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***Observational Study***

**Association of stiff-person syndrome with autoimmune endocrine diseases**

Lee YY *et al*. Stiff-person syndrome with other autoimmune diseases

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**Abstract**

***BACKGROUND***

Stiff-person syndrome (SPS) and its subtype, stiff limb syndrome (SLS), are rare neurological disorders characterized by progressive muscular rigidity and spasms. Glutamic acid decarboxylase (GAD) is the enzyme that catalyzes the production of γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter of the central nervous system. SPS is an autoimmune disease triggered by anti-glutamic acid decarboxylase antibody (anti-GAD Ab). Clinically, anti-GAD Ab is associated with SPS, type 1 diabetes mellitus (T1DM), and other autoimmune diseases.

***AIM***

To investigate the link of autoimmune endocrine disorders with anti-GAD Ab in SPS subjects.

***METHODS***

This retrospective study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan. We collected the patients with SPS from January 2001 to June 2018. By reviewing 14 patients from medical records, we analyzed the clinical findings with coexisting autoimmune diseases, particularly diabetes mellitus and thyroid disease, which are associated with anti-GAD antibody titers or other immunological test results (anti-thyroid peroxidase and anti-nuclear antibodies). We also evaluated malignancies, major complications, and reported treatment to improve symptoms. Anti-GAD antibodies were measured using radioimmunoassay and enzyme-linked immunosorbent assay (ELISA). The cut-off values of these tests are <1 U/mL and <5 U/mL, respectively.

***RESULTS***

The median age of all patients was 39.3 (range, 28.0-54.0) years with a median follow-up period of 6.0 (2.7-13.3) years. Five (35.7%) patients were female; twelve (85.7%) were diagnosed with classic SPS and two (14.3%) with SLS. The median age of onset of symptoms was 35.0 (26.0-56.0) years with a median follow-up duration of 9.0 (2.1-14.9) years in the classic SPS group; the SLS group had a median age of onset of 46.7 years and a shorter follow-up duration of 4.3 years. Among nine classic SPS patients who underwent the anti-GAD Ab test, three were anti-GAD Ab seropositive and each of these three patients also had T1DM, latent autoimmune diabetes in adults, and autoimmune thyroid disease, respectively. In contrast, other rare autoimmune diseases co-existed in six anti-GAD Ab seronegative SPS patients. None of the SLS patients had additional autoimmune diseases.

***CONCLUSION***

While typical clinical symptoms are crucial for the diagnosis of SPS, the presence of anti-GAD autoantibody may consolidate the diagnosis and predict the association with other autoimmune diseases.

**Key words:** Stiff-person syndrome; Glutamic acid decarboxylase antibody; Autoimmune disease; Type 1 diabetes mellitus; Latent autoimmune diabetes in adults; Autoimmune thyroid disease

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**Core tip:** Stiff-person syndrome (SPS) is an uncommon disorder that causes significant disability. Presence of typical clinical symptoms and anti-glutamic acid decarboxylase antibody are important clues for diagnosis. Several autoimmune diseases can be screened with related autoantibodies in SPS patients, and early diagnosis and appropriate treatment are significant to improve the prognosis of SPS. Recognizing these comorbid conditions can help avoid missing or delaying diagnosis in SPS patients.

