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Stiff Person Syndrome

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SUMMARY

Background: Stiff-person syndrome is a disorder of the central nervous system that manifests by progressive rigidity together with muscle spasms of the axial and limb muscles. After its initial description in 1956, significant progress has been made in its diagnosis and treatment, although there are still unclear elements about its pathogenesis. Case report: a patient initially presenting for suspected multiple sclerosis was diagnosed with Lumbago with sciatic neuralgia in 2018. After she responded poorly to the treatment she was re-examined in September 2018, where a positive test for glutamic acid decarboxylase alpha antibodies confirmed the diagnosis of stiff-person syndrome. Continuous treatment with oral diazepam resulted in immediate decrease of symptoms and together with repetitive plasmapheresis helped to control the disease for next 3.5 years. Keywords: stiff-person syndrome, stiff-man syndrome, glutamic acid decarboxylase antibodies, muscle stiffness, rigidity.

INTRODUCTION

Stiff-person syndrome (SPS), or stiff-man syndrome, is a rare disorder of the central nervous system of unclear cause. It is characterized by fluctuating rigidity and stiffness of the trunk and proximal limb muscles, as well as superimposed episodic painful spasms and gait impairment due to continuous motor activity. The second set of symptoms includes sudden spasms that are precipitated by startling noises, tactile or visual stimuli, or emotional distress (1). A phobia of falling can cause anxiety and task-specific phobias. These psychologic symptoms can be so severe that they can dominate the clinical picture and may lead to a mislabeled psychiatric diagnosis (2). Evidence has accumulated suggesting that SPS represents an autoimmune disorder. A study found that circulating antibodies against glutamic acid decarboxylase (GAD-65) are present in at least 60 percent of patients with SPS. GAD-65 is the rate-limiting enzyme for synthesizing a major inhibitory neurotransmitter, γ-aminobutyric acid (GABA) (3). The existence of other organ-specific autoimmune diseases is common in patients with antibodies against GAD-65 (4). The autoantibodies against GAD65 can impair the synthesis of GABA by inhibiting the activity of GAD-65, and thus result in low GABA levels in the brain and CSF. The reduction of GABA levels in the brain in SPS patients indicates that the inhibitory GABAergic pathways are involved in the disease (5). However, the overwhelming majority of people who have autoantibodies against GAD-65 do not develop SPS, indicating that the pathogenesis is more diverse, with other unknown components (6).

It is estimated that SPS occurs at a rate of about 1 in 1 million(7,8) and most frequently affects people in their 40s. The age of onset varies from 30 to 60 years (9).

Moersch and Woltman first described the disease in 1965, who coined the term “stiff-man syndrome”. They described a previously unknown neurological disorder characterized by progressive fluctuating muscular rigidity and spasm. The clinical picture was diverse and had occurred in 14 patients (10).

Since its first description, cases of the syndrome have been reported in both men and women, as well as children. As a consequence, “stiff-man syndrome” had been renamed stiff-person syndrome (11,12).

LITERATURE SEARCH STRATEGY

Literature search was performed by searching for “stiff-person syndrome”, “anti-GAD antibody syndrome”, “SPS” and “stiff-man syndrome” in PubMed and Google Scholar in spring 2022.

LITERATURE REVIEW

Pathophysiology: SPS is currently viewed as an autoimmune disease, in which antibodies against GAD are formed. GAD is the rate-limiting enzyme for the synthesis of the bodies primary inhibitory neurotransmitter for the central nervous system (CNS), GABA. GABA reduces neuronal excitability by inhibiting nerve transmission(13). Glutamate, although a precursor for GABA, carries an opposite role in the nervous system. It is considered an excitatory neurotransmitter, while GABA is considered an inhibitory neurotransmitter. GABA is formed from glutamate via glutamate decarboxylase and vitamin B6 (13). Data suggests that anti-GAD antibodies can be pathogenic. Certain peptide fragments of GAD can be expressed during exocytosis of GABA. Antigen-presenting cells will then present those fragments to T-cell receptors. Instead of causing structural change in GABAergic neurons, anti-GAD antibodies may block functions of still-intact cells (14). High levels of antibodies against GAD were first described in patients with diabetes, in which GAD is a major autoantigen in islet cells (15). While the anti-GAD antibody titer is elevated up to 10 times above baseline in diabetes, it is elevated up to at least 50 times in SPS (16). The enzyme has two isoforms, which differ in molecular weight, location, and activity. GAD65 can be found in synaptic vesicles, and its activity increases in response to surging demands for GABA. GAD67 localizes to the cytoplasm and creates a steady basal GABA level. GAD-65 antibodies were reported in approximately 80% of SPS cases (The terms anti-GAD and anti-

