Treatment of Stiff-Person Syndrome

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Case

A 62-year-old woman presented with trunk stiffness and rigidity manifested as slowly progressive difficulty turning and bending, slow-step walking, impaired balance, and sudden falls resulting in fear of walking alone, especially crossing a street or in crowded places. Her fears were interpreted as related to anxiety and depression, and she visited a neurologist who diagnosed "rigid parkinsonism." Brain MRI was normal, and a DaTscan was reported as suggestive of extrapyramidal disease. She was prescribed sertraline and carbidopa/levodopa, but there was no benefit. Over the ensuing 12 months, her symptoms worsened; the doses of both carbidopa/levodopa and sertraline were increased, and pramipexole was added, but again there was no benefit. When she came to see us, close to 2 years after symptom onset, there was prominent hyperlordosis with concomitant stiffness of both abdominal and lumbar paraspinal muscles. There was no cogwheel rigidity. She was talkative, with normal articulation, but very anxious, constantly emphasizing her fear to walk alone and her frequent falls especially in public spaces or with unexpected stimuli. The constellation of these symptoms raised the strong suspicion of stiff-person syndrome (SPS). We discontinued carbidopa/levodopa (over 1 month) and ordered anti-GAD antibodies which came back strongly positive at very high titers of 1:1000.0000. She also had history of thyroid disease with positive antithyroid antibodies. Pramipexole was also stopped. She was started on baclofen 10 mg TID along with diazepam 10 mg TID (first dose in the evening, increasing to TID over 3 weeks). After 6 weeks, she had clearly improved with better mobility, less stiffness, and reduced fear of walking. I asked her to increase the diazepam, but it made her sleepy; I added, instead, gabapentin 400 mg TID. She improved further, became able to walk easily without falling, moved about freely in open spaces without assistance, and was able to drive a car again. Sertraline was also discontinued. About 3–4 months after therapy, she became functional with minor limitations to the point that additional treatments were not deemed necessary. Because the improvement was clinically satisfactory and the drugs well tolerated, no need for immunotherapy was considered at this point.

Discussion

Stiff-person syndrome (SPS) is an autoimmune CNS disorder characterized by the triad of (1) *stiffness of truncal and proximal limb muscles* due to continuous co-contracture of agonist and antagonist muscles resulting in hyperlordosis, difficulty bending or turning, and slow, wide-based gait in an effort to improve balance; (2) *episodic spasms*, superimposed on the stiffness, precipitated by sudden unexpected noises and tactile and visual stimuli or emotional upset; and (3) *overt anxiety and task-specific phobias*, often leading to the erroneous diagnosis of a primary anxiety disorder and visits to psychiatrists. If anxiety dominates the clinical picture, SPS is discovered in retrospect when the administration of antianxiety agents, such as diazepam or alprazolam, improves the motor symptoms.

The symptoms vary in severity, from mild to severe, and can be fluctuating or fixed leading to disability. Up to 65% of SPS patients cannot independently perform daily activities because of body stiffness, phobias, anxiety-triggered muscle spasms, and frequent falls; others use walkers or wheelchairs, and still others are bedridden due to severe stiffness. At times, the muscle spasms are prominent and continuous and, if respiratory and thoracic paraspinal muscles are involved, may result in breathing difficulty, perfuse sweating, and other autonomic release phenomena ("status spasticus") requiring

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admission to the intensive care unit, intravenous diazepam administration, hydration, and supportive care.

The diagnosis of SPS is clinical, based on the aforementioned symptoms and signs, the exclusion of other neurological diseases that could explain stiffness and rigidity, and the absence of extrapyramidal or pyramidal tract signs. The diagnosis is aided by normal MRI of the brain and spinal cord; by the electrophysiologic recordings which demonstrate low-frequency motor unit firing at rest, simultaneously from agonist and antagonist muscles in spite of the patients' effort to relax (normally, when the agonist muscles contract, their respective antagonists are in a state of relaxation with no electrical activity); and the presence of high-titer antibodies against glutamic acid decarboxylase (GAD)-65 or against glycine receptors (other antibodies seen in rare SPS patients are listed on Table 77.1). SPS is frequently associated with other autoimmune diseases; among more than 100 patients we have followed, diabetes, thyroiditis, vitiligo, and pernicious anemia were the most common, with type I diabetes occurring in up to 35% of the patients. The presence of diabetes in a patient presenting with the aforementioned symptoms should raise the suspicion of SPS. Low titers of anti-GAD antibodies are also seen in diabetes as GAD is present in the β-cells of the pancreas, but there is distinction between the two antibodies; in diabetes the titers are low (below 1–2000 units), and the antibodies are directed against conformational GAD epitopes, while in SPS the titers are very high (above 5–10,000, usually in hundreds of thousands), and the antibodies are directed against linear epitopes.

Table 77.1 The spectrum and specificity of antibodies in stiff-person syndrome and other overlapping autoimmune CNS disorders

