Stiff-person Syndrome

Olavo M. Vasconcelos, MD
*Marinos C. Dalakas, MD**

Address
*Neuromuscular Diseases Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Drive MSC 1382, Building 10, Room 4N248, Bethesda, MD 20892, USA.
E-mail: dalakasm@ninds.nih.gov

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Opinion statement

Stiff-person syndrome (SPS) is a progressive neurologic disorder characterized by 1) stiffness that is prominent in axial muscles, with co-contraction of agonist and antagonist muscles; 2) sudden episodic spasms; and 3) absence of another disease that causes similar symptoms. The diagnosis of SPS is based on clinical grounds and requires a high degree of suspicion. The diagnosis is, however, aided by electromyography, which demonstrates motor unit firing at rest simultaneously from the agonist and antagonist muscles, and by high serum titers of antibodies against glutamic acid decarboxylase (GAD), the rate-limiting enzyme for the synthesis of gamma-aminobutyric acid (GABA), which is the brain's main inhibitory neurotransmitter. The reduced GABA level in the brain and cerebrospinal fluid explains the patients' stiffness and justifies the clinical improvement observed by drugs enhancing GABAergic transmission. The association of SPS with other autoimmune disorders or autoantibodies, the intrathecal GAD-specific immunoglobulin G antibody synthesis, and the suppression of GABA by the patient's antibodies supports the autoimmune nature of SPS and justifies the use of immunotherapies. At present, GABA-enhancing agents, such as benzodiazepines, valproate, vigabatrin, tiagabine, gabapentin, and baclofen, provide symptomatic relief. Plasmapheresis, steroids, and periodic intravenous immunoglobulin infusions provide additional and lasting benefit. In this article, the treatment options for patients with SPS are discussed based on the authors' experience and that of others. The beneficial effects from the first controlled study conducted in SPS using intravenous immunoglobulin are presented.

Introduction

CLINICAL SYMPTOMOLOGY

Stiff-man syndrome (SMS) was a term coined by Moersh and Woltman [1] to describe a series of 14 patients, who presented with progressive and fluctuating muscle stiffness, painful muscle spasms, and difficulties with ambulation, collected over many years. Since that time, a large number of patients have been described, diagnostic criteria have been defined, and the disease has been established as a distinct clinical entity [2–8]. Because women are frequently affected, the more appropriate term *stiff-person syndrome* (SPS) has been introduced to replace the original term *SMS* [5,6]. Stiff-person syndrome is a treatable disease, hence the need to identify it early and treat it properly. The disease typically begins with spasms and stiffness, which initially fluctuate but eventually become constant and more prominent in the trunk and the proximal lower extremity muscles. Because a reliable diagnostic marker is not available, identification of SPS relies heavily on clinical grounds and requires a high degree of suspicion [2–8]. At the Neuromuscular Diseases Section of the National Institute of Neurological Disorder and Stroke, the following criteria, useful not only for clinical diagnosis, but also for the conduct of clinical trials [5,6], have been used: 1) insidious, but rarely acute or sudden, onset of stiffness in the axial (trunk) or proximal lower extremity muscles, most prominently in the abdominal and thoracolumbar paraspinals, that

often result in difficulty turning or bending at the waist; 2) co-contraction of agonist and antagonist muscles that causes inability to relax (when an agonist muscle is activated, the antagonist muscle relaxes; in SPS both agonist and antagonist muscles are concurrently in spasms). The authors believe that such co-contraction is *sine que non* criterion for the disease; it can be seen clinically and confirmed electrophysiologically. 3) Sudden, episodic spasms superimposed on the underlying rigidity; the spasms may be painful and are precipitated by unexpected external stimuli, such as sudden noises, tactile stimuli, emotional upset, or fear of open spaces (heightened sensitivity). And 4) absence of any other neurologic disease or chronic pain syndrome that could account for these symptoms.

