Successful Treatment of Stiff-Person Syndrome with Plasmapheresis: Case Report and Literature Review

M. Nasvytis*
R. Kaladytë Lokominienë**

*Faculty of Medicine, Vilnius University, Lithuania
**Center of Neurology, Vilnius University, Lithuania

Summary. Stiff-person syndrome (SPS) is a rare neurological disease, most often caused by autoimmune process during which antibodies against glutamic acid decarboxylase (anti-GAD65) are synthesised. The main clinical symptoms, among which are axial and proximal leg muscle stiffness and painful spasms, are often provoked by external triggers. In addition to those, the disease presents with anxiety, phobias, and other psychiatric symptoms. The most notable SPS comorbidities include temporal lobe epilepsy and type 1 diabetes mellitus. In this article, we present a clinical case of a patient illustrating the course of the disease, diagnostic difficulties, and treatment options, all of which are discussed in the literature review.

Keywords: stiff-person syndrome, antibodies against glutamic acid decarboxylase, plasmapheresis.

INTRODUCTION

Stiff-person syndrome (SPS) is a rare neurological disease that affects 1-2 people in a million [1–3]. The most common clinical form is classic SPS, which is autoimmune in origin, associated with antibodies against glutamic acid decarboxylase (anti-GAD65), and occurs in approximately 70-80% of all SPS cases. The characteristic symptoms of this syndrome are progressive stiffness of the axial and proximal leg muscles accompanied by painful spasms in the affected muscle groups. The syndrome usually takes insidious course and progresses over several months. The absence of treatment leads to a complete impairment of daily activities and general disability [2–4]. The course of the disease mimics other neurological and psychiatric syndromes. For this reason and its rarity, SPS is usually misdiagnosed. Due to its autoimmune origin, SPS is often accompanied by disorders of the endocrine system [1, 4, 5]. Since gamma-aminobutyric acid (GABA)-mediated transmission is affected throughout the whole nervous system, psychiatric comorbidities are also common.

We report a clinical case that accurately illustrates the symptoms, course, and treatment of this syndrome. We discuss the clinical presentation, diagnostics, connection with autoimmune endocrine system and psychiatric disorders, treatment strategy and possibilities.

CASE REPORT

A 45-year-old woman was referred to a neurologist at Vilnius University Hospital Santaros Klinikos (VUH SK) with a suspicion of multiple sclerosis in September 2018. In February 2018, following a long stretch of fatigue (working long hours as a primary school teacher), the patient felt intense progressive pain and muscle tension in the right leg which eventually spread to both legs and the waist. Complaints included muscle “hardening” which made it difficult to bend her legs and walk. The patient fell several times and developed a fear of falling, it became difficult to get to the workplace. In April 2018, the patient was examined at VUH SK out-patient department. MRI of the brain, lumbar, and pelvic region showed no abnormalities, the suspicion of sacral plexopathy was rejected. Electroneurography (ENG) showed no signs of polyneuropathy. The patient was diagnosed with somatoform dysfunction of the autonomic nervous system (F45.8) and prescribed with baclofen and non-steroid anti-inflammatory...
medications (NSAIDs), but she did not tolerate these pharmacological agents. Subsequent rehabilitation and physiotherapeutic measures caused a partial improvement of the patient’s condition over time, but episodic leg muscle stiffness persisted. The patient’s symptoms exacerbated in the last 3 weeks before referral to a neurologist in September 2018.

The patient’s anamnesis revealed that in 2008 she was diagnosed with epilepsy presenting with frequent (up to 10 times a day) Déjà vu phenomenon and characteristic electroencephalographic (EEG) findings. Treatment with carbamazepine 200 mg three times a day helped to reduce the frequency of these episodes up to only 2-3 per month. Later, the dosage of carbamazepine was increased to 900 mg per day. The patient was referred to a psychotherapist to manage walking difficulties. In 2011, the patient was diagnosed with type 1 diabetes mellitus (T1DM) and was treated with insulin since then, but glycaemia control remained unsatisfactory (fasting blood sugar levels ranged from 8 to 16 mmol/L), especially when exposed to a stressful environment.

