

# World Journal of *Clinical Cases*

*World J Clin Cases* 2019 October 6; 7(19): 2916-3167



**REVIEW**

- 2916 DNA methylation detection methods used in colorectal cancer  
*Zhan YX, Luo GH*

**ORIGINAL ARTICLE****Case Control Study**

- 2930 Expression and predictive value of miR-489 and miR-21 in melanoma metastasis  
*Mo H, Guan J, Yuan ZC, Lin X, Wu ZJ, Liu B, He JL*

**Observational Study**

- 2942 Association of stiff-person syndrome with autoimmune endocrine diseases  
*Lee YY, Chen IW, Chen ST, Wang CC*

- 2953 Hyperthyroid heart disease in pregnancy: Retrospective analysis of a case series and review of the literature  
*Shan D, Bai Y, Chen QH, Wu YX, Chen Q, Hu YY*

- 2963 Changes of serum inflammatory factors and miR-145 expression in patients with osteoarthritis before and after treatment and their clinical value  
*Wang XZ, Li WX*

**Prospective Study**

- 2976 Immediate muscle strengthening by an end-effector type gait robot with reduced real-time use of leg muscles: A case series and review of literature  
*Hwang CH*

**Randomized Clinical Trial**

- 2986 Comparison of perceived pain and patients' satisfaction with traditional local anesthesia and single tooth anesthesia: A randomized clinical trial  
*Al-Obaida MI, Haider M, Hashim R, AlGheriri W, Celur SL, Al-Saleh SA, Al-Madi EM*

**SYSTEMATIC REVIEW**

- 2995 Treatment of laryngopharyngeal reflux disease: A systematic review  
*Lechien JR, Mouawad F, Barillari MR, Nacci A, Khoddami SM, Enver N, Raghunandhan SK, Calvo-Henriquez C, Eun YG, Saussez S*

**CASE REPORT**

- 3012 Keratoconus in a patient with Alport syndrome: A case report  
*Moshirfar M, Skanchy DF, Gomez AT, Ronquillo YC, Buckner B, Hoopes PC*

- 3018** Successful multidisciplinary clinical approach and molecular characterization by whole transcriptome sequencing of a cardiac myxofibrosarcoma: A case report  
*Saponara M, Indio V, Pizzi C, Serban ED, Urbini M, Astolfi A, Paolisso P, Suarez SM, Nannini M, Pacini D, Agostini V, Leone O, Ambrosini V, Tarantino G, Fanti S, Niro F, Buia F, Attinà D, Pantaleo MA*
- 3027** Laparoscopic hysterectomy as optimal approach for 5400 grams uterus with associated polycythemia: A case report  
*Macciò A, Chiappe G, Lavra F, Sanna E, Nieddu R, Madeddu C*
- 3033** Malignant sweat gland tumor of breast arising in pre-existing benign tumor: A case report  
*An JK, Woo JJ, Hong YO*
- 3039** Bronchobiliary fistula after ramucirumab treatment for advanced gastric cancer: A case report  
*Kim HB, Na YS, Lee HJ, Park SG*
- 3047** Severe heterotopic ossification in a seronegative spondyloarthritis patient after cervical Bryan disc arthroplasty: A case report  
*Huang CW, Tang CL, Pan HC, Tzeng CY, Tsou HK*
- 3055** Underlying IgM heavy chain amyloidosis in treatment-refractory IgA nephropathy: A case report  
*Wu HT, Wen YB, Ye W, Liu BY, Shen KN, Gao RT, Li MX*
- 3062** Diagnosis of myocardial infarction with nonobstructive coronary arteries in a young man in the setting of acute myocardial infarction after endoscopic retrograde cholangiopancreatography: A case report  
*Li D, Li Y, Wang X, Wu Y, Cui XY, Hu JQ, Li B, Lin Q*
- 3069** Hemophagocytic lymphohistiocytosis complicated by polyserositis: A case report  
*Zhu P, Ye Q, Li TH, Han T, Wang FM*
- 3074** Hair regrowth following fecal microbiota transplantation in an elderly patient with alopecia areata: A case report and review of the literature  
*Xie WR, Yang XY, Xia HHX, Wu LH, He XX*
- 3082** How should congenital absence of cruciate ligaments be treated? A case report and literature review  
*Lu R, Zhu DP, Chen N, Sun H, Li ZH, Cao XW*
- 3090** Kaposi's sarcoma manifested as lower gastrointestinal bleeding in a HIV/HBV-co-infected liver cirrhosis patient: A case report  
*Zhou QH, Guo YZ, Dai XH, Zhu B*
- 3098** Primary renal synovial sarcoma: A case report  
*Cai HJ, Cao N, Wang W, Kong FL, Sun XX, Huang B*
- 3104** Type I neurofibromatosis with spindle cell sarcoma: A case report  
*Zhang Y, Chao JJ, Liu XF, Qin SK*