Clinical symptomatology is aided by two laboratory tests, electromyographic (EMG) findings, and the presence of autoantibodies. Electromyographic abnormalities consist of continuous motor unit firing at rest simultaneously from the agonist and antagonist muscles. The autoantibodies are directed against the following known autoantigens: 1) glutamic acid decarboxylase 65 (GAD_{65}), the rate limiting enzyme for the synthesis of gamma-aminobutyric acid (GABA) [9,10]; 2) amphiphysin [11]; and 3) gephyrin [12]. Up to 70% of SPS patients have antibodies against GAD, and 5% have antibodies against amphiphysin and, very rarely, gephyrin. In patients with anti-amphiphysin or gephyrin antibodies, the disease is associated with cancer. High titer antibodies against GAD are specific for SPS [6,13••]; this is in contrast to low titer anti-GAD antibodies, which are also seen in patients with diabetes. In SPS, there is intrathecal synthesis of anti-GAD immunoglobulin G antibodies, indicating an autoimmune process within the central nervous system compartment.

Stiff-person syndrome is often associated with other autoimmune disorders, diabetes [5,6,13••], and disease-associated autoantibodies, including anti-thyroid, antinuclear antibodies, extractable nucleic acid, and antiparietal cells. At least 5% of the authors' patients had seizures [5,6], probably because of low levels of GABA observed in the brain and the spinal fluid [5,6,13••]. Some SPS patients may also have a concurrent cerebellar ataxia or signs of encephalitis [14–16]. Although in the authors' experience these are rare occurrences, the term *SPS-plus* has been coined to characterize these cases. Many patients also have more stiffness in one limb, hence the term *stiff-limb syndrome* [15,16]. The authors do not view the "stiff-limb" as a distinct subset, because most of the patients with SPS start asymmetrically with more prominent stiffness in one extremity, but then gradually evolve into generalized SPS [5,6].

QUANTIFICATION OF STIFFNESS FOR CLINICAL STUDIES

Because of the highly subjective nature of the symptoms in SPS patients, reproducible scales that assess stiffness and spasms are needed to perform clinical trials. The clinical tools the authors have used are the following (National Institutes of Health Stiffness Scales) [5,6]: distribution of stiffness—this is rated by the physician according to the number of stiff areas (0, no stiff areas; 1, stiffness of the lower trunk; 2, stiffness of the upper trunk; 3, stiffness of both legs; 4, stiffness of both arms; 5, stiffness of the face; and 6, stiffness of the abdomen and back). Heightened sensitivity—this measures the distribution of muscle spasms, their frequency, sensitivity to stimuli, frequency of falls, and the events predisposing to falls and environmental factors that precipitate or increase spasms, such as open spaces, anxiety, crowds, unexpected noises, sudden movement, jarring, approaching cars, a sense of a hurry, or emotional upset. The magnitude of heightened sensitivity is measured according to the factors that induce stiffness and spasms as follows: 1) induced by noise; 2) induced by visual stimuli; 3) induced by somatosensory stimuli (*ie,* light touch); 4) induced by voluntary activities; 5) induced by stress or emotional upset; 6) untriggered; and 7) induced when awakened by nocturnal spasms. The maximum score of 7 is the total score of heightened sensitivity. Timed activities—the time needed to perform the following tasks: 1) rising from a chair; 2) walking a 30-foot length of corridor; 3) turning 180° with feet together, clockwise and counterclockwise; and 4) going up and down a regular flight of stairs.

With these tools, SPS patients can be quickly and objectively assessed at regular visits and their status recorded on the chart for future reference. Among the noted measures, the most reproducible scales are the distribution of stiffness and heightened sensitivity, as described [6], which are the two scales the authors recommend and apply for therapeutic trials.