GAD65 antibodies are used interchangeably in the literature), while antibodies against GAD67 were reported in about 60% of SPS cases. Co-existence is presumed likely (17). Although high anti-GAD antibody concentration is considered a specific marker for SPS, it can also be seen in patients with neurological manifestations other than SPS, such as myoclonus, epilepsy, cerebellar ataxia, and neuromyotonia (3,18–20). In rare cases these diseases may co-exist with SPS, also known as SPS-plus (21). Differences in recognition of GAD epitopes could explain the range of symptoms: In SPS, the GAD-antibodies recognize linear epitopes detected on Western blots, while in e.g. type 1 diabetes, they recognize conformational epitopes (22). The antibodies against GAD do not transfer the disease from mother to infant (23). More than 60% of patients have at least one psychiatric diagnosis (24).

Etiology: SPS is usually idiopathic, but can also occur as paraneoplastic cases, with either anti-GAD antibodies or antibodies against other constituents (17). The main paraneoplastic antibodies are against amphiphysin, a presynaptic cytosolic vesicle protein. Particularly in breast and lung carcinoma can these antibodies be found (25). It is estimated that the disease occurs at a rate of approximately 1 in 1 million (7,8). The age of onset ranges from 30 to 60 years and most frequently affects people in their 40s (9). Despite its typical age of onset, the disease has been observed in children, although rarely (26). The disease affects both men and women in a ratio of 2:1 (27).

Clinical features and course of SPS: Pain is a frequently observed symptom. It is characterized as both chronic and fluctuating with exacerbations. It seems to be caused by the sustained and powerful muscle contractions (27). Other than that, SPS is characterized by two sets of symptoms that onset insidiously and show a progressive course: stiffness of the truncal and proximal limb muscles due to co-contracture of agonist and antagonist muscles, but also present in the abdomen and thoracolumbar paraspinals leading to hyperlordosis and difficulty bending or turning, as well as superimposed painful spasms, triggered by tactile or auditory stimuli (17,28–30). As a result, the patient’s gait becomes wide and slow in an attempt to increase balance, while simultaneously becoming more unstable. Some patients use devices such as canes or wheelchairs because of their fear of falling. Another important aspect is exacerbation by emotional stress, as it is not uncommon for the symptoms to be first seen during a period of extraordinary emotional stress (24). Although the above-mentioned criteria best define the classic SPS phenotype, it is now clear that some patients with positive anti-GAD antibodies may exhibit stiffness that only affects one limb. This most commonly affects the legs and has been called stiff-limb syndrome, SLS (31). Anxiety and task-specific phobias

are a frequent finding in patients with SPS. A small study by Henningsen and Meinck (32) found that 44% of their participants developed task-specific phobias – that is, fear and avoidance of situations difficult to master due to the motor symptoms of SPS. Another 7% developed a subthreshold phobia, which is anxiety without avoidance. Although the rates of phobia and anxiety are high in movement disorders (33), a combined incidence of about 50% is to be considered very high in SPS. Clinical examination of the patient shows limb rigidity without any signs of extrapyramidal or pyramidal tract involvement. The co-existence of another autoimmune disorder or autoantibodies, especially type 1 diabetes and anti-parietal cell antibodies should raise suspicion for SPS.