- 3111** Primary hypoparathyroidism accompanied by rhabdomyolysis induced by infection: A case report  
*Ding LN, Wang Y, Tian J, Ye LF, Chen S, Wu SM, Shang WB*
- 3120** Effects of combined rTMS and visual feedback on the rehabilitation of supernumerary phantom limbs in a patient with spinal cord injury: A case report  
*Lu YS, Tong P, Guo TC, Ding XH, Zhang S, Zhang XJ*
- 3126** Clear cell sarcoma of soft tissue in pleural cavity: A case report  
*Chen YT, Yang Z, Li H, Ni CH*
- 3132** Primary hyperparathyroidism in a woman with multiple tumors: A case report  
*Hui CC, Zhang X, Sun JR, Deng DT*
- 3138** Gastric adenocarcinoma mimicking a submucosal tumor: A case report  
*Cheng XL, Liu H*
- 3145** Hypereosinophilia, mastectomy, and nephrotic syndrome in a male patient: A case report  
*Wu J, Li P, Chen Y, Yang XH, Lei MY, Zhao L*
- 3153** Flapless immediate implant placement into fresh molar extraction socket using platelet-rich fibrin: A case report  
*Sun XL, Mudalal M, Qi ML, Sun Y, Du LY, Wang ZQ, Zhou YM*
- 3160** Advanced primary amelanotic malignant melanoma of the esophagus: A case report  
*Zhang RX, Li YY, Liu CJ, Wang WN, Cao Y, Bai YH, Zhang TJ*

**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Enver Zerem, MD, PhD, Professor, Department of Medical Science, Academy of Sciences and Arts of Bosnia and Herzegovina, University Clinical Centre Tuzla, Tuzla 75000, Bosnia and Herzegovina

**AIMS AND SCOPE**

The primary aim of *World Journal of Clinical Cases (WJCC, World J Clin Cases)* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

*WJCC* mainly publishes case reports, case series, and articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics including diagnostic, therapeutic, and preventive modalities.

**INDEXING/ABSTRACTING**

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for *WJCC* as 1.153 (5-year impact factor: N/A), ranking *WJCC* as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Xiang Li*

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Semimonthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Bao-Gan Peng, Sandro Vento

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/2307-8960/editorialboard.htm>

**EDITORIAL OFFICE**

Jin-Lei Wang, Director

**PUBLICATION DATE**

October 6, 2019

**COPYRIGHT**

© 2019 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjnet.com/bpg/gerinfo/240>

**PUBLICATION MISCONDUCT**

<https://www.wjnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Observational Study

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

Yi-Yin Lee, I-Wen Chen, Szu-Tah Chen, Chih-Ching Wang

**ORCID number:** Yi-Yin Lee (0000-0002-0422-3434); I-Wen Chen (0000-0002-8928-6417); Szu-Tah Chen (0000-0003-2262-1775); Chih-Ching Wang (0002-8222-0503).

**Author contributions:** Lee YY wrote the manuscript, analyzed the data, and contributed to discussion; Wang CC analyzed the data and contributed to discussion; Chen IW and Chen ST contributed to discussion and reviewed/edited the manuscript; Wang CC is the guarantor of this work, has full access to all the data in the study, and takes responsibility for the integrity of the data.

**Institutional review board**

**statement:** The study was reviewed and approved by the Chang Gung Memorial Hospital Institutional Review Board.

**Informed consent statement:**

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and informed consent was not required because that data was drawn from observing behavior and did not contain identifiable information.

**Conflict-of-interest statement:** The authors report no relevant conflicts of interest.

**Data sharing statement:** The authors confirm that the data supporting the findings of this study are available within the article.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the

Yi-Yin Lee, I-Wen Chen, Szu-Tah Chen, Chih-Ching Wang, Department of Internal Medicine, Division of Endocrinology and Metabolism, Chang Gung Memorial Hospital, Taoyuan City 333, Taiwan

**Corresponding author:** Chih-Ching Wang, MD, Attending Doctor, Endocrinologist, Department of Internal Medicine, Division of Endocrinology and Metabolism, Chang Gung Memorial Hospital, No. 5, Fuxing Street, Guishan District, Taoyuan City 333, Taiwan.