Treatment

Pharmacologic treatment

- According to the symptomatology, the goals of therapy in SPS patients include the following: 1) maximize control of stiffness and spasms and improve performance of the patients' daily activities without excessive sedation or adverse reactions; 2) document effectiveness of therapeutic

interventions with objective means and in a controlled design. This is fundamental because of the highly subjective nature of the symptoms and the emotional charge connected with a number of clinical phenomena. Asking the patients to keep a diary that records the frequency and severity of spasms, number of falls, startle responses, and changes in ambulation, mobility, or ability to perform activities of daily living is essential.
3) Control the other intercurrent conditions including diabetes, thyroid disease, or epileptic seizures.

- The wide range of therapeutic options in SPS is based on anecdotal experience from case reports and small series or trials. There has been only one controlled clinical trial. Because the disease is now increasingly recognized and more patients are cared for by large centers, there will be more opportunities for large-scale clinical trials. The pharmacologic treatment of SPS is divided into *symptomatic care* and *immunologic interventions*. In practice, the two strategies are used either separately or, more often, in combination according to the severity of the patient's symptoms.
- The reduction of symptoms is often attained with agents that enhance GABAergic transmission, underscoring the role of reduced GABA level in the pathogenesis of the disease [5,13••]. The wide range of drugs used for symptomatic care are sedative-anxiolytics, with the most common being the benzodiazepines, antiepileptic drugs that enhance GABAergic transmission, and anti-spasticity agents. Other, less commonly used drugs, reported in single case studies include muscle relaxants, botulinum toxin, and some centrally acting agents. Among the immunotherapeutic interventions, the most frequently used agents are corticosteroids, immunosuppressants, plasmapheresis, and intravenous immunoglobulin (IVIG) (Table 1). The rationale for selecting one of these options in the management of patients with SPS relies on their safety record, relative efficacy, ease of administration, cost, and patient compliance.

Sedative-anxiolytics

- Among this family of drugs, benzodiazepines are the most effective and most frequently used, exerting their action by increasing GABA and acting as a $GABA_A$ agonist. Diazepam is the drug of choice originally documented by Howard [17] and subsequently validated by others [2,18,19]. The response to diazepam is so common and clear that if a patient with assumed SPS does not respond to it, the diagnosis of SPS may be in doubt. Although the response to diazepam is gratifying, the required doses are so high that most patients cannot tolerate the drug because of unacceptable side effects, especially excessive sedation.
- The clinical efficacy of diazepam has been supported by concomitant EMG studies that showed that the continuous uninhibited motor unit activity at rest is abolished or greatly attenuated after intravenous administration of the drug. The daily doses needed vary from patient to patient and range from 20 mg up to 300 mg per day in divided doses every 3 to 6 hours. In the authors' experience, the average total daily dose required, but barely tolerated, is 20 to 40 mg. In addition to diazepam, other similar compounds include clonazepam, alprazolam, lorazepam, and tetrazepam with the average maintenance dose from 4 mg to 6 mg per day (Table 1). Treatment with these drugs is initiated at low doses followed by slow titration according to response or side effects. Switching from diazepam to clonazepam can be done [20], and although the authors do not recommend concurrent administration of two agents from this category, some patients with difficult disease have required a combination of diazepam with