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**INTRODUCTION**

Stiff-person syndrome (SPS) is a rare neurological disorder, which is an autoimmune disorder frequently associated with the presence of serum anti-glutamic acid decarboxylase (GAD) antibody (anti-GAD Ab). GAD is an endogenous enzyme that catalyzes the production of γ-aminobutyric acid (GABA), a major neurotransmitter of the central nervous system, and it is also found in pancreatic beta cells. The presence of the autoimmune anti-GAD Ab may lead to disruption of neuron and beta cell function[1]. Solimena *et al*[1] was the first to describe the important link between insulin-dependent diabetes mellitus, epilepsy, and SPS in 1988. Anti-GAD Ab is highly directed against GABAergic neurons, making it a useful marker for diagnosis of insulin-dependent diabetes mellitus, epilepsy, and SPS[1]. Another antibody to γ-aminobutyric acid receptor-associated protein (anti-GABARAP Ab) was first linked to SPS by Raju in 2006[2]. Researchers provided the clinical criteria for the diagnosis of classic SPS in 2009: (A) SPS characterized by progressive muscle stiffness, rigidity, and spasm involving the axial muscles, resulting in severely impaired ambulation; (B) Precipitated by sudden movement, noise, or emotional upset; (C) Confirmation of clinical and electromyography for continuous motor unit activity in agonist and antagonist muscles; (D) Absence of other neurological disorder that could lead to rigidity and stiffness; (E) Presence of GAD-65 autoantibody assessed by immunocytochemistry, radioimmunoassay (RIA), or Western blot; and (F) Response to diazepam treatment[2]. Barker *et al*[3] categorized SPS into three subgroups: classic SPS, stiff limb syndrome (SLS), and progressive encephalomyelitis with rigidity and myoclonus (PERM). SLS may start focally from one lower limb, while PERM is a more generalized disorder with prominent brain stem involvement and rapid progression with autonomic disturbances[3]. Around 5% of SPS patients have a paraneoplastic manifestation that more prominently affects the arms and neck[4]. Furthermore, two other autoantibodies have been linked to paraneoplastic SPS: anti-amphiphysin and anti-gephyrin[5].

SPS is strongly associated with other autoimmune diseases, such as type 1 diabetes mellitus (T1DM), autoimmune thyroid disease (AITD), pernicious anemia, vitiligo, and Sjögren syndrome[6], with symptoms ranging from mild to severe and the potential of developing into a significant disability[2]. In the present study, we reported the presence of various autoantibodies and the association with autoimmune disease including T1DM, AITD, Sjögren syndrome, and myasthenia gravis in a series of patients with clinical features of SPS.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH) in Taiwan. Patients diagnosed with SPS in CGMH from January 2001 to June 2018 were enrolled. Diagnosis of SPS was confirmed independently by a neurologist based on typical clinical symptoms (muscular rigidity in the axial muscles and episodic painful spasms induced by external stimuli such as noises, tactile, and stress), electromyogram with normal neuroimaging, response to diazepam treatment, and presence of anti-GAD Ab, according to Dalakas’[4] criteria in 2009. The patients were divided into two groups: classic SPS and focal SLS, and then were analyzed for demographic characteristics, clinical features, exacerbating factors, and neurological or psychiatric features. We also explored the presence of coexisting diseases associated with anti-GAD Ab, such as T1DM, AITD, or other immunological abnormalities. Coexisting malignancies, major complications, and medical treatment were also recorded. Initial anti-GAD Ab was measured by radioimmunoassay using a commercial kit (RSR, Cardiff, United Kingdom) with a cutoff value of <1 U/mL. Follow-up levels of anti-GAD Ab were measured by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (RSR, Cardiff L, United Kingdom) with a cutoff value of <5 U/mL.

The demographic and clinical characteristics of the patients studied are presented as numbers with percentages for categorical variables and medians and interquartile ranges for continuous variables. SPSS 22.0 statistical software (IBM Corporation, United States) was used for all analyses.

RESULTS

A total of 14 patients with clinical features of SPS were enrolled, with a median follow-up duration of 6.0 (range, 2.7-13.3) years. The median age of onset of all patients was 39.3 (28.0-54.0) years, and five (35.7%) patients were female. Twelve (85.7%) patients were diagnosed with classic SPS and two (14.3%) had SLS. Clinical features, exacerbating factors, and neurological or psychiatric features according to the types of symptoms are listed in Table 1.

As shown in Table 1, the median age of onset of symptoms was 35.0 (26.0-56.0) years with a median follow-up duration of 9.0 (2.1-14.9) years in the classic SPS group. Two patients in the SLS group were older than those in the classic SPS group, with a median age of onset of 46.7 years and a shorter follow-up period (4.3 years). All 12 patients with classic SPS had stiffness and painful spasms in the axial muscles with progression to the proximal leg muscles, and all had symptoms induced by cold, noises, or emotional stress. However, only ten out of twelve classic SPS patients had gait disturbances, and eight out of twelve experienced falls. In addition, among twelve patients with classic SPS, two had a history of seizures, twowere diagnosed with Parkinsonism, two had Alzheimer’s disease, and two had panic disorder. Some patients also showed symmetric spine deformity or hyperlordotic spine with limited flexibility. Two patients with SLS had gait disturbances and suffered from a fall. Furthermore, four classic SPS patients and one SLS patient had depression disorder, and seven classic SPS patients and one SLS patients had anxiety.