During physical examination in September 2018, the patient was agitated, suffered from an intense pain, presented with impaired spastic gait. Objective examination revealed hyporeflexia in the patient’s legs, a pathological Babinski reflex in the right leg, and episodic spontaneous activation of leg muscles, more prominent in the right and posterior chain. During these episodes the patient could hardly move her legs and reported about an acute increase of pain which eventually eased when lying down. The patient’s muscle strength was normal (scoring 5/5 points in MRC scale), the results of coordination tests were satisfactory, and no sensory impairment was detected. The EEG showed an increased excitability of the bioelectric field of the cerebral cortex, more prominent in the right temporal lobe, but no epileptic activity was registered.

Taking into account the patient’s symptoms (gait impairment, painful muscle spasms, and muscle stiffness) and possible relation with T1DM and epilepsy, SPS was suspected. The patient was admitted to the in-patient department of VUH SK Center of Neurology. EMG showed continuous firing of motor unit potentials in antagonist muscle groups at rest and when performing movements with both legs. After intramuscular injection of 10 mg of diazepam, firing of motor action potentials at rest ceased in the right leg. Stiffening of the anterior tibial muscle was observed during plantar extension. Based on EMG findings and positive serological anti-GAD65 testing in blood serum (>500 IU/mL), the patient was diagnosed with SPS. Treatment with diazepam up to 45 mg per day caused a noticeable improvement in the patient’s condition: functionality in activities of daily living was restored, though difficulties persisted when going to public places. Within a few weeks, optimal epileptic seizure control was achieved, and treatment with carbamazepine was discontinued. Over time, the dose of diazepam was maintained 30 mg per day with excellent tolerability.

In February 2019, the patient was diagnosed with hyperthyroidism, and treatment with thiamazole 5 mg three times a day was started. SPS symptoms began to fluctuate. Between 2019 and 2022, the patient was treated at the in-patient department of VUH SK Center of Neurology 3 more times. In August 2019, the patient experienced SPS exacerbation with fluctuating lower spastic paresis. She was continuously treated with diazepam 35 mg per day and underwent one cycle of 5 sessions of plasmapheresis. Since satisfactory control over the symptoms was regained with an increased dose of diazepam and the effectiveness of plasmapheresis therapy was limited (grade I), the decision to administer no further immunomodulatory treatment for at least 6 months was made.

In January 2020, the patient was admitted to the in-patient department of Endocrinology of VUH SK due to bad control over T1DM and significant daily fluctuations of glycaemia (2.8-18 mmol/L) associated with emotional stress. The patient was diagnosed with T1DM in sub-compensation phase, bad glycaemia control, diabetic non-proliferative retinopathy, diffuse nodular goiter (IB class, no signs of malignancy), and hyperthyroidism. A suitable diet was recommended, corrections in insulin therapy were made, thiamazole was prescribed for the treatment of hyperthyroidism.

In February 2020, the patient’s blood serum was tested to evaluate changes in the levels of anti-GAD65. The results showed persistently high levels (>500 IU/mL). The patient was re-hospitalised for treatment of exacerbation of SPS. The burden of disease consisted of intense nocturnal pain in lumbar region, disturbing sleep, stiffness in legs and waist, most prominent in the morning, and progressive walking difficulties. The daily dose of diazepam was increased to 40 mg and immune-modulating treatment with 5 plasmapheresis sessions was administered. The patient tolerated the treatment well, however, improvement after plasmapheresis was limited (Grade II).

In October 2020, the patient received one more cycle of plasmapheresis (5 sessions) which effectively improved her condition (Grade III).