Table 1. Most commonly used therapies in patients with stiff-person syndrome

Therapy	Route	Dosage range	Presumed mechanism of action
Symptomatic care			
Sedative-anxiolytics			
Diazepam	Oral, IV, rectal*	5 to 300 mg; 5 to 10 mg	Central $GABA_A$ agonist
Clonazepam	Oral	2.5 to 18 mg	Central $GABA_A$ agonist
Alprazolam	Oral	8.25 mg	Central $GABA_A$ agonist
Lorazepam	Oral	6 mg	Central $GABA_A$ agonist
Tetrazepam	Oral	6 mg	Central $GABA_A$ agonist
Anti-epileptic drugs			
Valproate	Oral	0.6 to g	Augment GABA transmission
Gabapentin	Oral	1200 mg per day	Structurally related to GABA, but mechanism of action is unknown
Vigabatrin	Oral	2 to 3 g per day	GABA transaminase inhibitor
Tiagabine	Oral	6 mg per day	Blocks GABA reuptake
Anti-spasticity agents			
Baclofen	Oral	10 to 140 mg†	$GABA_B$ agonist
Tizanidine	Oral	6 mg per day	Central alpha2-adrenergic action; inhibits norepinephrine release
Others			
Dantrolene	Oral	600 mg	Affect on GABA system unknown
Methocarbamol	Oral, IV	Unknown (oral); 1 g per hour IV‡	
Botulinum toxin A	Intramuscular	560 to 1000 U	NMJ blocking, prevents acetylcholine exocytosis
Clonidine	Oral	0.0025 mg/kg per day	Central alpha2-adrenergic action; inhibits norepinephrine release
Milacemide	Oral	2.4 g per day	Glycininergic (glycine precursor)
Immunotherapies			
Corticosteroids			
Prednisolone	Oral, IV‡	25 to 80 mg per day; 1 g per day IV	Immunosuppression/modulation
Prednisone	Oral	25 to 80 mg per day	Immunosuppression/modulation
Immunosuppresive agents			
Azathioprine	Oral	2.5 mg/kg per day	Immunosuppression/modulation
Methotrexate	Oral	15 to 20 mg per day	Immunosuppression/modulation
Mycophenolate	Oral	2 g per day	Immunosuppression/modulation
Plasmapharesis	IV	5 to 6 passes	Immunosuppression/modulation
Immunoglobulin	IV	2 g/kg	Immunosuppression/modulation

*For acute spasm or status spasticus.
†Intrathecal baclofen 58.5 to 1600 µg per day has also been used, but is not recommended.
‡Unproven benefit in the acute state of spasm.
GABA—gamma-aminobutyric acid; IV—intravenous; NMJ—neuromuscular junction.

alprazolam or clonazepam. The need for high doses of these drugs and the long-term administration required to control the disease have caused unacceptable side effects, especially excessive daytime sedation, that often limit the patients' activities more than the limitations imposed by the disease itself.

Antiepileptic drugs

- Although a controlled study has never been conducted, antiepileptic drugs that enhance the brain's GABAergic transmission have been helpful in improving the symptoms of SPS patients when used alone or concurrently with one of the benzodiazepines mentioned in this article.

Valproate

Dosages range between 600 mg to 2 g daily. Although valproate probably exerts its beneficial effect by enhancing GABAergic transmission, a concomitant effect on inhibition of excitatory neurotransmission (glutamate or aspartate) may also play a contributory role. Valproate is well tolerated and in some cases its effect is clinically significant [21, Class III].

Vigabatrin

A structural analogue of GABA, vigabatrin acts by irreversible inhibition of GABA-transaminase, which is the enzyme responsible for the breakdown of GABA [22]. Daily doses of 2 to 3 g are well tolerated and have been helpful in several cases [22–25, Class III].

Tiagabine

An inhibitor of GABA catabolism, tiagabine at a dose of up to 6 g per day has helped one patient who failed to respond to benzodiazepines, baclofen, and other antiepileptic drugs [26•, Class III].

Gabapentin

Gabapentin is a GABA-analogue that has been also used at daily doses ranging from 300 to 3600 mg. Even though in the authors' experience gabapentin has not resulted in dramatic benefits, the drug has an excellent safety profile. The other antiepileptic drugs, such as carbamazepine, phenobarbital, phenytoin, or lamotrigine, offer minimal benefit.