[p122020223@cgmh.org.tw](mailto:p122020223@cgmh.org.tw)

**Telephone:** +886-3-3281200

**Fax:** +886-3-3288257

**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  $\gamma$ -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**

manuscript was prepared and revised according to the STROBE Statement-checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Received:** June 27, 2019

**Peer-review started:** June 29, 2019

**First decision:** July 31, 2019

**Revised:** August 14, 2019

**Accepted:** August 27, 2019

**Article in press:** August 27, 2019

**Published online:** October 6, 2019

**P-Reviewer:** Gabriel S

**S-Editor:** Zhang L

**L-Editor:** Wang TQ

**E-Editor:** Li X



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

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

**Citation:** Lee YY, Chen IW, Chen ST, Wang CC. Association of stiff-person syndrome with autoimmune endocrine diseases. *World J Clin Cases* 2019; 7(19): 2942-2952

**URL:** <https://www.wjnet.com/2307-8960/full/v7/i19/2942.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v7.i19.2942>

## 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  $\gamma$ -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<sup>[1]</sup>. Solimena *et al*<sup>[1]</sup> 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<sup>[1]</sup>. Another antibody to  $\gamma$ -aminobutyric acid receptor-associated protein (anti-GABARAP Ab) was first linked to SPS by Raju in 2006<sup>[2]</sup>. 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<sup>[2]</sup>. Barker *et al*<sup>[3]</sup> 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<sup>[3]</sup>. Around 5% of SPS patients have a paraneoplastic manifestation that more prominently affects the arms and neck<sup>[4]</sup>. Furthermore, two other autoantibodies have been linked to paraneoplastic SPS: Anti-amphiphysin and anti-gephyrin<sup>[5]</sup>.

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<sup>[6]</sup>, with symptoms ranging from mild to severe and the potential of developing into a significant disability<sup>[2]</sup>. 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<sup>[4]</sup> 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, two were 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

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

Characteristic	Total number	Classical SPS	SLS
Number of patients ( <i>n</i> )	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 ( <i>n</i> )	12	12	0
Lower limb stiffness and spasm ( <i>n</i> )	14	12	2
Lumbar lordosis ( <i>n</i> )	8	8	0
Neck stiffness and spasm ( <i>n</i> )	9	9	0
Upper limbs stiffness and spasm ( <i>n</i> )	10	10	0
Abdominal wall stiffness and spasm ( <i>n</i> )	11	11	0
Falls ( <i>n</i> )	10	8	2
Exacerbating factors			
Cold, noises, and emotional stress ( <i>n</i> )	14	12	2
Excessive startle ( <i>n</i> )	9	8	1
Neurological/psychiatric feature			
Seizure/epilepsy ( <i>n</i> )	2	2	0
Gait disturbances ( <i>n</i> )	12	10	2
Parkinsonism ( <i>n</i> )	2	2	0
Alzheimer's disease ( <i>n</i> )	2	2	0
Depression ( <i>n</i> )	5	4	1
Anxiety ( <i>n</i> )	8	7	1
Panic disorder ( <i>n</i> )	2	2	0

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

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 gravis (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

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

Variable	Classical SPS	SLS
Number of patients ( <i>n</i> )	12	2
Associated disease		
≥2 coexisting autoimmune diseases ( <i>n</i> )	1	0
Type 1 diabetes mellitus ( <i>n</i> )	2	0
Latent autoimmune diabetes in adults ( <i>n</i> )	1	0
Autoimmune thyroid disease ( <i>n</i> )	2	0
Sjögren syndrome ( <i>n</i> )	1	0
Myasthenia graves ( <i>n</i> )	1	0
Malignancy <sup>1</sup> ( <i>n</i> )	1	0
Thymoma ( <i>n</i> )	1	0
Other disease ( <i>n</i> )	1 <sup>2</sup>	nil
Associated autoantibody ( <i>n/N</i> ) <sup>3</sup>		
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

<sup>1</sup>One patient had lung cancer.

<sup>2</sup>One patient had type 2 diabetes mellitus.

<sup>3</sup>Number 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.

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<sup>[2]</sup>. 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<sup>[7]</sup>. 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)<sup>[6,8,9]</sup>. 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<sup>[10]</sup>. Ocular abnormalities, including misalignment, nystagmus, and horizontal diplopia, may be caused by the depletion of GABA<sup>[11]</sup>. 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 psychiatric 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<sup>[12]</sup>. Sudden death occurs in approximately 10% of patients with life-threatening autonomic failure<sup>[8,13]</sup>. Clinicians treating SPS patients need to be aware of the frequent psychiatric symptoms, such as anxiety<sup>[14]</sup>, depression<sup>[15]</sup>, panic disorder<sup>[16]</sup>, specific phobia<sup>[17]</sup>, and eating disorder<sup>[18]</sup>. 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<sup>[19]</sup>.