In March 2022, the patient arrived for a routine monitoring visit to evaluate the disease control and effect of treatment. Episodic stiffness in lumbar, gluteal and leg muscles persisted, but was not as debilitating as before. Symptoms exacerbated after prolonged physical activity when walking in open spaces or with emotional stress. The patient developed a fear of falling, despite the fact that no falls were recorded during the last 2 years, she started to avoid large open areas in anticipation of stiffness attack. In addition to these fears, the patient complained of an increased level of anxiety, but not as high as 4-5 years ago. The patient showed no signs of depression or other mood disorders. She scored 10 points for anxiety and 4-5 points for depression on the Hospital Anxiety and Depression Scale (HADS). No sleeping disorders, drowsiness, or instances of falling asleep during daytime were recorded, the patient scored 9 points on the Epworth sleepiness scale. The control of diabetes remained unsatisfactory, fasting
glycaemia ranged from 3 to 20 mmol/L. No epileptic seizures were recorded in the past 3.5 years. As regards the patient’s mobility, her condition improved significantly: she was able to walk independently and reported no daily activity disturbances. Neurologic examination showed no paresis, muscle atrophy, fasciculations, or spasms. Hyperreflexia and pathological Babinski reflex remained present in the legs bilaterally. EEG showed repetitive episodes of rhythmical delta frequency waves in the right frontotemporal lobe without any typical epileptiform potentials. The patient is currently treated with diazepam 40 mg per day and is under the supervision of a neurologist.

**DISCUSSION AND LITERATURE REVIEW**

**Clinical presentation**

Classic SPS is a condition with an insidious onset and gradual progression over several months. It usually presents with progressive axial muscle stiffness and painful muscle spasms [6], hyperreflexia, continuous motor muscle activity, and heightened sensitivity to both external and internal stimuli [7, 8]. All these symptoms were observed in our case. Although the symptoms more often manifest in the axial muscles, in almost one third of the cases they are first observed in the proximal leg muscles [5] and manifest asymptomatically, intermittently, without pyramidal or extrapyramidal symptoms [8]. Stiffness is caused by simultaneous co-activation of antagonist muscle groups which, in turn, is caused by increased neuronal excitability due to insufficient GABA-ergic signaling. GABA-ergic signaling is reduced because GAD65, a vital enzyme responsible for GABA synthesis, is inactivated by anti-GAD65. Stiffness interferes with the movements of the limbs and trunk, disturbs the gait; as disease progresses, it may cause joint deformations, frequent falls, and inability to walk independently [3, 5, 7–9]. In our case, irreversible complications were avoided as a result of adequate and timely treatment.

Painful muscle spasms develop in 88% of all clinical SPS cases [5]. Sporadic and localized at the onset of the disease, they become generalized and debilitating as the condition progresses [8]. SPS symptoms are often provoked by sudden unexpected external and internal stimuli, such as loud, sudden noises, extreme cold, emotional stress, infection, or sudden movements in affected muscle groups [5, 7, 8]. Symptoms often fluctuate diurnally: increase in intensity during the daytime and decrease at night [3, 5, 8]. In our case, painful muscle spasms were triggered by emotional stress, they were debilitating, and decreased in intensity at night.

One of the key features of SPS is the overlap with other anti-GAD65 spectrum disorders (GAD65-SD), and in our case SPS was accompanied by autoimmune temporal lobe epilepsy (TLE). Anti-GAD65- associated TLE present in 2 main clinical forms. The first form is a clinical syndrome overlapping with acute limbic encephalitis (LE) and characterized by seizures of temporal origin, acute anterograde amnesia, behavior and personality disorders, headache, vertigo, and blurred vision, signs of mesiotemporal inflammation in brain MRI [10–12]. The second and more prevalent form is indolent chronic epilepsy without clinical or radiological signs of active CNS inflammation, manifested only by seizures, which originate in temporal lobe and generalize in 50% of cases [10, 11]. Anti-GAD65 associated-TLE differs from other autoimmune epilepsies in its higher incidence among young people, more frequent presentation with seizures rather than cognitive or psychiatric disorders, and more prevalent resistance to treatment with antiepileptic drugs [10]. Our patient’s epilepsy profile fits the anti-GAD65 associated TLE phenotype due to its temporal origin, indolent course, poor response to carbamazepine, and excellent response to treatment with benzodiazepines.

