Case Report

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

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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 muscles¹². The symptoms of SPS range from mild to severe, but can progress into disability if untreated³. 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 amphiphysin²⁵. 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...
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,
erthrocyte sedimentation rate, C-reactive protein (CRP),
infectious disease antibodies (toxoplasma, rubella virus,
cytomegalovirus, herpes simplex virus) and tumor markers
(a-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 did not present again,
and the titers of both antibodies were stable in the normal
ranges. The systemic physical examinations showed no
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

Discussion

Clinical response to benzodiazepines is considered to be a
diagnostic criterion for SPS.6 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
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in the Table 1. Common autoantigens in SPS are GABAergic
synaptic proteins, including presynaptic proteins GAD\textsuperscript{10} and amphiphysin\textsuperscript{11}, as well as postsynaptic proteins GABA\textsubscript{(A)} receptor-associated protein (GABARAP)\textsuperscript{12} and gephyrin\textsuperscript{13}. GAD and amphiphysin are membrane proteins concentrated in nerve terminals and associated with the cytoplasmic surface of synaptic vesicles\textsuperscript{11}. GAD is a \(\gamma\)-aminobutyric acid (GABA)-synthesizing enzyme, and amphiphysin plays a role in endocytosis\textsuperscript{14}. Anti-GAD antibodies is most commonly found in SPS patients (up to 80%)\textsuperscript{4}. GABARAP and gephyrin are cytosolic proteins, which can interact each other to assemble the GABA-A receptor\textsuperscript{15}. SPS patients with severe disease had a higher titer of anti- GABARAP antibody\textsuperscript{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\textsuperscript{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\textsuperscript{16}. Therefore diabetes-related autoantibodies (insulin antibody and islet antigen 2 (IA-2) antibody)\textsuperscript{16} and thyroid-related autoantibodies (thyroid antibody\textsuperscript{17}, thyroid peroxidase antibody and thyroglobulin antibody\textsuperscript{18}) have been detected in SPS patients. Other autoantibodies including gastric parietal cell antibody, \(\alpha\)-3 Ganglionic acetylcholine receptors (AChR) antibody, striational antibody, voltage-gated potassium channel, complex antibody have also been reported to be detected in SPS patients\textsuperscript{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-\(\beta\)-2-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\textsuperscript{19}. Anti-\(\beta\)-2-GPI antibodies have been also reported to be associated with thrombosis, pregnancy morbidity, and accelerated atherosclerosis in antiphospholipid syndrome and systemic lupus erythematosus\textsuperscript{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-\(\beta\)-2-GPI antibodies for the first time. It is worthy to further investigate if the elevated anti-cardiolipin and anti-\(\beta\)-2-GPI antibodies take part in pathological mechanism of SPS. Our findings also suggested that anti-cardiolipin and anti-\(\beta\)-2-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-\(\beta\)-2-GPI antibodies in this report. The patient was highly responsive to clonazepam therapy, and

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

GAD, glutamic acid decarboxylase; GABARAP, GABA\textsubscript{(A)}-receptor-associated protein; IA-2, Islet antigen 2; AChR, acetylcholine receptors; \(\beta\)-2-GPI, \(\beta\)2 glycoprotein I.
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had favorable outcome in the 3 years follow-up. Our report is helpful for better understanding the heterogeneous feature of SPS.

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Authors’ contributions

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

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