Diagnosis: The diagnosis of SPS is mainly based on clinical findings, and therefore requires a high degree of clinical suspicion. In 2009, after identification of the anti-GAD antibodies, Dalakas formulated revised diagnostic criteria, out of which all are required to be met to diagnose SPS: "1) stiffness of the axial muscles, particularly the abdominal and thoracolumbar paraspinal muscles, leading to hyperlordosis; 2) superimposed painful spasms triggered by tactile or auditory stimuli; 3) electromyographic evidence of continuous motor unit activity in agonist and antagonist muscles (may be abolished if the patient is fully treated with benzodiazepines (34)); 4) positive serology confirmed by immunocytochemistry, Western blot, or radioimmunoassay; 5) absence of other neurological findings that may present an alternative diagnosis" (35). Serum GAD antibodies should be measured in patients with suspected SPS. It is important to know the range of values found by the testing laboratory, as the level associated with SPS is many times higher than what the laboratory may have established as a cut-off for testing for diabetes (27).

As discussed earlier, these criteria best define the "classic" SPS phenotype. In SLS the stiffness is confined to a limb, although eventual spread of the stiffness to the trunk was described(31). SLS is likely due to local interneuronitis, where spinal interneurons in the gray matter get destroyed selectively (31). The exact cause of interneuronitis is unknown. About 50% of these patients have transient brainstem symptoms (31), and about 15% have seropositivity to anti-GAD antibodies with limited response to GABAergic treatments (26,31).

Diagnostic errors are frequent. Because the stiffness can also be present in the facial muscles, patients run the risk of being misdiagnosed with Parkinson's disease, primary lateral sclerosis, or multiple sclerosis. The prominent stiffness in the back and accompanying back pain have led patients to orthopedic surgeons in hopes of improvement (35). The presence of phobias

and anxiety often leads to psychiatric misdiagnoses. On the other hand, there are patients with psychiatric symptoms manifesting muscle cramps and/or unusual spasms that are being misdiagnosed with SPS, although they do not fit the clinical description of SPS (35).

Difficulty in the diagnosis may arise in patients who exhibit the typical clinical symptoms but lack the anti-GAD antibodies. According to Dalakas, these patients make up to 20% of those with SPS-like symptoms (35).

Classification: A paper by Sarva, Deik, Ullah, and Severt (17) argues that Dalakas' criteria for "classic" SPS can be ambiguous and instead advocate for a classification based on likely etiology, which offers better guidance in terms of prognosis and treatment efficacy. Under this new classification, SPS cases can be divided into one of three mutually exclusive groups: 1) autoimmune cases, which are defined by autoantibody positivity in the absence of underlying malignancy; 2) paraneoplastic cases, that is all cases emerging in the context of cancer; and 3) cryptogenic cases, all seronegative cases in which an immunologic cause cannot be identified. If a cancer therapy does not produce a response in paraneoplastic cases, the malignancy is more likely to be a comorbidity than a likely cause. There are several other variants of SPS, each less common than classical SPS. SLS, as discussed above, is a focal form typically affecting only one leg (36,37). While most cases of SPS show some degree of asymmetry, in SLS the opposite limb may appear entirely normal. The spine will show no impairment, and it is believed that it is also associated with higher titer of GAD-antibodies. Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a progressive debilitating disorder associated with increased mortality(28,31). The course of the disease is highly variable, although the findings are like those of SPS with fixed neurologic deficits added on top. Typical features include progressive rigidity, myoclonus, autonomic failure, and loss of sphincteric function. Many of these patients will have low-to-moderate levels of antibodies (25). Antibodies against amphiphysin are associated with a paraneoplastic form of SPS which has some distinguishing features from classic SPS. Lordosis is not a prominent feature, while arm involvement may be more prominent (38). The co-occurrence of GAD and ampiphysin antibodies is unlikely (25). Antibody negative SPS is a poorly defined disorder, that, if suspected, deserves a detailed workup and extensive search for other causes.

Treatment: As pointed out before, decreased GAD activity lowers GABA levels and raises levels of glutamate, which in turn causes muscle rigidity. Medical treatment for SPS can be divided into two main groups: GABAergic therapy and immunotherapy. GABAergic therapy includes benzodiazepines, pregabalin, levetiracetam, and baclofen. Immunotherapy includes

rituximab, tacrolimus, plasma exchange, and intravenous immunoglobulin (IVIG). Propofol is also being used, although its mechanism is not very clear (39).