Centrally acting anti-spasticity agents

Baclofen

A $GABA_B$ agonist, baclofen is the preferred compound of this family of agents. In the authors' experience, baclofen is the second most useful drug (diazepam is the first) for the symptomatic treatment of SPS. Both baclofen formulations (oral and intrathecal) have been tried [27–32, Class III]. Oral baclofen is the preferred route, with doses starting at 5 to 10 mg daily and reaching gradually up to a total of 60 to 90 mg daily [27,28, Class III]. Combination of diazepam with baclofen has been helpful, although the high doses needed for sufficient suppression of the muscle hyperactivity are hampered by the disabling cognitive side effects (sedation, vertigo, and cognitive clumsiness). To avoid the systemic side effects and increase the effectiveness of baclofen, therapy with intrathecal administration, using the baclofen pump, has been attempted [29–32, Class III]. In a controlled study, intrathecal baclofen showed a quick, objective, and statistically significant improvement in the reflex EMG activity with reduction in the summated EMG parameters compared with placebo [31, Class III]. However, serious complications have been observed, including catheter rupture resulting in severe spasms, catheter dislocation causing root symptoms, malfunction of the pump resulting in inaccurate dosing and transient coma-like state, and sudden pump failure resulting in acute withdrawal reactions or even death in two participants [30–32, Class III]. The risks and the inherent costs related to intrathecal baclofen, have limited its use.

Tizanidine

A centrally acting alpha2-adrenergic receptor agonist, tizanidine is a useful antispasticity agent [8]. Daily doses up to 12 mg have been tried, but the drug was poorly tolerated because of side effects, most notably drowsiness and fatigue. In one case, 0.005 mg/kg of tizanidine administered via intravenous drip was said to dramatically reduce muscle tone and suppress abnormal reflex activity within 10 to 20 minutes after the infusion [8]. Whether the fast and effective action of tizanidine is as sufficient for the treatment of acute crisis of painful spasms remains to be determined. The significant drop of blood pressure noted after intravenous administration of tizanidine may be an important factor limiting its use.

Other agents

Dantrolene

Dantrolene is a locally acting muscle relaxant given up to 600 mg per day that was reported to result in significant relief of spasms and stiffness in one case [20].

Methocarbamol

Methocarbamol is a centrally acting skeletal muscle relaxant given intravenously at 1 g per hour under continuous monitoring [33, Class III] that was helpful in arresting the refractory status spasticus of an SPS patient. The drug, a derivative of mephenesin carbamate, may act by facilitating GABAergic pathways.

Cyclobenzaprine

Cyclobenzaprine was also tried, but, paradoxically, it caused worsening of the symptoms.

Botulinum toxin A

Botulinum toxin was used in two women who had failed other symptomatic therapies [34,35, Class III]. Both patients received unilateral limb injections of diluted botulinum toxin A at 560 to 1000 U and contralateral limb injections of the same volume saline. Three days after the first treatment, a reduction in muscle spasms was noted on the site injected with botulinum toxin A, followed by a gradual generalized improvement of the muscle tone that was probably because of hematogeneous spread of the toxin. The benefits lasted for 4 months. Similar response was observed in the relief of spasms of the lumbar paraspinal musculature in a 36-year-old man with intractable painful lower back stiffness refractory to diazepam and baclofen [34, Class III]. In this case, injections (560 U) in L_1 to L_5 paraspinal muscles over a 3-week period improved the stiffness starting 1 week after the first injection, leading to a comfortable and independent ambulation. The clinical response lasted approximately 4 months. Although these preliminary results are intriguing, the efficacy and indications of botulinum toxin in patients with SPS remain unknown without performing a controlled study. Expertise of the personnel performing the injections, safety, and cost are additional unknown factors.

Clonidine

An alpha-adrenergic agonist and centrally acting antihypertensive drug, clonidine was reported helpful in SPS patients by inhibiting release of norepinephrine [8].

Clomipramine and levodopa

Clomipramine and levodopa have been tried with dramatic worsening of the patients' symptoms, which is caused by upregulation of catecholamines, which exacerbate SPS [8].

Milacemide

Milacemide is a glycine precursor that has been tested in three patients with SPS during an open-label trial [36]. Milacemide showed no benefit at 2400 mg per day. Drowsiness and constipation were noted in one individual, and a generalized seizure occurred in another.

Immunotherapy

- The rationale for applying immunotherapies in SPS patients is based on the autoimmune pathogenesis of the disease [5,6,9,10,37–40], as supported by 1) the circulating antibodies against GAD_{65} that have a distinct epitope specificity; 2) the intrathecal production of anti-GAD antibodies and their capacity to inhibit the synthesis of GABA; 3) frequent association of SPS with other autoimmune disorders or autoantibodies; and 4) distinct immunogenetic associations.