1. High titers of anti-GAD antibodies [>10 times, compared to the low titers (1–2000 units) seen in diabetes]
SPS, detected in 80% of patients (with IgG antibodies directed against linear GAD epitopes)
Limbic encephalitis
Myoclonus and temporal lobe epilepsy
Progressive encephalomyelitis with rigidity and myoclonus (PERM)
Cerebellar ataxia
Impaired eye movements with nystagmus and abnormal saccades
Neuromyotonia
Batten's disease (including the CLN3 knockout mice, the animal model of Batten's disease)
2. Low titers of anti-GAD antibodies
Insulin-dependent diabetes mellitus (in diabetes, serum IgG recognizes conformational GAD epitopes)
Other, autoimmune or not, disorders (these antibodies are transient or of unclear significance)
Transiently, after IVIg infusion because GAD antibodies are normally present within the various IVIg preparations
3. Anti-glycine receptor alpha 1 subunit (GlyRa1) antibodies
Seen in up to 10% of SPS patients (especially those with prominent spasms and phobias); they usually coincide with anti-GAD, but there may be rare SPS cases which are only GlyRa1-positive
Anti-GlyRa1 receptor antibodies are characteristic and diagnostic of PERM
4. Anti-GABARAP
Seen in up to 65% of SPS (in one series; not in clinical use)
5. Anti-amphiphysin
Seen in up to 5% of paraneoplastic SPS cases
6. Anti-gephyrin
Seen in a single case of paraneoplastic SPS
7. Anti-DPPX (dipeptidyl peptidase-like protein)
Seen in some patients with PERM. DPPX is an extracellular regulatory subunit of the Kv4.2 potassium channels present on neuronal surface and myenteric plexus that explains why patients may have gastrointestinal symptoms

Although high anti-GAD titers in the constellation of the aforementioned symptoms and signs secure the diagnoses of SPS, high tires of anti-GAD antibodies are also seen in other CNS autoimmune disorders including epilepsy, encephalitis, cerebellar ataxia, nystagmus, and myoclonus (Table 77.1). Among GAD-positive patients, there may be at times overlapping symptoms, most often SPS with epilepsy (in 5% of cases), ataxia (in 5–10%), and nystagmus. Diagnostic difficulties arise in about 10–20% of the patients who have the typical SPS clinical triad described above but have no detectable serum antibodies. In these cases of clinically "seronegative SPS," a trial with diazepam is advisable; a positive clinical response, objectively assessed after 6 weeks, is diagnostically helpful. Performing a spinal tap in seronegative patients to check for GAD antibodies in the CSF is not only difficult because of the stiffness but also uninformative, and I do not pursue it because GAD-seronegative patients are also GAD-negative in the CSF. At times, SPS starts focally in one lower limb ("stiff-limb syndrome"); these patients have mild disease, but many of them may later develop generalized symptoms. In 5% of patients, SPS is paraneoplastic, preceding or following certain cancers most often breast, lung, or thymomas. Paraneoplastic SPS is associated with either anti-GAD or more often with anti-amphiphysin or anti-gephyrin antibodies (Table 77.1).

Diagnostic errors are frequent; patients have been misdiagnosed as Parkinson's disease, primary lateral sclerosis, or multiple sclerosis. The prominent stiffness in the spine and the accompanying back pain has led patients to orthopedic surgeons and even to unnecessary surgery, including spinal fusion. The phobias and anxiety often lead to the diagnosis of a primary anxiety disorder and frequent visits to psychiatrists, only to discover in retrospect that after administration of diazepam for anxiety, the SPS improves. Although the phobias seem to stem from a realistic fear of falling caused by the stiffness and spasms, a concomitant primary anxiety disorder due to dysfunction of the CNS inhibitory pathways cannot be excluded. On the other end of the spectrum, there are patients with quite atypical symptoms, manifested with

clinically unusual or bizarre stiffness and painful spasms, often requiring narcotics, who either have very low anti-GAD antibody titers (which are not specific or diagnostic for SPS) or are GAD-negative; these patients do not have SPS but rather a complex functional disorder erroneously labelled "possible SPS."

In designing and understanding the rationale of therapies, the clinician needs to appreciate that two etiopathogenic factors are responsible for the SPS symptomatology; one is the reduction of GABA (presumably by antibodies against GABAergic pathways) which explains the stiffness, heightened sensitivity, phobias, and hyperexcitability and is helped by GABA-enhancing drugs and the second is the underlying autoimmunity which, like any other autoimmune disorder, requires immunotherapy. I typically start therapy with one to two GABA-enhancing drugs and I proceed to immunotherapy only if the response is unsatisfactory. My preference is to use a combination of two drugs, as follows:

(a) Diazepam, which is the initial treatment of choice. Because the doses required may at times be as high as 40–50 mg per day causing lethargy, drowsiness, and dependency, I try not to go higher than 10 mg TID. Similar compounds include clonazepam, alprazolam, lorazepam, and tetrazepam.
(b) Baclofen up to 50 mg daily; this is an excellent drug that I always start along with low doses of diazepam.
(c) Gabapentin up to 3–4000 mg daily. It helps the majority of patients in combination with the other two.
(d) Other GABA-enhancing drugs, such as levetiracetam, vigabatrin, or tiagabine, may offer supplementary benefit. In general, if the first three agents are not controlling the disease in a satisfactory manner, I proceed to immunotherapy. Anti-spasticity agents such as tizanidine and dantrolene offer minimal benefit. Botulinum toxin may help some patients, but the doses required are high and the benefit not overall substantial. I do not recommend intrathecal baclofen.

For immunotherapy, I start with intravenous immunoglobulin (IVIg), because in a controlled study, it was shown to be beneficial. I use 2gm/kg per month and try to maintain the improvement with 1 gm/kg as needed, usually every 2–3 months. For IVIg responders, I have tried to use as IVIg-sparing agents an immunosuppressant drug, such as CellCept or azathioprine, but their efficacy has been overall disappointing. For unclear reasons, corticosteroids are not very helpful. If IVIg is not helpful or sufficiently effective, I consider either plasmapheresis or rituximab, both of which can help a small number of patients. My personal preference is rituximab because in a controlled study we conducted, a small number of patients substantially improved with long-lasting benefit, even though the study did not overall demonstrate a statistically significant benefit owing to a strong placebo effect.

Suggested Reading

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