J Musculoskelet Neuronal Interact 2018; 18(3):389-392

Journal of Musculoskeletal and Neuronal Interactions JMNI

Case Report

Stiff person syndrome with elevated titers of antibodies against cardiolipin and β2 glycoprotein 1: a case report and literature review

Li-Ya Tang[1], Sheng-Yuan Yu[2], Yong-Hua Huang[1]

[1]Department of neurology, PLA Army General Hospital, Beijing, People's Republic of China; [2]Department of Neurology, Chinese PLA General Hospital, Beijing, People's Republic of China

Abstract

We reported a Stiff person syndrome (SPS) patient with elevated autoantibodies against cardiolipin and β2 glycoprotein 1 but without glutamic acid decarboxylase (GAD) antibodies. A 40-year male was admitted due to limited mouth opening for 1 week. His blood routine, biochemical, infectious diseases, tumor markers, radiographic examinations were all normal. At day 3 (D3) after admission, he developed paroxysmal systemic muscle rigidity. At D6, the on-duty physician occasionally gave oral clonazepam, which effectively relieved the symptom. At D13, the titers of cardiolipin and β2 glycoprotein 1 autoantibodies elevated but the remaining autoantibodies were all in normal ranges. After clonazepam treatment for 1 week, the symptoms were basically relieved, and the titers of these two antibodies returned to normal range with the relief of symptoms. During the 3 years of follow-up, the symptoms did not present again, and the titers of both antibodies were stable in the normal ranges. He had no tumor and other immune system diseases. In summary, we reported a SPS case with elevated cardiolipin and β2 glycoprotein 1 autoantibodies. The patient was highly responsive to clonazepam therapy, and had favorable outcome in the 3 years follow-up. Our report is helpful for better understand the heterogeneous feature of SPS.

Keywords: Stiff Person Syndrome, Anti-cardiolipin Antibodies, Anti-β2 Glycoprotein 1 Antibodies, Clonazepam

Introduction

Stiff person syndrome (SPS) is a rare central nervous system disorder with an annual incidence of 1:1000000, characterized by progressive rigidity and muscle spasms in the axial and limb muscles[1,2]. The symptoms of SPS range from mild to severe, but can progress into disability if untreated[3]. Approximately 60-80% of SPS patients are seropositive for antibodies against glutamic acid decarboxylase (anti-GAD antibodies)[4] and about 10% of patients are associated with antibodies against amphiphysin[2,5]. Here we reported a case of SPS with elevated titers of antibodies against cardiolipin and β2 glycoprotein 1 (β2-GPI) but without classical anti-GAD antibodies who had favorable outcome.

Case report

A 40-year male patient was admitted to our emergency department due to limited mouth opening for 1 week and eating difficulties for 4 days. The patient was a butcher and had always been very healthy. He had no medical history of hypertension, diabetes, thyroid disease, cancer and genetic diseases and no contact history of hepatitis, tuberculosis and other infectious diseases. He had been bitten twice by domestic dogs at 15 years and four months before onset of symptoms, respectively. His right middle finger was lost in an injury at work at 20 years ago. He underwent bilateral lithotripsy for kidney stones at two years ago, and had

The authors have no conflict of interest.

Corresponding authors:
Sheng-yuan Yu, Department of Neurology, Chinese PLA General Hospital, Beijing, China, No. 28 Fuxing Road, Haidian District, Beijing, China
E-mail: yusy1963@126.com
Yong-Hua Huang, Department of Neurology, PLA Army General Hospital, Beijing, China, No. 2 Chaoneibeixiaojie, Dongcheng District, Beijing, China
E-mail: huangyh@163.com

Edited by: G. Lyritis
Accepted 30 April 2018

no recent history of trauma and surgery. This study was approved by the institutional review board of our hospital. Written informed consent was obtained from the patient.

A week before admission, the patient had unexplained limited mouth opening, without fever, convulsions, and any mental or behavioral abnormalities. He was diagnosed with gingivitis at a local clinic and was given anti-inflammatory treatment (specific medications were unknown). However, the symptoms became severe at 4 days prior to admission; he cannot open mouth completely, and was gradually incapable of chewing and swallowing. After excluding the possibility of jaw joint disease in an oral hospital, the patient was admitted to our emergency department and hospitalized due to dystonia.