Table 2 shows the association of SPS with autoimmune diseases and the presence of autoantibodies. Among nine patients examined for anti-GAD Ab, three (33.3%) were positive for anti-GAD Ab and all had classic SPS. None of SLS patients were positive for anti-GAD Ab or any other autoimmune disease. As summarized in Table 3, T1DM and AITD were common among anti-GAD Ab seropositive patients. For example, one case each of T1DM, latent autoimmune diabetes in adults (LADA) coexisting with AITD, and AITD was found among three GAD Ab seropositive patients. An additional patient lost follow-up in our hospital was later diagnosed with T1DM without known anti-GAD Ab data. Of six patients who were negative for anti-GAD Ab, none had autoimmune diabetes or AITD; however, one had Sjögren syndrome (ANA positive and anti-Ro antibody positive), one had myasthenia graves (Ach-R antibody positive), two had neoplasms (1 lung cancer with paraneoplastic syndrome and 1 thymoma) found in classic SPS, and one SLS patient had type 2 diabetes mellitus (T2DM, onset at age 39 with insulin injection since age 49 years but with normal C-peptide level by that time).

We summarize our two cases with concomitant autoimmune diabetes mellitus and SPS in Table 4, with one T1DM and one LADA. Case 1 is a 43-year-old woman who had SPS at age 32 and was diagnosed with T1DM with diabetic ketoacidosis at age 43. The initial anti-GAD Ab level was 1496 U/mL by RIA method, while it became >2000 U/mL by ELISA when followed for the onset of T1DM and progression of symptoms. The second case is a 43-year-old man initially diagnosed with T2DM and treated with oral anti-diabetic drugs. LADA was suspected because the patient became insulin dependent at age 42 due to poor sugar control with frequent diabetic ketoacidosis. A glucagon-stimulated test demonstrated relative insulin deficiency (basal and stimulated C-peptide levels were 0.26 and 0.41 ng/mL, respectively). He was diagnosed with SPS at age 33 with an initial anti-GAD Ab level of 110 U/mL by RIA, and the later follow-up of antibody titer for the progression of symptoms and LADA showed that it became >2000 U/mL by ELISA. He also showed positive thyroid autoantibody (anti-TPO), indicating a coexisting autoimmune thyroid disease. Both patients received diazepam and other GABAergic treatment initially; however, plasmapheresis was required for episodic progression of refractory symptoms. The patient with coexisting LADA also received intravenous immunoglobulin (IVIG) therapy before plasmapheresis but was only temporarily relieved.

DISCUSSION

Rigidity and muscle stiffness in the axial and proximal limb area are early symptoms of SPS. When SPS progresses, the lumbar paraspinal muscles fluctuate between rigidity and fixed deformity, with the characteristic hyperlordosis limiting the range of truncal flexion[2]. The stiffness progresses slowly from the trunk up to the proximal limb, leading to walking difficulty, gait imbalance, and eventual increased risk of falls and fractures[7]. The rigidity is also accompanied by intermittent muscle cramps and painful spasms which are induced by external or internal stimuli (noises, touch, sudden movement, emotional upsets, and stress)[6,8,9]. Facial muscle involvement, although rare, gives rise to a mask-like appearance. If stiffness affects the thoracic muscles, chest expansion is restricted with breathing difficulty[10]. Ocular abnormalities, including misalignment, nystagmus, and horizontal diplopia, may be caused by the depletion of GABA[11]. Most of our patients suffered from classic SPS, all patients experienced lower limb stiffness and spasm, while lower back, abdominal area, and upper limb stiffness happened only in classic SPS. All symptoms were induced by cold, noises, or emotional stress. Around 86% of total patients had gait disturbances (83.3% classic SPS vs 100% SLS), and 71.4% experienced falls (66.7% classic SPS vs 100% SLS). In terms of psychiateric features, 35.7% of total patients had depression (33.3% classic SPS vs 50% SLS), 57.1% had general anxiety (58.3% classic SPS vs 50% SLS), 14.3% had panic disorder, which was only found in classic SPS (16.7%). About 14.3% of total patients had neurological syndrome such as epilepsy, parkinsonism and Alzheimer’s disease, those were investigated in classic SPS. Although not described in this study, some patients have been reported to exhibit autonomic dysfunction, comprising diaphoresis, tachycardia, tachypnea, pupil dilatation, hypertension, and hyperthermia[12]. Sudden death occurs in approximately 10% of patients with life-threatening autonomic failure[8,13]. Clinicians treating SPS patients need to be aware of the frequent psychiatric symptoms, such as anxiety[14], depression[15], panic disorder[16], specific phobia[17], and eating disorder[18]. A startle response to unexpected stimuli is also common and appears similar to phobic disorders, which may lead to misdiagnosis of a psychiatric disease. Whether these phobias are primarily associated with reduced GABA levels or secondary to the physical disability remains to be investigated[19].