Movement and walking disorders caused by SPS are closely related to psychiatric symptoms. Most common of these are specific, task-related phobias, such as fear of climbing stairs, falling, or walking in open or crowded places in anticipation of stiffness attack [13]. Different authors disagree whether these phobias are caused primarily by the disease itself due to the inhibition of the GABA-ergic system, or whether they are simply the result of progressing disability. The main argument in favour of direct origin is the occurrence of phobias as the first symptom [13], however, secondary origin is supported by the fact that phobias are rapidly resolved after adequate control of motor symptoms is achieved [14]. Specific, task-related phobias are often accompanied by increased levels of anxiety, depression, behaviour and personality disorders [13]. Due to this comorbidity, walking disorders caused by SPS are often misdiagnosed to be of psychiatric origin. Unfortunately, psychotherapy, which is usually recommended in these cases, is ineffective, while treatment of SPS and good symptom control allow a rapid resolution of psychiatric symptoms [3, 13]. In our case, the patient had specific task-related phobias such as fear of walking in public spaces and falling, increased levels of anxiety, and depressive mood. Psychotherapy, recommended for the treatment of walking disorder, as the patient was diagnosed with somatoform dysfunction of the autonomic nervous system (F45.8), proved to be ineffective. However, after SPS treatment, at the last visit, the patient reported a decrease in phobias and anxiety level and the absence of depressive mood.

Apart from the CNS, GAD65 is also expressed in various sites throughout the endocrine system. For this reason, SPS comorbidity with endocrine disorders, such as T1DM, Grave’s disease, and hypopituitarism, is common. Since one of GAD65 expression sites is pancreatic beta cells, anti-GAD65 is detected in approximately 80% of patients with T1DM [1, 4, 5]. Accordingly, our patient was diagnosed with T1DM and developed thyroid gland dysfunction. Although up to 30% of patients with SPS are also diagnosed with T1DM, only 1/10 000 of patients with T1DM...
are diagnosed with SPS. Some authors believe it to be a consequence of different antibodies binding to different epitopes of GAD65 enzyme and thus having heterogenous effect on its activity throughout different sites in the organism [15]. Another theory claims CNS lesions to be associated with higher levels of antibodies allowing them to pass the blood-brain barrier and access the cerebrospinal fluid (CSF). This theory is supported by the fact that patients with T1DM who develop SPS and other GAD65-SD always have higher levels of anti-GAD65 antibodies than those who do not [7, 15, 16].

Diagnostics

To date, the diagnostic criteria described by M. Dalakas in 2009 (presented in the Table) remain the gold standard for diagnosing SPS.

Typical SPS feature observed in EMG is spinal cord and brainstem hyperexcitability which manifest by 3 types of findings: continuous motor unit (MU) firing, exaggerated acoustic startle reflexes, and enhanced exteroceptive (cutaneo-muscular) responses [2, 4, 8, 17]. Muscle stiffness is caused by involuntary MU firing and co-activation of muscles in agonist and antagonist groups. Failure of reciprocal inhibition is evident, as MU firing does not cease at rest or while performing various movements [2, 3, 5, 8, 17]. Thus, EMG is crucial in diagnosing SPS due to its availability and informativeness. EMG diagnostic accuracy is decreased by GABA-ergic drugs (such as baclofen and benzodiazepines) since they inhibit MU firing. This is consistent with our case, as MU ceased firing at rest after the patient was administered diazepam [2, 4, 5, 18]. The role of imaging in SPS diagnostics is only to exclude other pathologies, as anti-GAD65 associated SPS presents with no changes in brain or spinal cord MRI [3, 4, 19]. In the reported case, MRI was used to exclude the pathology of sacral plexus and did not reveal any relevant abnormalities. Anti-GAD65 in blood serum and CSF can be detected by two main methods: radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA). Levels of anti-GAD65 play an important diagnostic role in anti-GAD65-associated syndromes though only high levels of anti-GAD65 (>10 000 IU/mL) are definitive for diagnosing these nozologies. However, levels below 10 000 IU/mL are considered to be of limited diagnostic significance and should be supplemented by clinical data to reach a definitive diagnosis. In our case, laboratory findings alone would have been insufficient, however clinical findings and good response to treatment with benzodiazepines confirmed the diagnosis of SPS [3, 7, 19].