Corticosteroids

Corticosteroids have been used in patients with SPS, but a controlled trial has not been conducted [41–43]. Oral prednisone has been used in combination with one of the anti-symptomatic drugs or with other immunotherapies. Steroids can be used at the standard doses and regimens as in other autoimmune disorders [44], starting at high single daily doses followed by a gradual taper for the lowest possible effective dose on an alternate day schedule [44]. A varying degree of improvement is usually seen. In one patient, study of the humoral and cellular reactivity before and after steroids showed no reduction in antibody concentrations or a detectable switch in epitope recognition, despite the patients' clinical improvement [43]. In a patient with SPS with adrenocorticotropic hormone and growth hormone deficiency, administration of corticotropine (adrenocorticotropic hormone) resulted in a rapid and marked improvement [41]. Adrenocorticotropic hormone therapy was combined with prednisone for maintenance in two patients who eventually became steroid-dependent [42]. Whether intravenous methylprednisolone can be of benefit in alleviating acute spasms remains untested. In the authors' experience, steroids can help certain patients who failed to respond adequately to other therapies. Triggering diabetes, or exacerbating overt diabetes, is a serious consideration that may limit the general use of steroids in SPS patients.

Immunosuppressive agents

There is no data on the efficacy of these agents in the treatment of SPS. Azathioprine has been used, but its effect remains unclear in spite of some promising case reports and the possibility of lowering serum and spinal fluid GAD antibody titers [30]. Cyclophosphamide and mycophenolate mofetil have also been used in conjunction with plasmapheresis and IVIG in a patient with intractable SPS, but the benefit derived from these drugs was not clear [45, Class III]. The authors have observed two patients who claimed an enhanced benefit from IVIG when methotrexate was added. The authors have not, however, validated the benefit of methotrexate in a more systematic fashion.

Plasmapheresis

The results from the anecdotal reports of plasma exchange are encouraging. Six from a total of 11 SPS patients reported (five women and six men), age 36 to 65 years (mean 50.5 years), improved in various small series [46–52,53•, Class III]; two patients claimed marginal and transient response [53•], and three others reported no benefit [47,48]. Gender, disease duration, or presence of GAD antibodies in the serum or spinal fluid did not correlate with or predict response to plasmapheresis. Clinical improvement varied from case to case, lasting from several weeks in some patients to many months in others. Because the synergistic effect of the concurrently used anti-symptomatic or immunosuppressive drugs could not be

clearly sorted out in these reports, the exact number of patients whose benefit was derived exclusively from plasma exchange is unclear. Plasma exchange is an option for some patients, but, based on the data, it seems that less than 50% show meaningful benefit.

High-dose intravenous immunoglobulin

Intravenous immunoglobulin has been reported of benefit in several open-label small series [55–57] or anecdotal case reports [58–60,61•]. Such encouraging reports prompted one of the authors of this paper to conduct a controlled study with IVIG [62••]. This was the first controlled, large-scale, therapeutic trial conducted in SPS. The authors used reproducible and objective measurements of stiffness and heightened sensitivity index, as described earlier, to assess the outcome of therapy. Sixteen patients who had SPS and anti-GAD_{65} antibodies were randomly assigned to receive IVIG or placebo for 3 months, followed by a 1-month washout period, and then 3 months of therapy with the alternative agent [62••]. Efficacy was judged by improvements in scores on the distribution-of-stiffness (month 1) to the 2nd and 3rd month of each treatment phase. Direct and carryover effects of treatment were compared in the two groups [62••].