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

**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
Malignancy <sup>1</sup>	0	0	1	0	0	0
Thymoma	0	0	1	0	0	0
Type 2 diabetes mellitus	0	0	0	1	0	0

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

40 years)<sup>[9]</sup>. 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<sup>[2]</sup>. In addition to SPS, anti-GAD Ab has also been associated with cerebellar ataxia<sup>[20,21]</sup>, epilepsy (10%-20% positive for anti-GAD Ab)<sup>[1,22]</sup>, limbic encephalopathy<sup>[9]</sup>, myasthenia gravis<sup>[23]</sup>, myoclonus<sup>[20]</sup>, neuromyotonia, and Batten's disease<sup>[2]</sup>. In addition, SPS is strongly associated with other autoimmune diseases, with up to 30%-40% also having T1DM<sup>[24]</sup>. Although we do not know the incidence of SPS in Taiwan, a total of 14 SPS patients were diagnosed 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<sup>[21]</sup>, 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<sup>[9,25,26]</sup>. The two isoforms of GAD, GAD67 and GAD65, differ in molecular size and amino acid sequence<sup>[27]</sup>. 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<sup>[9,28]</sup>. 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<sup>[29]</sup>, therefore, deficiencies in GABA synthesis lead to hyperexcitability of neurons and cause muscle spasms in SPS<sup>[28]</sup>.

GAD65 is a common autoantigen in SPS and T1DM, and the triggered immune response not only impairs neurotransmission, but also destructs insulin secretion<sup>[30]</sup>. 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<sup>[26,31,32]</sup>. 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<sup>[24,33]</sup>, which have been demonstrated to block the enzyme activity<sup>[33,34]</sup>. 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<sup>[28]</sup>. 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<sup>[9,28]</sup>. Meanwhile, the anti-GAD Ab isotype can reflect the type of T helper cell response,

**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) <sup>1</sup>	1496 (before T1DM)	110 (before LADA)
GAD-Ab titer before receiving plasmapheresis (U/mL) (Ref < 5 units) <sup>2</sup>	> 2000 (after T1DM)	> 2000 (after LADA)
GAD-Ab titer after receiving plasmapheresis (U/mL) (Ref < 5 units) <sup>2</sup>	> 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

<sup>1</sup>Radioimmunoassay;<sup>2</sup>Enzyme-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.

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<sup>[35]</sup>. Furthermore, the CTLA-4 gene also shares a susceptibility locus for T1DM and AITD<sup>[36]</sup>.

In addition to T1DM, about 5%–10% of SPS patients also have AITD, Graves' disease, pernicious anemia, or vitiligo<sup>[25]</sup>. 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<sup>[34,37]</sup>. 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<sup>[36,38]</sup>. 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<sup>[39]</sup>, 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  $\beta$ -cell failure has been reported in the literature<sup>[40]</sup>.

DR and DQ alleles are strongly associated with insulin-dependent diabetes mellitus (IDDM), autoimmune hepatitis, myasthenia gravis, systemic lupus erythematosus, and inflammatory bowel disease<sup>[41]</sup>. 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<sup>[41,42]</sup>. In contrast, the DQB1 0602 allele is protective for T1DM in SPS patients<sup>[42]</sup>. Studies in Caucasians suggested that the haplotype DR3-DQB1 0201 may predispose to T1DM and AITD<sup>[43]</sup>. The DRB1 0405/DQA1 0301/DQB1 0401 haplotype was also significantly increased in patients with both T1DM and AITD in a Taiwan study<sup>[44]</sup>. 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 gravis, 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<sup>[45]</sup>. T2DM may coincidentally coexist, but not immunologically associated with SPS<sup>[46]</sup>. 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<sup>[47]</sup>. 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<sup>[48]</sup>. Baclofen is used orally with diazepam as GABA-B agonist activity to manage spasticity<sup>[49]</sup>. 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<sup>[2]</sup>. In addition, tizanidine, an  $\alpha_2$ -adrenergic receptor ( $\alpha_2$ -AR) agonist<sup>[50]</sup>, and botulinum toxin (inhibitor of acetylcholine release) were used to treat spasticity<sup>[51]</sup>. IVIG therapy is efficacious and safe for severe or refractory SPS<sup>[52]</sup>. Corticosteroids have often been used as monotherapy or in combination with other agents to improve spasms<sup>[53]</sup>. Other immunomodulating agents such as mycophenolate mofetil, azathioprine, cyclophosphamide, cyclosporine, tacrolimus, and sirolimus may also give variable benefits<sup>[2]</sup>. Plasmapheresis can improve symptoms with severe SPS in previous studies<sup>[54]</sup>. 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<sup>[55]</sup>. 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.