Management

SPS treatment consists of two main lines of therapy: symptomatic and immunomodulating. The first line of treatment is symptomatic and based on agents that enhance GABA-ergic transmission. According to various studies, this treatment reduces symptoms in 78-100% of all cases [4]. One group of drugs used in this line of treatment are benzodiazepines (BZD), of which diazepam is the oldest, most effective, and most well regarded first choice treatment [3, 4, 17, 20]. Most patients respond very well to treatment with BZD: muscle stiffness and painful spasms, especially caused by external triggers, are noticeably decreased [7]. In our case, treatment with diazepam yielded similar results: after starting diazepam, the patient’s condition improved rapidly and significantly, allowing discontinuation of anti-seizure medication. Quite often, to reach a therapeutic effect in patients with SPS, large doses of BZD (up to 60 mg diazepam daily) are required which increase the risk of dependence, withdrawal syndrome, or drowsiness and narcolepsy [4, 7, 17, 19, 20]. This was not the case with our patient, who reached sufficient control of symptoms with 45 mg of diazepam per day and scored 9 points on the Epworth sleepiness scale which is considered normal, at her last visit. Second choice treatment of GABA-ergic transmission enhancing therapy is baclofen which was administered to the patient at one time, but she did not tolerate the treatment.

Second line of therapy is immunotherapy which is administered when symptomatic treatment fails to improve the patient’s condition. Based on research, immunotherapy is effective in 39-80% of cases, however, the condition of most patients remains severe and 30-57% of them require mobility aid. In the reported case, the symptoms exacerbated over time despite continuous symptomatic treatment and repetitive plasmapheresis. According to the American Society for Apheresis (ASFA), Guidelines on the Use of Therapeutic Apheresis in Clinical Practice, published 2019, SPS is considered III category indication (optimum role of apheresis therapy is not established; decision making should be individualized) with 2C grade of evidence (weak recommendation, low-quality or very low-quality evidence). The guidelines recommend that plasmapheresis should be administered only when response to conventional therapy is insufficient and in combination with pharmacotherapy [21] which was precisely the strategy chosen in our case. According to different studies, the effectiveness of plasmapheresis in the treatment of SPS varies, the improvement of symptoms can be

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<th>Table. SPS diagnostic criteria, 2009 [6]</th>
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<td>1. muscular rigidity in the limbs and axial (trunk) muscles, prominent in the abdominal and thoraco-lumbar paraspinals;</td>
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<td>2. continuous co-contraction of agonist and antagonist muscles, confirmed clinically and electrophysiologically (EMG);</td>
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<td>3. episodic spasms precipitated by unexpected noises, tactile stimuli, or emotional upset;</td>
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<td>4. absence of any other neurologic disease that could explain stiffness and rigidity;</td>
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<td>5. positive anti-GAD65 (or amphiphysin) antibodies detected in blood serum or CSF;</td>
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<td>6. improvement of clinical condition in response of treatment with benzodiazepines.</td>
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divided into 3 grades: Grade I – no clinical improvement, Grade II – minimal or some improvements that do not result in significant change in daily activities, and Grade III – improvements are significant to impact daily activities [22]. It is noteworthy that the response of the same patient to plasmapheresis can differ during the course of the disease [22–25] According to literature, in 50-80% of reported cases, patients show at least a short-term regression of symptoms [22, 23]. Most authors describe and recommend chronic plasmapheresis therapy (1 session every 1-2 weeks) [23, 24], but some describe cases of long-term regression of symptoms after a single cycle of plasmapheresis [23]. In our case, a different strategy was chosen: plasmapheresis was administered only during periods of symptom exacerbation. The treatment was successful, as the patient’s condition remained stable over the past year, the symptoms have regressed and are currently controlled only by pharmacological treatment. A similar case was described in 2014 by MB Pagano, when plasmapheresis administered every few months during periods of symptom exacerbation resulted in stabilization and improvement of the patient’s condition [25]. Differences in treatment efficiency lead to the conclusion that treatment strategy should be individualized and chosen in accordance with the patient’s tolerance and response to plasmapheresis [24]. Most studies report persistence of high levels of serum anti-GAD65 even with weekly plasmapheresis, but levels of anti-GAD65 do not correlate with the severity of symptoms [22–25]. One possible explanation is the intrathecal synthesis of anti-GAD65 and the localized effect on the CNS during circulation in the CSF which is separated from the blood serum by blood-brain barrier [15]. Another question arises: how and why does plasmapheresis improve the condition of patients without decreasing anti-GAD65 blood serum levels? This can be explained by the elimination of various cytokines and other immune response components from the blood serum, thus modulating autoimmunity [24].