Among patients who received IVIG first, stiffness scores decreased significantly (P=0.02), and heightened sensitivity scores decreased substantially during IVIG therapy, but rebounded during placebo administration. In contrast, the scores in the group that received placebo first remained constant during placebo administration, but dropped significantly during IVIG therapy (P=0.01) (Fig. 1A and 1B). When the data were analyzed for a direct and a first-order carryover effect, there was a significant difference in stiffness scores (P=0.01 and P<0.001, respectively) between the IVIG and placebo groups. Intravenous immunoglobulin therapy also had a significant direct treatment effect on heightened sensitivity scores (P=0.03). Eleven patients who received IVIG became able to walk better or without assistance, their frequency of falls decreased, and they were able to perform work-related or household tasks. The duration of the beneficial effects of IVIG varied from 6 weeks to 1 year. Anti-GAD_{65} antibody titers declined after IVIG, but not after placebo administration.

Intravenous immunoglobulin had a positive effect on patients' activities and quality of life including degree of stiffness, frequency of falls, ability to walk unaided, shower independently, and work or perform household chores [62••, Class I]. Also, it significantly decreased the episodic spasms triggered by unexpected noises, tactile stimuli, fear, or emotional upset. The results are especially gratifying because SPS, if untreated, can result in total disability [6]. Considering that up to 65% of patients with SPS cannot perform routine daily activities despite efforts to control or reduce symptoms with daily intake of the variety of the drugs already mentioned, IVIG becomes an important, although expensive, regimen in the treatment of SPS.

In some of the patients, the efficacy was short-lived (lasting only up to 6 weeks), which is a response that is commonly seen in other autoimmune neuromuscular disorders [63]. In others, however, the benefit was sustained, lasting for up to a year. The mechanisms of such a long-lasting effect are unclear. Although the role of anti-GAD antibodies in SPS has not been clearly established, there is enough evidence that they are pathogenic and inhibit the synthesis of GABA, resulting in low GABA levels in the brain and spinal cord [13••]. Because 25% to 35% of the brain synapses are GABAergic, a reduction in GABA because of anti-GAD antibodies could easily explain the spasms and the increase muscle tone seen in SPS patient [62••, Class I]. That IVIG decreased the symptoms of the disease supports the view that SPS is primarily a functional rather than a structural disorder with an ongoing immune response that impairs GABAergic transmission [62••, Class I]. Because GABA is involved in many brain circuits that control muscle tone, autonomic responses, fear, arousal, and behavior, increased transmission of GABA, as a result of the immunoregulatory effects of IVIG, can explain the reduction in both muscle stiffness and the frequency of spasms triggered by fear or other external stimuli.