SPS has an estimated prevalence rate of 1 per million per year and classic SPS affects women twice as many as men, almost all in the 20-60 year range (median age is 40 years)[9]. The incidence rate remains very low because the diagnosis of SPS is difficult in clinical practice, with only about 60%-80% of classic SPS cases seropositive for anti-GAD Ab[2]. In addition to SPS, anti-GAD Ab has also been associated with cerebellar ataxia[20,21], epilepsy (10%-20% positive for anti-GAD Ab)[1,22], limbic encephalopathy[9], myasthenia gravis[23], myoclonus[20], neuromyotonia, and Batten’s disease[2]. In addition, SPS is strongly associated with other autoimmune diseases, with up to 30%-40% also having T1DM[24].Although we do not know the incidence of SPS in Taiwan, a total of 14 SPS patients were diagnozed in a medical center during a period of 17.4 years. Again, even though the seropositive rate of anti-GAD Ab was not sure, we detected anti-GAD Ab in three out of seven SPS patients. Consistent with the previous finding that the presence of high GAD Ab levels may associate with concomitant T1DM and other autoimmune endocrine diseases[21], the anti-GAD Ab titers of the two patients in our series rose significantly when they developed T1DM and LADA.

The role of autoimmunity against GAD in the pathogenesis of SPS and T1DM remains unclear. GAD is the rate-limiting enzyme in the synthesis of GABA, an inhibitory neurotransmitter in the central nervous system and pancreatic beta cells[9,25,26]. The two isoforms of GAD, GAD67 and GAD65, differ in molecular size and amino acid sequence[27]. GAD67 and GAD65 proteins are homologous products encoded by the GAD1 gene located on chromosome 2q31 and the GAD2 gene located on chromosome 10p11.23, respectively. There are three functional domains in the linear sequence of GAD isoforms: (A) Amino (N)-terminal domain - amino acid (aa) 1-188 in GAD65 and aa 1-197 in GAD67; (B) The middle part of pyridoxal 5′-phosphate (PLP) that contains the active catalytic site of the enzyme (aa 189-464 in GAD 65 and aa 198-473 in GAD67); and (C) The carboxyl (C)-terminal domain (aa 465-585 in GAD65 and aa 474-594 in GAD67). Overall, these two isoform sequences are 74% homologous in the middle part and at the C-terminal segment, but differ in the N-terminal segment that is mainly located in the first 100 aa, comprising only 25% of its identity[9,28]. Physiologically, GAD67 catalyzes the steady-state production of GABA in the cytoplasm and GAD65 catalyzes the pulse production of GABA on demand in synaptic vesicles[29], therefore, deficiencies in GABA synthesis lead to hyper-excitability of neurons and cause muscle spasms in SPS[28]