**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 (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.

## ARTICLE HIGHLIGHTS

### Research background

Glutamic acid decarboxylase (GAD) is known to synthesize the inhibitory neurotransmitter of  $\gamma$ -aminobutyric acid, and it is also found in the  $\beta$ -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.

## ACKNOWLEDGEMENTS

The authors sincerely thank the primary care physicians who kindly provided data on the study population. The authors would also like to thank Convergence CT for

assistance with English editing during preparation of the manuscript.

## REFERENCES

- 1 **Solimena M**, Folli F, Denis-Donini S, Comi GC, Pozza G, De Camilli P, Vicari AM. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. *N Engl J Med* 1988; **318**: 1012-1020 [PMID: 3281011 DOI: 10.1056/NEJM198804213181602]
- 2 **Hadavi S**, Noyce AJ, Leslie RD, Giovannoni G. Stiff person syndrome. *Pract Neurol* 2011; **11**: 272-282 [PMID: 21921002 DOI: 10.1136/practneurol-2011-000071]
- 3 **Barker RA**, Revesz T, Thom M, Marsden CD, Brown P. Review of 23 patients affected by the stiff man syndrome: clinical subdivision into stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. *J Neurol Neurosurg Psychiatry* 1998; **65**: 633-640 [PMID: 9810930 DOI: 10.1136/jnnp.65.5.633]
- 4 **Dalakas MC**. Stiff person syndrome: advances in pathogenesis and therapeutic interventions. *Curr Treat Options Neurol* 2009; **11**: 102-110 [PMID: 19210912 DOI: 10.1007/s11940-009-0013-9]
- 5 **Balint B**, Bhatia KP. Stiff person syndrome and other immune-mediated movement disorders - new insights. *Curr Opin Neurol* 2016; **29**: 496-506 [PMID: 27262149 DOI: 10.1097/WCO.0000000000000351]
- 6 **Meinck HM**, Thompson PD. Stiff man syndrome and related conditions. *Mov Disord* 2002; **17**: 853-866 [PMID: 12360534 DOI: 10.1002/mds.10279]
- 7 **Buechner S**, Florio I, Capone L. Stiff Person Syndrome: A Rare Neurological Disorder, Heterogeneous in Clinical Presentation and Not Easy to Treat. *Case Rep Neurol Med* 2015; **2015**: 278065 [PMID: 26106494 DOI: 10.1155/2015/278065]
- 8 **Egwuonwu S**, Chedebau F. Stiff-person syndrome: a case report and review of the literature. *J Natl Med Assoc* 2010; **102**: 1261-1263 [PMID: 21287911 DOI: 10.1016/S0027-9684(15)30757-4]
- 9 **Baizabal-Carvalho JF**, Jankovic J. Stiff-person syndrome: insights into a complex autoimmune disorder. *J Neurol Neurosurg Psychiatry* 2015; **86**: 840-848 [PMID: 25511790 DOI: 10.1136/jnnp-2014-309201]
- 10 **Bhatti AB**, Gazali ZA. Recent Advances and Review on Treatment of Stiff Person Syndrome in Adults and Pediatric Patients. *Cureus* 2015; **7**: e427 [PMID: 26848416 DOI: 10.7759/cureus.427]
- 11 **Economides JR**, Horton JC. Eye movement abnormalities in stiff person syndrome. *Neurology* 2005; **65**: 1462-1464 [PMID: 16275836 DOI: 10.1212/01.wnl.0000183068.42803.33]
- 12 **Manesa PK**, Aslam SM, Varghese M, Elipulikattu L. Stiff-Person Syndrome: A Case Report. *J Med Cases* 2016; **7**: 426-8 [DOI: 10.14740/jmc2619w]
- 13 **Mitsumoto H**, Schwartzman MJ, Estes ML, Chou SM, La Franchise EF, De Camilli P, Solimena M. Sudden death and paroxysmal autonomic dysfunction in stiff-man syndrome. *J Neurol* 1991; **238**: 91-96 [PMID: 1649913 DOI: 10.1007/bf00315688]
- 14 **Cervantes CE**, Lee Lau H, Binazir TA, O'Brien KO, Cross JS. Why It Is Not Always Anxiety: A Tough Diagnosis of Stiff Person Syndrome. *Case Rep Neurol Med* 2017; **2017**: 7431092 [PMID: 28890837 DOI: 10.1155/2017/7431092]