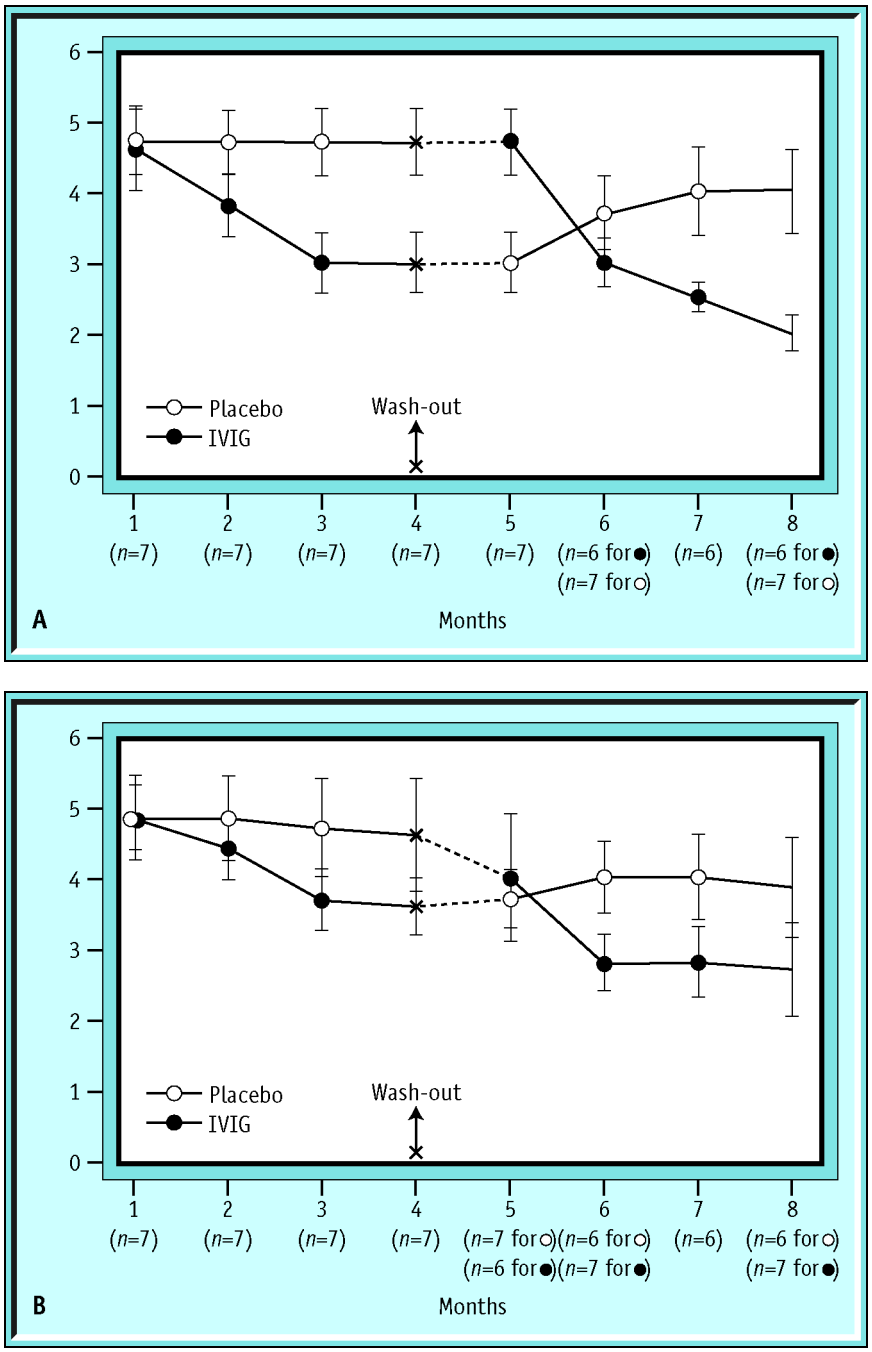

Figure 1. A, Mean (±SE) distribution-of-stiffness scores. **B,** Heightened sensitivity scores. According to whether patients were assigned to receive intravenous immunoglobulin (IVIG) or placebo first, the differences in the stiffness scores between placebo and IVIG were significant at months 3, 4, 5, 7, and 8 (**A**); the differences for the heightened sensitivity scores were significant at months 6 and 7 (**B**). *Open symbols* indicate placebo administration, and *solid symbols* indicate IVIG administration. The wash-out period is marked by the *letter X*.

The authors' study with IVIG also led to a dose reduction of anti-symptomatic medications in most of the patients. Whether combination with other immunotherapies is more effective, or if IVIG is as effective in anti-GAD-negative patients, remain unclear.

Although the anti-GAD_{65} antibodies declined after IVIG therapy, the titers did not correlate with the severity of disease or the magnitude of the clinical response. If anti-GAD_{65} antibodies are pathogenic, IVIG may have inhibited their activity by accelerating the rate of immunoglobulin G catabolism [64], by acting directly on Fc receptors of B cells to suppress autoantibody production, or by inducing anti-idiotypic antibodies [63,65••]. Other effects of immune globulin on T cells and cytokines [63,65••] may also have had a complementary role in suppressing disease activity.

The importance of the controlled study with IVIG is that its efficacy proves that SPS is an autoimmune disorder. Consequently, treatment with other immunomodulating agents is anticipated to add additional benefit to patients who do not respond adequately to IVIG or whose response declines with time.

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