GAD65 is a common autoantigen in SPS and T1DM, and the triggered immune response not only impairs neurotransmission, but also destructs insulin secretion[30]. GAD65 autoantibodies are detected in 80% of patients with newly diagnosed T1DM; but the titer of anti-GAD Ab is much higher (around 50-100 fold) in SPS than in T1DM[26,31,32]. The epitopes are different in the two autoantibodies; in T1DM, the conformational epitopes are located in the C-terminal and part of the PLP of GAD65. In contrast, autoantibodies of SPS recognize a linear N-terminal epitope in GAD65[24,33], which have been demonstrated to block the enzyme activity[33,34]. Apart from this, patients with SPS have anti-GAD65 antibodies against a linear epitope in the N-terminal segment, especially within the first 100 aa, which is not found in T1DM[28]. About 50%-60% of SPS patients have anti-GAD67 Ab, while about 10% of T1DM patients have anti-GAD67; this may represent cross-reactivity against GAD65[9,28]. Meanwhile, the anti-GAD Ab isotype can reflect the type of T helper cell response, with one study demonstrating a restriction of islet cell antibody to the IgG1 subclass in T1DM, and this finding indicates that patients with SPS respond at the cellular level to GAD 65 *via* epitope recognition, whereas those with T1DM have a humoral response *via* the isotype pattern[35]. Furthermore, the CTLA-4 gene also shares a susceptibility locus for T1DM and AITD[36].

In addition to T1DM, about 5%–10% of SPS patients also have AITD, Graves’ disease, pernicious anemia, or vitiligo[25]. Moreover, SPS and a spectrum of anti-GAD ab positive neurologic disorders are also associated with autoimmune polyglandular syndrome type 1 (APS1) and type 2 (APS2). APS1 includes muco-cutaneous candidiasis, hypoparathyroidism, and Addison’s disease, but is less frequently associated with T1DM, Hashimoto’s thyroiditis, or chronic hepatitis. APS2 consists of Addison’s disease plus either AITD or T1DM, and is associated with hypogonadism, pernicious anemia, celiac disease, and primary biliary cirrhosis[34,37]. It has been observed that autoimmune diabetic patients with a higher anti-GAD-Ab titer may also have higher prevalence of anti-TPO antibodies and a higher risk of thyroid autoimmunity[36,38]. As it has been reported that the presence of AITD may be associated with an insulin secretion defect in both T1DM and T2DM and the rarity of the alternative forms of autoimmune diabetes, such as LADA, with SPS[39], we report one case of SPS with T1DM, one case of SPS concomitant with LADA and AITD, and a third case of SPS coexisting with AITD but without DM in our series. Whether a longer time is needed for the third case to develop DM is still unknown, because the progressive β-cell failure has been reported in the literature[40].

DR and DQ alleles are strongly associated with insulin-dependent diabetes mellitus (IDDM), autoimmune hepatitis, myasthenia gravis, systemic lupus erythematosus, and inflammatory bowel disease[41]. The most frequently detected immunogenetic alleles, DQB1 0201 and DRB1 0301, found in about 70% of SPS patients, also increase susceptibility to IDDM and other autoimmune diseases[41,42]. In contrast, the DQB1 0602 allele is protective for T1DM in SPS patients[42]. Studies in Caucasians suggested that the haplotype DR3-DQB1 0201 may predispose to T1DM and AITD[43]. The DRB1 0405/DQA1 0301/DQB1 0401 haplotype was also significantly increased in patients with both T1DM and AITD in a Taiwan study[44]. Another study observed DQA1 03-DQB1 0401 haplotype in T1DM and AITD, which supported the association with both diseases.

Among the six (4 SPS and 2 SLS) patients negative for anti-GAD Ab, one had Sjögren syndrome, one had myasthenia graves, and two had neoplasms (1 lung cancer with paraneoplastic syndrome and 1 thymoma). One case of T2DM has been known for 16 years and has received insulin treatment since 5.5 years ago at the time of diagnosing SLS. In summary, cancer was rarely reported among anti-GAD Ab seropositive SPS patients. Autoimmune disease like T1DM or AITD was common in anti-GAD Ab seropositive, but uncommon in seronegative patients. Anti-GAD Ab seronegative patients usually had partial SPS (including SLS and PERM), rarely concomitant with other autoimmune disease[45]. T2DM may coincidentally coexist, but not immunologically associated with SPS[46]. A summary of coexisting diseases and their related autoantibodies is shown in Table 5.

