A Systematic review of 192 cases of Stiff-person Syndrome in China

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Abstract—to investigate stiff person syndrome (SPS) in Chinese patients. Combining 192 patients currently reported in China with previous literature review, the authors report the disease incidence, pathogenesis, clinical manifestation, treatment methods, causes of death and related research progress. The occurrence of this disease is mainly due to influenza and tumor induced, characterized by fluctuating muscle rigidity and spasm of features. It often influences trunk and limb muscles. When respiratory muscle is affected, it would lead to death. In conclusion, SPS is a disease which may relate to immune system. Its diagnosis mainly relies on the examination of clinical symptoms. Benzodiazepines can be used as experimental medication and electromyography is also of great significance. Finally, benzodiazepines and TCM are both effective methods of treatment.

Keywords—Stiff person syndrome; pathogenesis; treatment

I. INTRODUCTION

The Stiff person Syndrome (SPS) is a rare, autoimmune, neurological disease characterized by progressive muscular stiffness and episodic spasms that prominently involve the axial and limb muscles. SPS was discovered and named by Moersch and Woltman in 1956 [1], There are 192 cases of SPS reported in China in the past thirty more year, with which ideas for the diagnosis and treatment of SPS could be summed up.

II. MATERIALS AND METHODS

A. Data sources

We retrieved reports about SPS from the major Chinese electronic databases, including China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Chinese Biomedical Literature Database (CBM), and Wan fang Database (Wan fang) from 1980 to 2012. "Stiff person" was used as search term in the CNKI, VIP, and CBM, Wan fang, yielded 162, 98, 128 and 88 articles, respectively. We also used "stiff person syndrome" as search term, which yielded 235, 93, 123 and 83 articles, respectively.

B. Inclusion and exclusion criteria

All studies about SPS were published in Chinese journals. Articles were included in this paper only if they reported pathogenesis, clinical features and treatment for SPS. Clinical features should meet the 2002 Kyriako’s proposed SPS clinical new diagnostic criteria [2]: ① initial stiffness of rigidity in the axial muscles, ② slow progression of stiffness to include proximal limb muscles, making volitional movements and ambulation difficult, ③ a fixed deformity of the spine, as in lordosis, and with some patients a restriction of hip movement, ④ the presence of superimposed episodic spasms precipitated by sudden movements, jarring noise, and emotional upset, ⑤ normal findings on motor and sensory nerve examinations, ⑥ normal intellect, ⑦ electromyographic findings typical of continuous motor activity that can be abolished by intravenous or orally administered diazepam. Symptoms which did not appear in the criteria, or were not easily to be classified should be retained.

We excluded studies according to one of the following criteria: ① Articles without presenting detailed SPS patients information, e.g., reviews, theoretical studies, ② Articles with similar content as other articles, regardless of title differences, ③ Research reported in other media or in incomplete formats (e.g., abstracts or conference proceedings ), ④ Articles with misdiagnosing of stiff person syndrome.

Finally, 115 articles were included in the study.

C. Analytical method

Frequencies about the incidence, clinical feature, treatment method were reported and the result was compared to the results in international studies.

III. RESULTS

A. Incidence

Among the 184 cases of incidence, there were 118 acute cases (64.1%) and 66 chronic cases (35.9%). The ratio of acute and chronic incidence was 1.79:1, which was different from those in international reports [3] where there were more chronic incidence cases.

B. Gender

Among the 189 cases reporting patients’ gender, there were 125 male cases and 62 female cases. The ratio of male and female was 2:1, which was different from Guo Xiuhai’s [4] report where the ratio was 5:2. In addition, young and middle-aged men and elder women were more susceptible to suffer from SPS.

C. Cause

There were 168 cases reporting the cause of SPS, described in TABLE I. Induced factors such as infection, overwork and mood were reported in 113 cases. Moreover, the occurrence of SPS was often accompanied with other diseases such as hyperthyroidism, asthma, myasthenia gravis, tumor (including thymoma, myeloma, ovarian cancer, lung cancer, breast cancer, etc.), hepatitis B, ichthyosis, vitiligo, diabetes, lumbar disc herniation, epilepsy, cerebral infarction, herpes zoster, etc. These diseases related to immune dysfunction, so it suggested that SPS was an immune system disease. Among them, there were 8 cases of hyperthyroidism and 5 cases of diabetes and
thymoma, respectively. These complications were mainly chest diseases. It could be a future topic whether or not chest disease might induce SPS.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Cases</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>39</td>
<td>23.21%</td>
</tr>
<tr>
<td>Overwork</td>
<td>23</td>
<td>13.69%</td>
</tr>
<tr>
<td>Mood</td>
<td>18</td>
<td>10.71%</td>
</tr>
<tr>
<td>Other diseases</td>
<td>43</td>
<td>25.60%</td>
</tr>
<tr>
<td>Unknown incentive</td>
<td>45</td>
<td>26.79%</td>
</tr>
<tr>
<td>Total</td>
<td>168</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Some reports involved more than one type of causes.