Diazepam is commonly used in high dosages as a first line treatment for SPS (40,41). Benzodiazepines work by enhancing GABA transmission by acting as direct agonists of GABA-A receptors (42). In comparison, baclofen acts as a selective agonist of GABA-B receptors (43). Pregabalin does not appear to affect GABA receptors, but binds to the alpha-2-delta binding site, which is associated with voltage calcium channels and their inhibition (44). Levetiracetam, in addition to being a calcium channel blocker, also has GABAergic activity (45).

Rituximab causes a depletion of B cells by targeting the CD20 expression on their surface (46). Tacrolimus inhibits calcium-dependent signal transduction pathways in T cells (47). Both aforementioned mechanisms inhibit anti-GAD antibody production. Intravenous immunoglobulin G (IVIG) is a potent immunomodulating agent based on antigen-antibody interactions. A recently completed randomized cross-over trial showed strong support for IVIG. Stiffness scores decreased significantly when compared to the placebo (18). The efficacy of treatment may vary from patient to patient, but the duration of the effect can be sustained for up to one year (48). Side effects include headache and vasomotor symptoms (49). It is important to note that anaphylaxis may initially begin with vasomotor symptoms, and mandates end of treatment if suspected. Serious side effects include worsening of underlying renal failure, an increased risk for deep venous thrombosis and stroke, which is infrequent but may be fatal (50). Lastly, plasmapheresis depletes circulating antibodies or immunocomplexes and pro-inflammatory proteins, although conflicting therapy results have emerged from the use of plasmapheresis (39,51).

Tricyclic antidepressants should be discontinued in patients with SPS. They have been shown to worsen the abnormal EMG activity of SPS and will lead to clinical deterioration. If a patient is referred already taking tricyclic antidepressants and not showing deterioration of his symptoms, the diagnosis of SPS should be questioned.

CASE REPORT

The patient, a 49-year-old female, was referred by her general practitioner to the outpatient department of Vilnius University Hospital Santaros Clinics (VUHSC) in September 2018 for an urgent neurological consultation for suspected multiple sclerosis. She complained of severe pain in the right leg, muscle tightness, hardening of the muscles and inability to bend her legs

at the knee joint and inability to walk. The patient's initial complaints first occurred in February 2018 as inability to walk after prolonged fatigue. She furtherly describes a sense of "Déjà vu" up to ten times per day Occurring for more than 10 years previously. Examination showed intact cranial nerves, intact tendinous reflexes although possibly hyperreflexic, with a tendency of the right leg to show Babinski's sign. Muscle tone of the arms is normal, while the right hamstrings show episodic increase of tension. The left leg muscles show decreased tone and difficulty with pain in active and passive flexion, which partially resolves when lying down. No sensory disturbance is noted.

The patient had strabismus and amblyopia of the right eye since her childhood and was otherwise healthy. She worked as a teacher. In 2008 the patient started experiencing a sense of "Déjà vu" up to ten times per day and was diagnosed with focal temporal epilepsy. Abnormalities of the EEG were documented, and the patient was prescribed carbamazepine 200 mg thrice daily. As the control of the seizures was not satisfactory, the daily dose of carbamazepine was increased to 900 mg by the epileptologist. The frequency of seizures remained at two to three times per month. In 2011 she was diagnosed with diabetes mellitus type I and treated with Insulin with incomplete control of hyperglycemia (ranging from 8 to 16 mmol/l; normal <7.8 mmol/l). The patient started complaining about a progressive gait disturbance after prolonged exertion in February 2018. In April 2018 she has been consulted by a neurologist and has been diagnosed with lumbago and sciatic neuralgia. Treatment with baclofen and NSAIDS (although not well tolerated) was prescribed but ineffective. Symptoms fluctuated and were exacerbated with repetitive stress. The brain magnetic resonance imaging (MRI) was done in an outpatient setting; results: no change in the intensity of signal in the brain; the cisterna quadrigemina was not markedly dilated; the fourth ventricle was medium-sized and showed no midline shift; the third and lateral ventricle were of medium size; the third ventricle has a width of 3.5mm (normal: 3.6 ±1.8mm) and the Huckman index was 44mm; the subarachnoid spaces were differentiated; bilateral cochlear and optical nerves were normal; no pathological lesion in retrobulbar region, normal pituitary gland, normal nasal sinuses, normal position of the cerebellar tonsils; the right eye was shaped irregularly. The thoracic MRI showed marked kyphosis and scoliosis mainly at Th6/Th7 level with more expressed degenerative changes in TH2-Th7, the spinal cord was without visible pathological changes, and the spinal and intervertebral canals were free. As electroneurography did not reveal any changes in peripheral nerves, spinal thoracic and brain magnetic resonance imaging (MRI) were without clinical abnormalities, in May 2018 the patient had been diagnosed with somatoform autonomic dysfunction and prescribed escitalopram. Her