The patient had a temperature of 36.7°C, a pulse of 74 times/min, a breathing rate of 18 times/min, and a blood pressure of 127/76 mmHg at admission. There was no rash or pigmentation on the body skin. He had normal heart rhythm, clear breath sounds but tense abdominal muscles. He was conscious but cannot speak, and his pupils were equal in size and shape, having normal response to a bright light. His eye movements were normal in all directions. He had symmetric forehead lines but extremely tense temporal and masseter muscles, so that he cannot show teeth. However, he can shrug and turn his neck, and the limbs can move freely, having normal muscle strength and muscle tension without involuntary movements. The finger-nose test and heel knee shin test were both positive, and his pain and tactile sensations were normal. The meningeal irritation sign was negative.

The results of examinations of blood routine, biochemical, erythrocyte sedimentation rate, C-reactive protein (CRP), infectious disease antibodies (toxoplasma, rubella virus, cytomegalovirus, herpes simplex virus) and tumor markers (α-fetoprotein, carcinoembryonic antigen, prostate specific antigen, free prostate specific antigen, cancer antigen [CA] 15-3, CA 19-9, CA 72-4, non-small cell lung cancer, nerve enolase, and serum ferritin), skull base MRI, cerebrospinal fluid cell count, common bacteria, anaerobic bacteria and cryptococcosis examinations were all normal. According to the symptoms and the findings of medical examinations, the possibilities of rabies and tetanus were initially considered. Given that tetanus is a fatal disease, the patients was given penicillin 6,000,000 U, 4 times/day, metronidazole 0.5 g, 2 times/day, and tetanus immune globulin 250 IU, 1 time/day for tetanus prophylaxis. Nevertheless, in spite of the treatments patient's condition gradually became worse. He had significant abdominal distension. At day 3 (D3) after admission, the patient developed the symptom of paroxysmal systemic muscle rigidity, with each episode lasting for 0.5-2 hours. During the onset, he had good consciousness, and presented rigidity in the extensor muscles of all the limbs without twitching. The frequency of symptoms onset increased gradually. At D6 night, the symptoms presented again, and the on-duty physician occasionally gave oral clonazepam 0.5 mg. After falling asleep, the symptoms of patient were relieved. From that time, the patient was given clonazepam treatment (2 mg) at each onset of symptoms, and the symptoms were significantly relieved. At D11 after admission, a consultation was held and the consulting expertise suggested that the symptoms of patients seemed in line with those with SPS. Skull base enhanced CT and B-scan ultrasonography for head and neck lymph nodes had been performed to rule out the possibility of skull base infection. Due to SPS is an immune related disorder, the patient received examinations for autoantibodies, anti-tumor antibodies, anti-GAD antibodies and anti-amphiphysin antibodies. The results at D13 showed that patient had elevated titers of anti-cardiolipin (48.0 mg/dl, normal range 0-12 mg/dl) and anti-β2-GPI (28.4 mg/dl, normal range 0-20 mg/dl) antibodies. The titers of the remaining assessed antibodies were all in normal ranges.

As SPS is particularly responsive to benzodiazepines, the patient was given oral clonazepam treatment, 2 mg, 3 times/day. After clonazepam treatment for 1 week, the symptoms were basically relieved. When getting angry, the patient had significant abdominal distension and rigidity in all the limbs (especially the lower limbs), and clonazepam treatment can effectively relieved the symptoms. The patient then discharged at D23 after admission with normal muscle strength and without other discomfort. After discharge, he proceeded with clonazepam treatment of the same dosage. At 4 months follow-up post-discharge, the titers of anti-cardiolipin and anti-β2-GPI antibodies were 6.2 mg/dl and 30.2 mg/dl, respectively. Patients had reduced the dose of clonazepam to 2 mg, 1 time/day by himself. At one year follow-up post-discharge, the symptoms were completely resolved, and the patient stopped the lonazepam treatment by himself. The titers of anti-cardiolipin and anti-β2-GPI antibodies were both in normal ranges. During the following 2 years of follow-up, the symptoms did not present again, and the titers of both antibodies were stable in the normal ranges. The systemic physical examinations showed no tumor and other immune system diseases.

Discussion

Clinical response to benzodiazepines is considered to be a diagnostic criterion for SPS[2]. In this report, the patient was highly responsive to clonazepam treatment. After eliminating the possibilities of infectious disease, inflammatory disease, trauma, tumor, the patient was diagnosed with SPS based on the following symptoms and clinical findings: highly responsive to benzodiazepines, paroxysmal changes of muscle tone, rigidity in lower extremities, abdominal distension, belly bulging, walking difficulties and the altered immunological profiles. It has been shown that SPS patients responsive to benzodiazepines treatment usually have a good prognosis[6,7].