Physiotherapy to reduce spastic movement is helpful, but some therapies may also increase muscle tone and spasms. Cognitive behavioral therapy may help reduce the anxiety-related stiffness reported in one case study[47]. Therapeutic consideration is aimed for symptomatic relief and modulation of the autoimmune process. Two main therapeutic approaches, *i.e.* GABA-enhancing drugs and immunomodulating agents, are suggested based on the pathogenesis of SPS. Benzodiazepines is the first line of treatment, and diazepam is prescribed for its muscle relaxant and anxiolytic properties as a GABA-A agonist[48]. Baclofen is used orally with diazepam as GABA-B agonist activity to manage spasticity[49]. Second line GABAergic drugs like gabapentin (similar to GABA), vigabatrin (GABA-transaminase inhibitor), tiagabine (blocks GABA reuptake), and valproate (augments GABA transmission) may improve SPS symptoms. Levetiracetam has been applied to treat with benefit for the symptoms[2]. In addition, tizanidine, an α2-adrenergic receptor (α2-AR) agonist[50], and botulinum toxin (inhibitor of acetylcholine release) were used to treat spasticity[51]. IVIG therapy is efficacious and safe for severe or refractory SPS[52]. Corticosteroids have often been used as monotherapy or in combination with other agents to improve spasms[53]. Other immunomodulating agents such as mycophenolate mofetil, azathioprine, cyclophosphamide, cyclosporine, tacrolimus, and sirolimus may also give variable benefits[2]. Plasmapheresis can improve symptoms with severe SPS in previous studies[54]. And finally, rituximab has been reported to successfully eliminate autoantibody producing B cells in the central nervous system of patients with refractory SPS by rapidly decreasing anti-GAD Ab[55]. All patients received diazepam treatment in our series, and symptoms of the two patients with autoimmune diabetes progressed and eventually improved after receiving series of plasmapheresis; it should be mentioned that the LADA and AITD coexisting SPS patient did not improve with IVIG before plasmapheresis (Table 4).

This retrospective observation study had a couple of limitations. Due to the rarity of SPS and the difficulty in its diagnosis, our sample size was small and not all patients had received the relevant autoantibody examination.

In conclusion, despite the fact that T1DM and SPS are both autoimmune diseases characterized by the presence of anti-GAD Ab, the rates of co-occurrence of SPS, AITD, and T1DM or LADA remain unknown. Disability in these SPS patients will affect their quality of life; therefore, a better understanding of the natural history, mechanism of disease, clinical course, and treatment for SPS will help physicians optimize treatment. By recognizing the association of SPS with autoimmune diseases and/or malignancy, physicians may predict the development of T1DM and thereby prevent its co-morbidities in SPS patients.

**ARTICLE HIGHTLIGHTS**

***Research background***

Glutamic acid decarboxylase (GAD) is known to synthesize the inhibitory neurotransmitter of γ-aminobutyric acid, and it is also found in the β-cells in the pancreas. Clinically, anti-GAD Ab is associated with stiff-person syndrome (SPS), type 1 diabetes mellitus (T1DM), and other autoimmune diseases.

*Research motivation*

There is still a plausible and unclear mechanism in SPS with autoantibodies and related other autoimmune diseases.

*Research objectives*

To investigate the link of autoimmune endocrine disorders with anti-GAD Ab in SPS subjects.

*Research methods*

Patients with SPS collected from January 2001 to June 2018 were retrospectively analyzed. Anti-GAD antibodies were measured using radioimmunoassay and enzyme-linked immunosorbent assay to determine the diagnosis of and association with other autoimmune diseases.

*Research results*

Of the 14 patients, 12 (85.7%) were diagnosed with classic SPS and 2 (14.3%) with stiff limb syndrome (SLS). Among nine classic SPS patients who underwent the anti-GAD Ab test, three were anti-GAD Ab seropositive and each of these three patients also had T1DM, latent autoimmune diabetes in adults, and autoimmune thyroid disease. In contrast, other rare autoimmune diseases co-existed in six anti-GAD Ab seronegative SPS patients. None of the SLS patients had additional autoimmune disease.

*Research conclusions*

The presence of typical clinical symptoms and anti-GAD autoantibody are not only important clues for diagnosis of SPS but also for early detection of this disease and prediction of the association with other autoimmune diseases.

*Research perspectives*

This article reflects that anti-GAD autoantibody may demonstrate the diagnostic accuracy of SPS, although there is a lack of large sample size and unclear mechanism due to rarity. SPS is associated with other autoimmune diseases like T1DM and malignancy, which can cause morbidity and mortality. Further investigation of the link between SPS and T1DM could predict DM and prevent significant disabilities.