condition in terms of gait and painful spasms gradually worsened during summer 2018 and the control of seizures and diabetes was poor. After the aforementioned neurological evaluation in VUHSC in September 2018 the preliminary diagnosis was: a gait and mobility disorder with suspicion of stiff-person syndrome; a symptomatic epilepsy with complex partial seizures, depending on the location of the brain lesion, excluding intractable epilepsy; diabetes mellitus, type I. Oral diazepam 5mg twice daily was initiated and in two days she was admitted into the in-patient department of Neurology at VUHSC for further examination were she was treated for 8 days. Electroneuromyography (ENMG) showed spontaneous discharges in both antagonistic muscles in both legs observed at rest and during voluntary flexion or extension of the foot which resolved after an intramuscular injection of 10 mg diazepam. A positive anti-GAD antibody test of over 500 IU/mL (normal: <5 IU/mL) confirmed the diagnosis of stiff-person syndrome. Diazepam was titrated up to 45 mg, was very well tolerated and the condition improved significantly, she was seizure free, discontinued carbamazepine in February 2019, was independent in her professional and daily activities but noted some difficulties when being in public places (anxiety, phobia to fall).

In July 2019 the patient was investigated for heart arrhythmia after experiencing episodes of low blood pressure, where hyperthyroidism was found. It was treated with two tablets of 5 mg of Methizol thrice daily followed by tapering down the dosage in accordance with endocrinologic schemes.

In August 2019 she was admitted to the neurological department due to worsening of the gait disturbance and painful muscle spasms. On arrival the patient was conscious, oriented, and aware; arm strength was graded 5 out of 5 in MRC scale; the muscle tone was symmetrical and normal; deep tendon reflexes in arms were symmetrical; the patient was able to walk independently with some limitations, mild spasticity was observed when lying down; proximal leg strength was 4 out of 5 points, distally 5 out of 5 points; during leg movements there was tension in both the tensors and flexors; Babinski reflex was negative; there was no sensory impairment and no meningeal symptoms; somatic examination was unremarkable: the skin and mucous membranes were without rashes, the tongue was moist; blood pressure wass 110/70 mmHg (normal <120/<80 mmHg) and a heart rate of 66 bpm (normally between 60 and 100 bpm); on lung auscultation there was vesicular wheezing heard on both sides without rales; respiratory rate was 13 breaths per minute (normally between 12 and 20 breaths per minute); no renal succussion signs and no leg oedema. An EEG showed sparse peaked waves, which were more pronounced in the right temporal region; there were more abundant peak

alpha waves in the right temporal region; the recovery of background activity was good after functional testing; no epileptiform or paroxysmal activity was recorded

The final diagnosis was: Stiff-person syndrome associated with glutamic acid decarboxylase alpha antibodies, symptomatic epilepsy and epileptic syndromes with complex partial seizures, depending on the location of the brain lesion, excluding intractable epilepsy; spastic paraplegia, partial, chronic; type I diabetes mellitus with unspecified complication. Treatment during the stay was *Tresiba* (insulin) 12-14 units in the evening, *Humalog* (insulin) 4-5 units before meals, diazepam 10 mg three times per day orally, and therapeutic plasmapheresis. Therapeutic plasmapheresis was a choice of immunotherapy for this deterioration episode, was well tolerated and successful as the daily dose of diazepam decreased to 30 mg. On discharge there was no significant change in objective symptoms, with a slight improvement of general weakness. Due to the patient's symptoms being controlled satisfactorily at the time by 30-35 mg diazepam per day, it was decided to abstain from immunomodulatory therapy for at least 6 months. Recommendations for future treatment were pulse taking twice per day, oral diazepam in a scheme of 10 mg in the morning, afternoon, and evening, Tresiba 12-16 units in the evening, and 2-6 units of Humalog in the morning, 6-8 units at lunch, and 2-6 units in the evening. A follow-up with a neurologist after 6 months or if the condition worsens, and a follow-up by the family doctor is recommended.

