our knowledge on neurological disease mechanisms has improved and more specific treatment alternatives have become avail-

able. Yet, established therapeutic options such as intravenous immunoglobulins and plasma exchange are still high on the list for many neuroimmunological disorders. Myasthenia gravis is the first autoimmune disease that was treated successfully with plasma exchange.⁶ By understanding the etiology of neurological diseases; the number of diseases treated with therapeutic plasma exchange (TPE) had increased.⁷⁻¹¹ Here we report a male patient with SPS treated in our intensive care unit (ICU) and underwent TPE, as he was unresponsive to medical treatment.

CASE REPORT

A 39-year-old male with the complaints of generalized muscle spasms and seizures was admitted to our intensive care unit for TPE. His complaints began 1 year before his admission. The patient reported inability to walk because of his stiffness and was bedridden with involuntary spasms lasting all day. He was too disabled to walk or move, and he was afraid to leave the house because street noises, such as the sound of a horn, were triggering spasms and falls. Three months before his admission to our hospital, he was diagnosed as 'SPS' in neurology clinic of a tertiary hospital.

Anti-glutamic acid decarboxylase (anti GAD) antibodies were detected in serum with a level $>30 \text{ U mL}^{-1}$ (normal: $0-1 \text{ U mL}^{-1}$). To ameliorate sudden-onset spasms, the patient was treated with benzodiazepines, baclofen and clonazepam. These drugs did not alter the clinical status, so intravenous immunoglobulin (IVIg) therapy (0.4 g/kg/day for 4 days) was initiated, but no improvement was achieved at all. Despite all these treatments, he still had stiffness and could not walk by himself.

After 15 days, from the hospital where these treatments were applied, he was referred to our ICU for plasmapheresis. On admission, he was consulted to neurology clinic of our hospital and physical examination showed marked rigidity in the abdomen, lower back and both legs. Deep tendon reflexes had bilateral increased activity. Magnetic resonance imaging and electroencephalography

were normal. Electromyography (EMG) demonstrated a continuous motor unit activity of agonist and antagonist muscles at the same time.

The local ethical committee and the consultant team approved plasmapheresis indication given by the hospital he admitted priorly. After obtaining informed consent, we planned TPE for the patient in the ICU, and obtained blood samples for complete blood count and coagulometry, all of which were normal. We used fresh frozen plasma for TPE with a volume of 40 ml per body weight; and for anticoagulation 10 U/kg heparin infusion was used. The patient underwent a course of seven plasma exchanges in a period of 14 days. TPE was done with Prismaflex (Gambro Lundia AB, Branding & Market Com, Sweden) using Prismaflex TPE 2000 set (Gambro Lundia AB, Branding & Market Com, Sweden).

TPE resulted in marked clinical improvement. The disappearance of muscular cramps and a reduction of stiffness occurred within 72 hours after the forth plasmapheresis session, and after the seventh session of TPE, his symptoms decreased significantly, and he was able to walk unassisted. The patient became mobilized in about a 14 days' time and the hypertonicity of the muscles decreased. On the 20th day, he was discharged home.

After three months, the neurological examination and EMG were reviewed. The EMG recordings showed that the continuous motor unit activity had disappeared in most muscle groups, but there was still some activity in abdominal muscles. He was called in 6-month periods for controls. After two years time of his discharge, he still had stiffness in abdominal muscles and lower back; but he had no painful spasms and he was able to live on his own; and his neurological consultancy revealed no necessity for re-treatment with TPE.

DISCUSSION

SPS is characterized by progressive, usually symmetric rigidity of the axial muscles with superimposed painful spasms precipitated by tactile stimuli, passive stretch, volitional movement of affected or

unaffected muscles, startling noises, and emotional stimuli.^{1,2,9} Our patient also had involuntary spasms lasting all day. EMG was performed and there was a continuous motor unit activity of both agonist and antagonist muscles at the same time, which was pathognomonic for SPS.

The presence of anti GAD antibodies is well-reported in SPS, but most reports indicate that the level of the enzyme does not correlate directly with the severity of the disease or the outcome. The thecal synthesis of antiGAD antibodies is specific for SPS.^{3,4,10,12} We could only investigate serum anti-GAD Ab in our patient and we could not perform the test for thecal antibodies.

Antibodies against GAD are involved in the pathophysiology of SPS and type 1 diabetes.^{12,13} GAD catalyses the conversion of glutamate to GABA. GABA acts as a neurotransmitter between neurons while it plays an integral role in normal insulin secretion in pancreatic beta cells; hence the clinical presentation is muscular spasms in SPS and insulin deficiency in diabetes. Despite this apparent major overlap in pathophysiology, SPS only rarely occurs in individuals with type 1 diabetes. However, our patient had type 1 diabetes mellitus, and he was on insulin treatment.

The SPS is clinically elusive but potentially treatable and should be considered in patients with unexplained stiffness and spasms.^{1,2,9} Drugs that enhance GABA neurotransmission, such as diazepam, vigabatrin, and baclofen, provide mild to modest relief of clinical symptoms.¹⁴ The rarity of this condition limits the feasibility of controlled clinical trials in the treatment of SPS, but the available evidence suggest that drugs that increase cortical and spinal inhibition such as benzodiazepines and drugs that provide immune modulation such as intravenous immunoglobulin, TPE, and prednisone are effective treatment options.^{3,4,8,10,11,14,15} Treatment with IVIg, anti-anxiety drugs, muscle relax-

ants, anti-convulsants and pain relievers will improve the symptoms, but will not cure the disorder. TPE is an alternative treatment for the patients resistant to other treatments.^{10,11,15,16} Our patient had taken benzodiazepines, baclofen, IVIg and methyl prednisone before admitting to our ICU; but all these treatments did not alter his clinical status. He was undertaken to seven sessions of TPE treatment in the ICU; and he produced a good response to this treatment and the clinical and neurophysiological findings improved quite rapidly. His response to plasma exchange, which is carried out because of the presence of high serum titers of antibodies with GAD-like immunoreactivity, was striking.

Similarly, in a previous report by Hao et al., repeated plasmapheresis improved the condition of a medication-resistant patient with stiff man syndrome and type 1 diabetes.¹⁶ Over two years, the patient received numerous rounds of TPE plus intravenous immunoglobulin and a variety of immunosuppressive drugs, as well as diazepam and intrathecal baclofen. TPE, but not IVIg or immunosuppressants, repeatedly lowered anti-GAD antibody titers; however, IVIg did lead to significant temporary clinical improvement. In our case we did not reevaluate anti-GAD antibody titers after the treatment, but TPE resulted in marked clinical improvement and his clinical condition did not require repeated plasmapheresis sessions in two years time of his control.

CONCLUSION

TPE can be an alternative treatment for SPS. Reports about the benefits of plasma exchange in the treatment of SPS is not so sufficient. We believe that studies on large numbers of patients are needed to find out the role of plasma exchange in SPS which can also enlighten the pathogenesis of this rare syndrome.

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