- 15 **Culav-Sumić J**, Bosnjak I, Pastar Z, Jukić V. Anxious depression and the stiff-person plus syndrome. *Cogn Behav Neurol* 2008; **21**: 242-245 [PMID: 19057174 DOI: 10.1097/WNN.0b013e318185e6d2]
- 16 **Ho CS**, Ho RC, Wilder-Smith EP. Stiff person syndrome masquerading as panic attacks. *Lancet* 2014; **383**: 668 [PMID: 24529469 DOI: 10.1016/S0140-6736(14)60127-6]
- 17 **Henningsen P**, Meinck HM. Specific phobia is a frequent non-motor feature in stiff man syndrome. *J Neurol Neurosurg Psychiatry* 2003; **74**: 462-465 [PMID: 12640064 DOI: 10.1136/jnnp.74.4.462]
- 18 **Cuturic M**, Harden LM, Kannaday MH, Campbell NN, Harding RK. Stiff-person syndrome presenting as eating disorder: a case report. *Int J Eat Disord* 2011; **44**: 284-286 [PMID: 20186723 DOI: 10.1002/eat.20794]
- 19 **Ameli R**, Snow J, Rakocevic G, Dalakas MC. A neuropsychological assessment of phobias in patients with stiff person syndrome. *Neurology* 2005; **64**: 1961-1963 [PMID: 15955955 DOI: 10.1212/01.WNL.0000163984.71993.FE]
- 20 **Vianello M**, Tavolato B, Giometto B. Glutamic acid decarboxylase autoantibodies and neurological disorders. *Neurol Sci* 2002; **23**: 145-151 [PMID: 12536283 DOI: 10.1007/s100720200055]
- 21 **Saiz A**, Blanco Y, Sabater L, González F, Bataller L, Casamitjana R, Ramió-Torrentà L, Graus F. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. *Brain* 2008; **131**: 2553-2563 [PMID: 18687732 DOI: 10.1093/brain/awn183]
- 22 **Liimatainen S**, Honnorat J, Pittock SJ, McKeon A, Manto M, Radtke JR, T1D Exchange Biobank, Hampel CS. GAD65 autoantibody characteristics in patients with co-occurring type 1 diabetes and epilepsy may help identify underlying epilepsy etiologies. *Orphanet J Rare Dis* 2018; **13**: 55 [PMID: 29636076 DOI: 10.1186/s13023-018-0787-5]
- 23 **Aso Y**, Sato A, Narimatsu M, Takiguchi Y, Yamaguchi Y, Inukai T, Takemura Y. Stiff-man syndrome associated with antecedent myasthenia gravis and organ-specific autoimmune neuropathy. *Intern Med* 1997; **36**: 308-311 [PMID: 9187573 DOI: 10.2169/internalmedicine.36.308]
- 24 **Kim J**, Namchuk M, Bugawan T, Fu Q, Jaffe M, Shi Y, Aanstoot HJ, Turck CW, Erlich H, Lennon V, Baekkeskov S. Higher autoantibody levels and recognition of a linear NH2-terminal epitope in the autoantigen GAD65, distinguish stiff-man syndrome from insulin-dependent diabetes mellitus. *J Exp Med* 1994; **180**: 595-606 [PMID: 7519242 DOI: 10.1084/jem.180.2.595]
- 25 **Solimena M**, Folli F, Aparisi R, Pozza G, De Camilli P. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. *N Engl J Med* 1990; **322**: 1555-1560 [PMID: 2135382 DOI: 10.1056/NEJM199005313222202]
- 26 **Alexopoulos H**, Dalakas MC. A critical update on the immunopathogenesis of Stiff Person Syndrome. *Eur J Clin Invest* 2010; **40**: 1018-1025 [PMID: 20636380 DOI: 10.1111/j.1365-2362.2010.02340.x]
- 27 **Kaufman DL**, Erlander MG, Clare-Salzler M, Atkinson MA, Maclaren NK, Tobin AJ. Autoimmunity to two forms of glutamate decarboxylase in insulin-dependent diabetes mellitus. *J Clin Invest* 1992; **89**: 283-292 [PMID: 1370298 DOI: 10.1172/JCI115573]
- 28 **Ali F**, Rowley M, Jayakrishnan B, Teuber S, Gershwin ME, Mackay IR. Stiff-person syndrome (SPS) and anti-GAD-related CNS degenerations: protean additions to the autoimmune central neuropathies. *J Autoimmun* 2011; **37**: 79-87 [PMID: 21680149 DOI: 10.1016/j.jaut.2011.05.005]
- 29 **Bu DF**, Erlander MG, Hitz BC, Tillakaratne NJ, Kaufman DL, Wagner-McPherson CB, Evans GA, Tobin