In January 2020 the patient experienced a generalized epileptic seizure with fall and co-occurrence of right distal radius fracture. After several weeks she was treated in the endocrinologic department of VUHSC for a total of seven days. She presented due to poor glycemic (2,8-18 mmol/l) and thyroid control. Her methizol dosage was lowered to 5mg twice daily. She was examined and educated on nutrition and insulin therapy. Additional history included regular menstruation and two births, one at 3000g and one at 3500g. Her mother has had thyroiditis.

Condition assessment on arrival 2020-01-28: the patient's height was 164cm, weight 57kg, waist circumference 85cm, BMI of 21.2m²/kg; her general condition was moderate; conscious, contactable, and oriented; skin and mucous membranes were without rashes, and tongue was moist; heart sounds were rhythmic without extra sounds; blood pressure was 120/70 mmHg (normal: <120/<80 mmHg) and heart rate 70 bpm (normal: between 60 and 100 mmHg); lung sounds were vesicular without rales, respiratory rate was 14 breaths per minute (normal between 12 and 20 breaths per minute); renal percussion sign was negative on both sides, and no edema in the legs; dorsalis pedis pulse is palpable bilaterally; deep and

superficial senses are intact; diabetic foot examination was within normal limits. An ultrasound of the thyroid showed inhomogeneous tissue with locally reduced echogenicity and increased blood flow. Several nodes with cystic degenerations were observed on both sides. Dimensions are 14.7 mm by 14.6 mm by 41.7 mm of the left lobe and 17.7 mm by 16.9 mm by 40.7 mm of the right lobe (normal values are approximately 8-16 mm by 10-18 mm by 40-48 mm) Nodules were without signs of malignancy.

The patient was additionally diagnosis with Thyrotoxicosis with toxic multinodular goiter.

Laboratory tests: Capillary blood glucose tests were carried out multiple times a day, with most days being above 7.8 mmol/L.

For treatment the patient was hospitalized for training of diabetic control, treatment correction and complication detection. Insulin doses were adjusted, glycemia improved and episodes of hypoglycemia were rarely recorded. Lipoic acid intravenous infusions were used to treat diabetic polyneuropathy. With improvement of glycemia and the completion of investigations and treatment plan, the patient was discharged for further outpatient treatment. Treatment included: 1) appropriate diet; 2) continued insulin therapy: *Humalog* 5-6 IU before breakfast, 6 IU before lunch, 3-5 IU before dinner (dosage dependent on dietary carbohydrate intake and fasting glycemia). In case of hyperglycemia, increasing the fasting dose to 30 IU/day was recommended. 3) *Tresiba* 15 IU in the evening (dose to be adjusted according to morning glycemia). In case of hyperglycemia increase to 20 IU/day. 4) *Methizol* 2 tables of 5 mg twice daily. Diazepam 30mg per os. One tablet of 600 mg lipoic acid per day. 5) Glycemic self-monitoring: measuring of glycemia in the morning, fasting glucose <7mmol/l, after two hours <8.5mmol/l at fasting, no hypoglycemia. 5) Follow-up of by family physician for comorbidities; HbA1c control every three months with a target HbA1c <7%, lipogram control, examination for diabetic comorbidities including an ophthalmologist consultation, creatinine levels, and urine albumin/creatinine ration. 6) Endocrinologist consultation according to place of residence after one month for control of hyperthyroidism treatment.

The patient’s condition at discharge was satisfactory though as she had experienced an epileptic seizure after which the diazepam dose was increased to 35 mg per day. She complained of ongoing worsening of gait and painful muscle spasms. in February 2020 the patient was treated for a week at in-patient department of VUHSC with plasmapheresis. An EEG was conducted. It showed moderate amplitude synchronized alpha-beta background activity at 12-18 Hz well-modulated. IFS was normal, recovery of background activity was good after functional testing. Interhemispheric asymmetry, epileptiform activity or

paroxysmal activity was not recorded. An increase in cortical bioelectrical excitability was noted. There were no changes during clinical examination except for marked asthenisation.