As an autoimmune disease, SPS is commonly associated with a variety of autoantibodies[8,9]. Autoantibodies detected in SPS patients which reported in the literatures are summarized in the Table 1. Common autoantigens in SPS are GABAergic

Table 1. Autoantibodies detected in SPS patients reported in the literatures.

Autoantibodies	No. of Cases	Country	Authors
GABAergic synaptic proteins			
GAD	1	Italy	Solimena et al. 1988[10]
Amphiphysin	1	USA	De Camilli et al. 1993[11]
GABARAP	19	USA	Raju et al. 2006[12]
Gephyrin	1	USA	Butler et al. 2000[13]
Diabetes-related autoantibodies			
Insulin antibody	8	USA	McKeon et al. 2012[16]
IA-2 antibody	3	USA	McKeon et al. 2012[16]
Thyroid-related autoantibodies			
Thyroid antibody	1	Japan	Katoh et al. 2010[17]
Thyroid peroxidase antibody	1	Singapore	Chia et al. 2007[18]
Thyroglobulin antibody	1	Singapore	Chia et al. 2007[18]
Other autoantibodies			
Gastric parietal cell antibody	12	USA	McKeon et al. 2012[16]
α-3 Ganglionic AChR antibody	2	USA	McKeon et al. 2012[16]
Striational antibody,	1	USA	McKeon et al. 2012[16]
Voltage-gated potassium channel,	1	USA	McKeon et al. 2012[16]
Complex antibody			
Cardiolipin	1	China	The current report
β2-GPI antibodies	1	China	The current report

GAD, glutamic acid decarboxylase; GABARAP, GABA(A)-receptor-associated protein; IA-2, Islet antigen 2; AChR, acetylcholine receptors; β2-GPI,β2 glycoprotein I.

synaptic proteins, including presynaptic proteins GAD[10] and amphiphysin[11], as well as postsynaptic proteins GABA(A) receptor-associated protein (GABARAP)[12] and gephyrin[13]. GAD and amphiphysin are membrane proteins concentrated in nerve terminals and associated with the cytoplasmic surface of synaptic vesicles[11]. GAD is a c-aminobutyric acid (GABA)-synthesizing enzyme, and amphiphysin plays a role in endocytosis[14]. Anti-GAD antibodies is most commonly found in SPS patients (up to 80%)[4]. GABARAP and gephyrin are cytosolic proteins, which can interacted each other to assemble the GABA-A receptor[15]. SPS patients with severe disease had a higher titer of anti- GABARAP antibody[12], suggesting that anti-GABARAP antibodies may be associated with the disease severity. Although the pathological mechanism of SPS is still not completely understood, the elevated titers of autoantibodies are believed to be involved in its pathogenesis[5,15].

Patients with SPS have been reported to coexist with several autoimmune diseases, including Type I diabetes, thyroiditis, Graves' disease, pernicious anemia, vitiligo and celiac disease[16]. Therefore diabetes-related autoantibodies (insulin antibody and islet antigen 2 (IA-2) antibody)[16] and thyroid-related autoantibodies (thyroid antibody[17], thyroid peroxidase antibody and thyroglobulin antibody[18]) have been detected in SPS patients. Other autoantibodies including gastric parietal cell antibody, α-3 Ganglionic acetylcholine receptors (AChR) antibody, striational antibody, voltage-gated potassium channel, complex antibody have also been reported to be detected in SPS patients[16].

In this report, the SPS patient was seronegative for anti-GAD antibodies and anti-amphiphysin antibodies. Instead, the titers of anti-cardiolipin and anti-β2-GPI antibodies were elevated. In addition, the titers of these two antibodies returned to normal range with the relief of symptoms. Anti-cardiolipin antibodies are pathogenic and have been found in several diseases, such as syphilis, antiphospholipid syndrome, idiopathic spontaneous abortion, and systemic lupus erythematosus[19]. Anti-β2-GPI antibodies have been also reported to be associated with thrombosis, pregnancy morbidity, and accelerated atherosclerosis in antiphospholipid syndrome and systemic lupus erythematosus[20]. So far, there is no study reporting the association between SPS and these two antibodies. To our best knowledge, we reported that SPS patient with elevated anti-cardiolipin and anti-β2-GPI antibodies for the first time. It is worthy to further investigate if the elevated anti-cardiolipin and anti-β2-GPI antibodies take part in pathological mechanism of SPS. Our findings also suggested that anti-cardiolipin and anti-β2-GPI antibodies could be considered to be included in the examinations of immunological profiles for SPS patients.