Other immunotherapy options in SPS include intravenous immunoglobulin (IVIg) and rituximab, a monoclonal CD20 antibody. However, in our case, good results were achieved with plasmapheresis, and other options were not explored. IVIg is widely used in clinical practice and is the only immunotherapy option that has been proven effective in clinical trials. Rituximab is considered by many authors as the third choice of treatment, as some studies report occasional effectiveness of this agent. Rituximab is usually recommended when symptomatic treatment and immunotherapy with IVIg are ineffective [4, 7, 20, 26].

CONCLUSIONS

Classical SPS is a rare disease of insidious onset and progressive course that is often misdiagnosed. Due to its frequent and significant psychiatric symptoms such as anxiety, depression, and phobias combined with exacerbation of symptoms related to emotional stress, neurological symptoms are often considered to be secondary and patients are often misdiagnosed with somatofrom dysfunction of the autonomic nervous system or anxiety disorder. In everyday clinical practice, the suspicion of this disease should be raised by specific comorbidities (TLE, late onset T1DM, and other endocrine disorders). The diagnosis of SPS should be based on clinical and EMG findings and detection of anti-GAD65 in blood serum. First line of therapy is symptomatic, enhancing GABA-ergic transmission: benzodiazepines (diazepam) or baclofen (second choice agent). Second line of therapy is immunotherapy that should be implemented when first line of treatment is ineffective. One of immunotherapy choices is plasmapheresis. In most cases, plasmapheresis yields limited results, namely a short-term clinical improvement, but in our case it was effective (grade III) and helped to improve the patient’s symptoms which resulted in restored functionality in daily activities.

References


M. Nasvytis, R. Kaladytė Lokominienė

SĖKMINGAS SUSTINGUSIO ŽMOGAUS SINDROMO GYDYMAS PLAZMAFERĖZE: ATVEJO PRISTATYMAS IR LITERATŪROS APŽVALGA

Santrauka

Sustingusio žmogaus sindromas (SPS) – reta nervų sistemos liga, dažniausiai sukeliama autoimuninio proceso, kurio metu susidaro antikūnai anti-GAD65 prieš glutamo rūgšties dekarboksilazą. Klinikinius simptomus (asių ir apatinio galūnio proksimalinių raumenų sustingimą bei skausmingus spazmus) dažnai provokuoja išoriniai dirgikliai. Sindromi taip pat būdinga psichiatrinių patologijų: nerimos, fobiųjų ir elgesio sutrikimų. Kartu su SPS dažniausiai pastebėta ir gretintinės autoimuninės kilmės ligos, tokios kaip autoimuninės temporalinės kilmės epilepsijos bei I tipo cukrinis diabetas. Šiame straipsnyje pateikiamos pacientės atvejais gerai išsukiusios ligos eigą, diagnostikos sunkumus ir galimus gydymo pasirinkimus, kurie plačiau aptariami literatūros apžvalgoje.

Raktazodžiai: sustingusio žmogaus sindromas, antikūnai prieš glutamo rūgšties dekarboksilazą, plazmaferezė.