Treatment during her stay consisted of the patient's continued insulin regimen, 40 mg of diazepam per day, lipoic acid 600 mg per os, thiamazole 5 mg per os. 5 plasmapheresis procedures were performed. The patient's condition at discharge was satisfactory. General weakness and muscle stiffness decreased slightly during treatment. Plasmapheresis was well tolerated.

From May 2020 to March 2022 the patient did not undergo any significant exacerbations nor epileptic seizures and was monitored by general practitioner and local neurologist, maintaining the stable dosages of medications prescribed.

In March 2022 the patient presented again in an outpatient setting at VUHSC for a follow-up with referral from the family doctor. The patient reported a general improvement over the last 3.5 years as she was continuing her job as a teacher and active in her daily settings. Though she complained of episodic stiffness in the waist, buttocks, and leg muscles. The stiffness became worse after walking, climbing stairs, walking in high heels, and in open spaces such as crossing a street. At that point the stiffness made it hard to initiate movement, and the patient would bend forward at the waist and become afraid of falling over – although she had not fallen in two years. The condition worsened under emotional stress or after physical exertion. The patient also complained of increased anxiety that would occur with the stiffness, although she noted that the anxiety levels were better than they were four to five years ago. She did not report a depressed or otherwise altered mood. She did not report any daytime sleepiness or sudden episodes of falling asleep. She has had no recurrence of epileptic seizures for the past 2 years. Her diabetic control was inappropriate, with frequent hypoglycemic episodes. Glycemia fluctuated between 3 and 20 mmol/L daily. It is noted that after the last visit at the endocrinologist she was no longer treated for multinodular goiter and thyrotoxicosis. The patient tolerates the prescribed diazepam well. She was evaluated for anxiety and depression according to Hospital Depression and Anxiety Scale, with an anxiety score of 10 and depression score of 4-5 (normal is 0-7 for both). Sleepiness on the Epworth Sleepiness Scale was 9 points (normal <10). Another EEG was conducted, which showed symmetrical, regularly modulated, moderate-amplitude beta frequency activity. The R-force is age-appropriate, and not expressed for IFS. There are repeated episodes of rhythmic delta-frequency waves in the right frontotemporal region. They are overlaid by the same background beta frequency activity. There were no typical epileptic potentials recorded

during the study. Treatment shall be continued with 40 mg of diazepam per day. Treatment by an endocrinologist and diabetic control is recommended, as well as consultation by a neurologist every six months.

CONCLUSIONS

Stiff-person syndrome is a rare disorder characterized by episodic stiffness of the axial muscles with painful superimposed episodic spasms. Spasm can be triggered by tactile and auditory stimuli, and symptoms may be exacerbated emotional stress. Patients develop gait problems and fear of falling over, which disables them in daily life activities and carries task-specific phobias as a consequence. Despite being a rare condition, it should be included in the differential diagnosis of psychogenic movement disorders due to the condition posing a significant impact on the quality of life of the patient and a relatively long period of time passing from the onset of symptoms to the correct diagnosis. An enduring question is the pathogenesis of stiff-person syndrome, as there is a significant number of patients who have a clinical syndrome much like SPS but will not have any antibodies to currently known antigens. This does not necessarily suggest that there is not autoimmune process at work, it is possible that there are undiscovered antigens that are associated with SPS.

The case report is of a 49-year-old female presenting with type I diabetes mellitus, hyperthyroidism, epilepsy and undefined movement disorders. She complained of inability to walk, pain, and muscle tightness. Her symptoms significantly improved after a repeat visit a year later, where diazepam was given and subsequently prescribed. After an admission to the neurological department another year later due to worsening of symptoms, an anti-GAD antibody test was performed and showed highly increased levels, which lead to the diagnosis of SPS. She was released under an increased diazepam regimen, and eventually returned for a worsening condition. Several courses of plasmapheresis were well tolerated and alleviated her symptoms. During the most recent follow-up in an outpatient setting the patient still complains of stiffness and rigidity, but notes that the condition improved over the last years of treatment and considers herself generally quite stable. Treatment with diazepam will be continued with consultation by a neurologist every six months.

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