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**Table 1 Clinical features of patients with stiff-person syndrome**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Total number** | **Classical SPS** | **SLS** |
| Number of patients (*n*) | 14 | 12 | 2 |
| Male (%) | 9 (64.3) | 7 (58.3) | 2 (100) |
| Age of onset (yr) | 39.3 (28.0-54.0) | 35 (26.0-56.0) | 46.7 |
| Follow-up duration (yr) | 6 (2.7-13.3) | 9 (2.1-14.9) | 4.3 |
| Clinical feature |  | | |
| Low back stiffness and spasm (*n*) | 12 | 12 | 0 |
| Lower limb stiffness and spasm (*n*) | 14 | 12 | 2 |
| Lumbar lordosis (*n*) | 8 | 8 | 0 |
| Neck stiffness and spasm (*n*) | 9 | 9 | 0 |
| Upper limbs stiffness and spasm (*n*) | 10 | 10 | 0 |
| Abdominal wall stiffness and spasm (*n*) | 11 | 11 | 0 |
| Falls (*n*) | 10 | 8 | 2 |
| Exacerbating factors | | | |
| Cold, noises, and emotional stress (*n*) | 14 | 12 | 2 |
| Excessive startle (*n*) | 9 | 8 | 1 |
| Neurological/psychiatric feature | | | |
| Seizure/epilepsy (*n*) | 2 | 2 | 0 |
| Gait disturbances (*n*) | 12 | 10 | 2 |
| Parkinsonism (*n*) | 2 | 2 | 0 |
| Alzheimer’s disease (*n*) | 2 | 2 | 0 |
| Depression (*n*) | 5 | 4 | 1 |
| Anxiety (*n*) | 8 | 7 | 1 |
| Panic disorder (*n*) | 2 | 2 | 0 |

SPS: Stiff-person syndrome; SLS: Stiff limb syndrome; GAD: Glutamic acid decarboxylase.

**Table 2 Autoimmune diseases and autoantibodies associated with stiff-person syndrome**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Classical SPS** | **SLS** |
| Number of patients (*n*) | 12 | 2 |
| Associated disease | | |
| ≥2 coexisting autoimmune diseases (*n*) | 1 | 0 |
| Type 1 diabetes mellitus (*n*) | 2 | 0 |
| Latent autoimmune diabetes in adults (*n*) | 1 | 0 |
| Autoimmune thyroid disease (*n*) | 2 | 0 |
| Sjögren syndrome (*n*) | 1 | 0 |
| Myasthenia graves (*n*) | 1 | 0 |
| Malignancy1 (*n*) | 1 | 0 |
| Thymoma (*n*) | 1 | 0 |
| Other disease (*n*) | 12 | nil |
| Associated autoantibody (*n*/*N*)3 | | |
| GAD antibody | 3/7 | 0/2 |
| IA-2 antibody | 0/2 | nil |
| Anti-TPO | 2/5 | nil |
| ATA | 1/1 | nil |
| Ach-R antibody | 1/1 | nil |
| ANA | 1/1 | nil |
| Anti-Ro antibody | 1/1 | nil |

1One patient had lung cancer. 2One patient had type 2 diabetes mellitus. 3Number of patients positive for the associated antibody/number of patients tested for the associated antibody. SPS: Stiff-person syndrome; SLS: Stiff limb syndrome; GAD: Glutamic acid decarboxylase; IA-2: Islet antigen 2; TPO: Thyroid peroxidase; ATA: Anti-thyroglobulin antibody; AchR: Acetylcholine receptor; ANA: Anti-nuclear antibody.