- AJ. Two human glutamate decarboxylases, 65-kDa GAD and 67-kDa GAD, are each encoded by a single gene. *Proc Natl Acad Sci U S A* 1992; **89**: 2115-2119 [PMID: 1549570 DOI: 10.1073/pnas.89.6.2115]
- 30 **Lohmann T**, Hawa M, Leslie RD, Lane R, Picard J, Londei M. Immune reactivity to glutamic acid decarboxylase 65 in stiffman syndrome and type 1 diabetes mellitus. *Lancet* 2000; **356**: 31-35 [PMID: 10892762 DOI: 10.1016/S0140-6736(00)02431-4]
- 31 **Enuh H**, Park M, Ghodasara A, Arsura E, Nfonoyim J. Stiff man syndrome: a diagnostic dilemma in a young female with diabetes mellitus and thyroiditis. *Clin Med Insights Case Rep* 2014; **7**: 139-141 [PMID: 25525403 DOI: 10.4137/CCRRep.S16941]
- 32 **Rakocevic G**, Floeter MK. Autoimmune stiff person syndrome and related myelopathies: understanding of electrophysiological and immunological processes. *Muscle Nerve* 2012; **45**: 623-634 [PMID: 22499087 DOI: 10.1002/mus.23234]
- 33 **Raju R**, Foote J, Banga JP, Hall TR, Padoa CJ, Dalakas MC, Orqvist E, Hampe CS. Analysis of GAD65 autoantibodies in Stiff-Person syndrome patients. *J Immunol* 2005; **175**: 7755-7762 [PMID: 16301686 DOI: 10.4049/jimmunol.175.11.7755]
- 34 **Björk E**, Velloso LA, Kämpe O, Karlsson FA. GAD autoantibodies in IDDM, stiff-man syndrome, and autoimmune polyendocrine syndrome type I recognize different epitopes. *Diabetes* 1994; **43**: 161-165 [PMID: 7505244 DOI: 10.2337/diabetes.43.1.161]
- 35 **Millward A**, Hussain MJ, Peakman M, Pyke DA, Leslie RD, Vergani D. Characterization of islet cell antibody in insulin dependent diabetes: evidence for IgG1 subclass restriction and polyclonality. *Clin Exp Immunol* 1988; **71**: 353-356 [PMID: 3127094]
- 36 **Jin P**, Huang G, Lin J, Yang L, Xiang B, Zhou W, Zhou Z. High titre of antiglutamic acid decarboxylase autoantibody is a strong predictor of the development of thyroid autoimmunity in patients with type 1 diabetes and latent autoimmune diabetes in adults. *Clin Endocrinol (Oxf)* 2011; **74**: 587-592 [PMID: 21470281 DOI: 10.1111/j.1365-2265.2011.03976.x]
- 37 **O'Sullivan EP**, Behan LA, King TF, Hardiman O, Smith D. A case of stiff-person syndrome, type 1 diabetes, celiac disease and dermatitis herpetiformis. *Clin Neurol Neurosurg* 2009; **111**: 384-386 [PMID: 19150172 DOI: 10.1016/j.clineuro.2008.11.006]
- 38 **Buzzetti R**, Di Pietro S, Giacari A, Petrone A, Locatelli M, Suraci C, Capizzi M, Arpi ML, Bazzigaluppi E, Dotta F, Bosi E; Non Insulin Requiring Autoimmune Diabetes Study Group. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. *Diabetes Care* 2007; **30**: 932-938 [PMID: 17392553 DOI: 10.2337/dc06-1696]
- 39 **Fourlanos S**, Neal A, So M, Evans A. Latent autoimmune diabetes in Stiff-Person Syndrome. *Diabetes Care* 2014; **37**: e214-e215 [PMID: 25249677 DOI: 10.2337/dc14-1444]
- 40 **Katahira M**, Ogata H, Ito T, Miwata T, Goto M, Nakamura S, Takashima H. Association of Autoimmune Thyroid Disease with Anti-GAD Antibody ELISA Test Positivity and Risk for Insulin Deficiency in Slowly Progressive Type 1 Diabetes. *J Diabetes Res* 2018; **2018**: 1847430 [PMID: 30116734 DOI: 10.1155/2018/1847430]
- 41 **Dalakas MC**, Fujii M, Li M, McElroy B. The clinical spectrum of anti-GAD antibody-positive patients with stiff-person syndrome. *Neurology* 2000; **55**: 1531-1535 [PMID: 11094109 DOI: 10.1212/Wnl.55.10.1531]