D. Pathogenesis

At present, the disease was considered relating to autoimmunity. Solimena [5] argued that SPS was an autoimmune disease. Yu found [6] high titer of anti-GAD antibody in the cerebrospinal fluid and sera of SPS of the patients, suggesting that there was an autoimmune reaction in the central nervous system of SPS patients. Guo [4] found that gamma globulin was effective for the disease, which confirmed that the pathogenesis of SPS was autoimmune. However, the debate whether the antibody mediated the occurrence of SPS or there was a pathogenic antigen in the cells has been long existed. It remains unknown whether autoantibody is the cause or the result of the disease. Some patients had an infection history, suggesting that infection may induce autoimmune diseases. Furthermore, because there were many cases where SPS was induced by trauma and surgery, it could be easily misdiagnosed as tetanus. Doctors should be aware of the complexity of this disease which was a kind of syndrome, may be just one manifestation of a serious underlying disorder such as autoimmune disease or cancer.

SPS was often accompanied with tumor, especially the thymoma. Sun [7] argued that autoimmune T cells of a variety of antigens may go into the peripheral circulation in thymus of thymoma patients. Together with lack of adjustive T cells, the negative autoimmune reaction was in the abnormal adjustment. Thus it could result in specific autoimmune diseases of many organs. Whereas other tumors usually were caused by same epitope expression with nerve tissue itself [8], or related to the autoimmune mechanism in thymoma, which change functioning of the nerve system. In addition, in one case report [9] some argued that the occurrence of SPS may relate to the amygdala and hippocampus dysregulation.

E. Manifestation

SPS often was insidious in onset and its manifestations were multiform. There were 172 cases that reported the initial manifestation, among which there were 63 cases with limbs rigidity, 47 cases with trunk (including thoracic dorsal abdominal waist) pain and stiffness, 16 cases with neck stiffness, 37 cases with limited mouth opening, 6 cases with facial pain (sometimes accompanied with hearing loss), 2 cases with dyspnea, and 1 case with blurred vision. Most of initial manifestations involved muscles innervated by cranial nerve. This accorded with the argument that lesions happened in the spinal cord and brain stem.

TABLE II. CLINICAL FEATURES OF SPS IN CASE REPORT PUBLISHED IN CHINESE JOURNALS

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Cases</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiffness facial muscles</td>
<td>116</td>
<td>25.38%</td>
</tr>
<tr>
<td>abdominal muscles</td>
<td>105</td>
<td>22.98%</td>
</tr>
<tr>
<td>Cramp</td>
<td>77</td>
<td>16.85%</td>
</tr>
<tr>
<td>Tendon reflexes</td>
<td>hyberactive 42</td>
<td>9.19%</td>
</tr>
<tr>
<td></td>
<td>active 22</td>
<td>4.81%</td>
</tr>
<tr>
<td>Emotional disorder</td>
<td>32</td>
<td>7.00%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>31</td>
<td>6.78%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21</td>
<td>4.60%</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>11</td>
<td>2.41%</td>
</tr>
<tr>
<td>Total</td>
<td>457</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Some reports more than one type of features

From table II, it showed that the main clinical features included muscle stiffness, rigidity, and painful spasms triggered by sensory or emotional stimuli. These symptoms may disappear while sleeping. Moreover, SPS often related to multiple muscle groups, for instance, abdominal muscles, facial muscles, chewing muscles, tongue muscle, orbicularis oris muscle etc. Stiffness mainly occurred in the thoracolumbar paraspinal muscles or abdominal muscles and may eventually spread to proximal limb muscles. It has been reported that the occurrence of SPS may be due to the imbalance between catecholaminergic neurons and GABA neurons systems, which led to muscle stiffness and myoclonus [10]. Because the muscle spasm mainly occurred at the first or second stage of non-rapid eye movement (NREM) sleep after the rapid eye movement (REM) sleep, patients may suffer from nightmare or low sleep quality [11]. In addition, in international articles [12-13] there was no pyramidal sign in classic SPS, but the active tendon reflexes were common. This was inconsistent with what we have found. Fang [14] argued that the inhibition of pyramidal tract and nuclear damage may be the cause because most pyramidal sign were hyperfunction.