**Table 3 Correlation of associated diseases and glutamic acid decarboxylase autoantibodies among stiff-person syndrome patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Subgroup** | **Seropositive** | | **Seronegative** | | **Unknown** | |
| **Classical** | **SLS** | **Classical** | **SLS** | **Classical** | **SLS** |
| Patient number | 3 | 0 | 4 | 2 | 5 | 0 |
| Type 1 diabetes mellitus | 1 | 0 | 0 | 0 | 1 | 0 |
| Latent autoimmune diabetes in adults | 1 | 0 | 0 | 0 | 0 | 0 |
| Autoimmune thyroid disease | 2 | 0 | 0 | 0 | 0 | 0 |
| Sjögren syndrome | 0 | 0 | 1 | 0 | 0 | 0 |
| Myasthenia graves | 0 | 0 | 1 | 0 | 0 | 0 |
| Malignancy1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Thymoma | 0 | 0 | 1 | 0 | 0 | 0 |
| Type 2 diabetes mellitus | 0 | 0 | 0 | 1 | 0 | 0 |

1Lung cancer with paraneoplastic syndrome. SPS: Stiff-person syndrome; SLS: Stiff limb syndrome; GAD: Glutamic acid decarboxylase.

**Table 4 Summary of two stiff person syndrome cases associated with autoimmune diabetes**

|  |  |  |
| --- | --- | --- |
|  | **Case 1: T1DM** | **Case 2: LADA** |
| Gender | Female | Male |
| Age of diagnosis of DM | 43 | 30 |
| Age of diagnosis of SPS | 32 | 33 |
| Age of requirement for insulin | 43 | 42 |
| HbA1c at diagnosis of DM (%) | 13.2 | 13.1 |
| Basal C-peptide (ng/mL) | 0.31 | 0.26 |
| Glucagon-stimulated C-peptide (ng/mL) | 0.6 | 0.41 |
| Initial GAD Ab (U/mL) (Ref < 1 units)1 | 1496 (before T1DM) | 110 (before LADA) |
| GAD-Ab titer before receiving plasmapheresis (U/mL) (Ref < 5 units)2 | >2000 (after T1DM) | >2000 (after LADA) |
| GAD-Ab titer after receiving plasmapheresis (U/mL) (Ref < 5 units)2 | >2000 | >2000 |
| IA2 antibody (U/mL) (Ref < 7.5) | 0.97 | 0.65 |
| Anti-TPO (IU/mL) (Ref < 5.6) | <1.0 | 18.81 |
| Medications | Diazepam, clonazepam, baclofen, lamotrigine, azathioprine | Diazepam, clonazepam, baclofen, tizanidine |
| IVIG | No | Yes (IVIG 0.4/kg/d) |
| Plasmapheresis | Yes, 10 times | Yes, 15 times |

1Radioimmunoassay; 2Enzyme -linked immunosorbent assay. SPS: Stiff-person syndrome; T1DM: Type 1 diabetes mellitus; LADA: Latent autoimmune diabetes in adults; GAD: Glutamic acid decarboxylase; IA-2: Islet antigen 2; TPO: Thyroid peroxidase; IVIG: Intravenous immunoglobulin.

**Table 5 Coexisting diseases and related autoantibodies in stiff-person syndrome patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Autoimmune disease** | **Associated antibody** | **Neoplasm** | **Associated antibody** |
| Type 1 DM | Anti-GAD  Anti-IA2 | Breast cancer | Gephyrin |
| LADA | Lung cancer | Amphiphysin |
| Hashimoto’s thyroiditis | Anti-TPO, ATA, anti-TSHR | Thyroid cancer | ATA |
| Graves’ disease | Colon cancer |  |
| Pernicious anemia | Anti-parietal cells | Renal cell carcinoma |  |
| Celiac disease | [Anti-transglutaminase antibodies](https://en.wikipedia.org/wiki/Anti-transglutaminase_antibodies) (anti-tTG), anti-endomysial antibodies | Thymoma | Anti-AchR |
| Myasthenia graves | Anti-AchR | Neuroendocrine tumor |  |
| Sjögren syndrome | ANA, anti-Ro | Hodgkin lymphoma |  |
| Systemic lupus erythematosus | ANA, ds-DNA | Multiple myeloma |  |
| Vitiligo |  |  |  |
| Autoimmune polyglandular Syndrome type 1 or type 2 or type 3 |  |  |  |

DM: Diabetes mellitus; LADA: Latent autoimmune diabetes in adults; GAD: Glutamic acid decarboxylase; IA-2: Islet antigen 2; TPO: Thyroid peroxidase; ATA: Anti-thyroglobulin antibody; AchR: Acetylcholine receptor; ANA: Anti-nuclear antibody; TSHR: Thyroid-stimulation hormone receptor.