- 42 **Pugliese A**, Solimena M, Awdeh ZL, Alper CA, Bugawan T, Erlich HA, De Camilli P, Eisenbarth GS. Association of HLA-DQB1\*0201 with stiff-man syndrome. *J Clin Endocrinol Metab* 1993; **77**: 1550-1553 [PMID: 8263140 DOI: 10.1210/jcem.77.6.8263140]
- 43 **Huang W**, Connor E, Rosa TD, Muir A, Schatz D, Silverstein J, Crockett S, She JX, Maclaren NK. Although DR3-DQB1\*0201 may be associated with multiple component diseases of the autoimmune polyglandular syndromes, the human leukocyte antigen DR4-DQB1\*0302 haplotype is implicated only in beta-cell autoimmunity. *J Clin Endocrinol Metab* 1996; **81**: 2559-2563 [PMID: 8675578 DOI: 10.1210/jcem.81.7.8675578]
- 44 **Chuang LM**, Wu HP, Chang CC, Tsai WY, Chang HM, Tai TY, Lin BJ. HLA DRB1/DQA1/DQB1 haplotype determines thyroid autoimmunity in patients with insulin-dependent diabetes mellitus. *Clin Endocrinol (Oxf)* 1996; **45**: 631-636 [PMID: 8977762 DOI: 10.1046/j.1365-2265.1996.00857.x]
- 45 **McKeon A**, Robinson MT, McEvoy KM, Matsumoto JY, Lennon VA, Ahlskog JE, Pittcock SJ. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. *Arch Neurol* 2012; **69**: 230-238 [PMID: 22332190 DOI: 10.1001/archneurol.2011.991]
- 46 **Weitgasser R**, Somavilla B, Stieglbauer K. Insulin treatment in a patient with Type 2 diabetes and Stiff-person syndrome. *Diabet Med* 2009; **26**: 111-112 [PMID: 19125773 DOI: 10.1111/j.1464-5491.2008.02605.x]
- 47 **Morris LL**, Dysch L, Salkovskis PM, Giffin N. Reducing excess stiffness in Stiff Person Syndrome using CBT: A case study. *NeuroRehabilitation* 2014; **35**: 627-631 [PMID: 25238861 DOI: 10.3233/NRE-141147]
- 48 **Cohen L**. Stiff-man syndrome. Two patients treated with diazepam. *JAMA* 1966; **195**: 222-224 [PMID: 5951806 DOI: 10.1001/jama.1966.03100030116038]
- 49 **Miller F**, Korsvik H. Baclofen in the treatment of stiff-man syndrome. *Ann Neurol* 1981; **9**: 511-512 [PMID: 7271246 DOI: 10.1002/ana.410090516]
- 50 **Zdziarski P**. A Case of Stiff Person Syndrome: Immunomodulatory Effect of Benzodiazepines: Successful Rituximab and Tizanidine Therapy. *Medicine (Baltimore)* 2015; **94**: e954 [PMID: 26061327 DOI: 10.1097/MD.0000000000000954]
- 51 **Pakeerappa PN**, Birthi P, Salles S. Botulinum toxin a injection to facial and cervical paraspinal muscles in a patient with stiff person syndrome: a case report. *PM R* 2015; **7**: 326-328 [PMID: 25459656 DOI: 10.1016/j.pmrj.2014.10.013]
- 52 **Dalakas MC**, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; **345**: 1870-1876 [PMID: 11756577 DOI: 10.1056/NEJ-Moa01167]
- 53 **Liran O**, Kots E, Amital H. Stiff person syndrome: a tough and rigid case. *Isr Med Assoc J* 2015; **17**: 261-262 [PMID: 26040059]
- 54 **De la Casa-Fages B**, Anaya F, Gabriel-Ortemberg M, Grandas F. Treatment of stiff-person syndrome with chronic plasmapheresis. *Mov Disord* 2013; **28**: 396-397 [PMID: 23239368 DOI: 10.1002/mds.25167]
- 55 **Baker MR**, Das M, Isaacs J, Fawcett PR, Bates D. Treatment of stiff person syndrome with rituximab. *J Neurol Neurosurg Psychiatry* 2005; **76**: 999-1001 [PMID: 15965211 DOI: 10.1136/jnnp.2004.051144]



Published By Baishideng Publishing Group Inc  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
Telephone: +1-925-2238242  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