In summary, we described a SPS case with elevated anti-cardiolipin and anti-β2-GPI antibodies in this report. The patient was highly responsive to clonazepam therapy, and

had favorable outcome in the 3 years follow-up. Our report is helpful for better understanding the heterogeneous feature of SPS.

Acknowledgement

This report was supported by the grant from the China Postdoctoral Science Foundation.

Authors' contributions

Li-Ya Tang collected data, searched literatures and drafted the manuscirpt. Sheng-Yuan Yu and Yong-Hua Huang critically revised the manuscirpt. All authors read and approved the final manuscript.

References

1. Sarva H, Deik A, Ullah A, et al. Clinical Spectrum of Stiff Person Syndrome: A Review of Recent Reports. Tremor Other Hyperkinet Mov (N Y) 2016;4(6):340.
2. Baizabal-Carvallo JF, Jankovic J. Stiff-person syndrome: insights into a complex autoimmune disorder. J Neurol Neurosurg Psychiatry 2014;86(8):840-48.
3. Gershanik OS. Stiff-person syndrome. Parkinsonism Relat Disord 2009;15:S130-S134.
4. Solimena M, De Camilli P. Autoimmunity to glutamic acid decarboxylase (GAD) in Stiff-Man syndrome and insulin-dependent diabetes mellitus. Trends Neurosci 1991; 14(10):452-57.
5. Dalakas MC. Stiff person syndrome: Advances in pathogenesis and therapeutic interventions. Vol. 11, Current Treatment Options in Neurology 2009; 11(2):102-10.
6. Lorish TR, Thorsteinsson G, Howard FM. Stiff-man syndrome updated. Mayo Clin Proc 1989;64(6):629-36.
7. Barker RA, Revesz T, Thom M, et al. 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(5):633-40.
8. Solimena M, Folli F, Aparisi R, et al. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med 1990;322(22):1555-60.
9. Grimaldi LME, Martino G, Braghi S, et al. Heterogeneity of autoantibodies in stiff-man syndrome. Ann Neurol 1993;34(1):57-64.
10. Solimena M, Folli F, Denis-Donini S, et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. N Engl J Med 1988;318(16):1012-20.
11. De Camilli P, Thomas A, Cofiell R, et al. The synaptic vesicle-associated protein amphiphysin is the 128-kD autoantigen of Stiff-Man syndrome with breast cancer. J Exp Med 1993;178(6):2219-23.
12. Raju R, Rakocevic G, Chen Z, et al. Autoimmunity to GABAA-receptor-associated protein in stiff-person syndrome. Brain 2006;129(12):3270-76.
13. Butler MH, Hayashi A, Ohkoshi N, et al. Autoimmunity to gephyrin in Stiff-Man syndrome. Neuron 2000; 26(2):307-12.
14. Takei K, Slepnev VI, Haucke V, et al. Functional partnership between amphiphysin and dynamin in clathrin-mediated endocytosis. Nat Cell Biol 1999;1(1):33-39.
15. Alexopoulos H, Dalakas MC. A critical update on the immunopathogenesis of Stiff Person Syndrome. Eur J Clin Invest 2010;40(11):1018-25.
16. McKeon A, Robinson MT, McEvoy KM, et al. Stiff-Man Syndrome and Variants. Arch Neurol 2012;69(2):230.
17. Katoh N, Matsuda M, Ishii W, et al. Successful treatment with rituximab in a patient with stiff-person syndrome complicated by dysthyroid ophthalmopathy. Intern Med 2010;49(3):237-41.
18. Chia S-Y, Chua R, Lo Y-L, et al. Acute ataxia, Graves' disease, and stiff person syndrome. Mov Disord 2007; 22(13):1969-71.
19. Reddel S, Krilis S. Testing for and clinical significance of anticardiolipin antibodies. Clin Diagn Lab Immunol 1999;6(6):775-82.
20. Willis R, Pierangeli SS. Anti-β 2 -glycoprotein I antibodies. Ann N Y Acad Sci 2013;1285(1):44-58.