F. Auxiliary examination

There were 188 cases involving auxiliary examination, out of which there were 142 cases using electromyography (EMG). For the cases using EMG, continuous motor unit activity at rest was reported in 126 of them. Low transmission of waves was reported in 6 of them, and 10 of them were normal. When patients were treated with diazepam, continuous motor unit activity disappeared, which was the characteristic manifestation in SPS's EMG. In
some studies, normal EMG was reported [15-16]. But this was rare and the reason remained unknown. In 192 cases of SPS patients, GAD antibody was only tested in 16 cases due to limited level of medical treatment. Ten of them were positive and six negative. The detection rate was 62.5%. It was report [17] that 60%-80% patients were positive in GAD antibody test, whereas patients with cancer tended to be negative. In this study ,only2 cases suffered from cancer in 6 negative patients.

In addition, no abnormal brains or muscle was found in the biopsy using Magnetic resonance imaging (MRI) ,suggesting that SPS may be a functional disease [18].

G. Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Efficient cases</th>
<th>Inefficient cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>5-200mg</td>
<td>188</td>
<td>0</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>5-45mg</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>2.5-21mg</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>Baclofen</td>
<td>10-60mg</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>IVIG</td>
<td>0.4-2g/kg</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0.5-1g/d</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1.5-15mg/d</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chinese herbal medicine</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operation</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

There were 192 cases reporting treatment, described in TABLE III, 188 of them treated with benzodiazepines. For the 4 cases without benzodiazepines, but 2 of them were treated with traditional Chinese medicine, 1 with Extractum Glycyrrhizae Liquidum, and 1 with baclofen. Benzodiazepines were the most ideal medicine for SPS so far. Ameli et.al. [19] believed that patient’s emotional disorder such as horror or anxiety came from the SPS disease per se but not an inherent pubic neurosis. So the effect of anxiolytics was not significant. Most patients can tolerate heavy dose of benzodiazepines. Xie [20] preferred clonazepam, because its muscle relaxant effect is at least five to times better than diazepam or clonazepam. The reason was that the half-life of clonazepam was about 28 - 49h, which implied a longer metabolic cycle. However, clonazepam may lead to orthostatic hypotension easily, so the blood pressure of the patients who took clonazepam should be monitored frequently.

In our review, there were 5 cases reporting operation, Stiff symptoms were completely disappeared at 2 of the cases, 1 cases relieved, 1 cases remaining the same, and 1 cases aggravated. Li [21] argued that thymoma operation alone did not eliminate the cause that may induce SPS. Although thymectomy excision can remove the specific antigen, sensitized T cells, regulating immune cytokine and antibody-secreting B cells, all of which participate stimulating autoimmune response, but the preoperative immune disorder does not disappear with thymoma excision. The disorder may even aggravate due to lymphocyte spillover in the operation process. So the control of the occurrence of SPS required immunosuppressant.

It has been found out that the effect of TCM should be recognized in this review. The issue was that patients took different herbal medicine. Common prescriptions were as follows: Sanjia Fumai decoction [22], Shaoyaotang Gancao decoction [23], Danggui Sini decoction [24], Bazhen decoction[25], Guizhi Decoction [26], Siwu decoction [27], Xiao Chaihu decoction [28] , Dihuang yinzi [29]so on. This is the embodiment of individual treatment characteristics of TCM. These findings indicate that TCM therapies have potential advantages in SPS treatment, but evidence is week.

H. Analysis of the death

There were 6 cases of death, 3 case dead of respiratory failure, 1 case dead of suffocation, 1 case dead of cardiac arrest and 1 case without reporting death cause. Sudden death of SPS may be related to spasms caused by paroxysmal autonomic nerve dysfunction.

IV. CONCLUSION

Two conclusions were drawn based on these retrospective case series. Firstly, benzodiazepines can be used as experimental medication, starting from a light dose. This is important for diagnosis and treatment. Secondly, we recommend that further studies should focus on the effect of TCM therapy for SPS. Controlled clinical trials or randomized controlled trials could be applied for this purpose.

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REFERENCES


