

# Stiff-person syndrome--AN EXPLANATION

## Contributors

## Publication dates

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## Synonyms

Stiff-man syndrome

## Key points

- Stiff-person syndrome is a rare disorder that causes continuous muscle contraction with spasm, abnormal postures, and progressive disability.
- Stiff-person syndrome is often associated with other autoimmune signs and symptoms as well as nonspecific and organ-specific [plasmapheresis](#) is variable. [dysphagia](#) with disordered esophageal and gastric motility ([Soykan and McCallum 1997](#)). Total esophageal obstruction due to spasm of the cricopharyngeus muscle has also been reported ([Sulway et al 1970](#)). [ataxia](#), oculomotor abnormalities, and [rigidity](#). Voluntary movements are restricted in range and slowed. The gait is slow and deliberate, resembling that of "a tin soldier" ([Ornstein 1935](#)). [GAD](#) antibodies and evidence of other autoimmune disease; it responds to pharmacotherapy with [myasthenia gravis](#) with or without thymoma ([Aso et al 1997](#); [Nicholas et al 1997](#)), adrenal and ovarian failure ([McEvoy 1991a](#)), pernicious anemia, vitiligo ([Brashear and Phillips 1991](#)), [organ-specific antibodies](#) (such as those directed against islet cells, parietal cells, thyroid microsomal fraction, and thyroglobulin) are more commonly seen. Non-organ-specific antibodies, such as antinuclear, antimitochondrial, and antismooth muscle antibodies are also common in stiff-person syndrome ([Grimaldi et al 1993](#)). These patients are also more likely to have a personal or family history of organ-specific autoimmune disease ([Solimena et al 1990](#)).

Because GAD-antibody-positive patients may represent a homogeneous subgroup of stiff-person syndrome patients, Dalakas and colleagues looked at a series of such patients. In this series of 20 patients with stiff-person syndrome and positive anti-GAD antibodies, the average age at the onset of symptoms was 41 years. Diagnosis was made an average of 6 years after symptom onset. The predominant symptoms were muscular rigidity and episodic superimposed spasms. Most had asymmetric onset, and rigidity began as an intermittent phenomenon, but later became fixed. Falls occurred commonly, and chest restriction caused respiratory symptoms in 50% of the patients. On examination, all patients had increased paraspinal tone with hyperlordosis. Stiffness in facial and neck muscles was common. Nearly half the patients had hyperreflexia, and 2 patients intermittently had Babinski signs. Assistive devices were required by all the patients for ambulation. Spasms were common and were provoked by unexpected tactile or auditory stimuli or by psychological factors. Diabetes mellitus and thyroid disease were present in 8 patients. Three patients had pernicious anemia, 1 had celiac disease, and 1 had notalgia paresthetica. Family members with diabetes or thyroid disease were common. Also seen in family members were [diurnal myoclonic jerks](#) in the axial and proximal appendicular muscles ([Martinelli et al 1978](#); [Leigh et al 1980](#); [Alberca et al 1982](#)). Usually, the myoclonic jerks first appear many years into the course of the illness and respond well to [pain](#) associated with exaggerated lumbar lordosis. Superimposed on [EMG](#) demonstrated continuous firing of paraspinal and leg muscles.

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## Etiology

Although earlier studies suggested no neuropathological changes in postmortem tissue from stiff-person syndrome patients, later studies suggested loss of anterior horn cells and spinal interneurons associated with perivascular inflammatory changes and gliosis.

Stiff-person syndrome may not reflect a single pathophysiologic process. However, the association of symptoms with disorders of organ-specific and non-organ-specific autoimmunity as well as the demonstration of CSF using immunocytochemistry or radioimmunoassay in as many as 85% of persons with clinically diagnosed stiff-person syndrome (Murinson et al 2004), and there is evidence of intrathecal antibody synthesis (Dalakas et al 2001b). Intrathecal synthesis of GAD65 antibodies persists for years (Skorstad et al 2009). Radioimmunoassay is 96% sensitive and 95% specific compared with immunocytochemistry for the detection of GAD antibodies (Chang and Lang 2004; Murinson et al 2004). Anti-GAD antibodies are not specific for the diagnosis of stiff-person syndrome. They can be seen in 22% of patients with type 1 diabetes and in 3% of patients with neurodegenerative diseases. However, in these disorders, antibody titers are usually low, and there is no immunoreactivity to recombinant GAD65 (Levy et al 1999). On Western blot, serum and CSF from persons with stiff-person syndrome recognize a 65-kDa protein corresponding to GAD65 (Levy et al 1999). Luciferase immunoprecipitation analysis of anti-GAD antibodies has demonstrated dramatic titer differences between persons with stiff-person syndrome and other disorders associated with these antibodies, with 100% sensitivity and specificity. Anti-GAD antibodies in persons with stiff-person syndrome showed high immunoreactivity, particularly with the central region containing decarboxylase catalytic domain (Burbelo et al 2008). Autoantibodies to the GAD antibody titers in hyperekplexia (Molloy et al 2002; Khasani et al 2004). Electromyography suggests that the motor unit is excessively active in stiff-person syndrome; its activity does not decrease when the subject attempts to relax the muscle or to activate its antagonist and increases when the skin overlying the muscle is stimulated (Martinelli et al 1978). Meinck and colleagues have described a phenomenon called "spasmodic reflex CNS. Immunologically identical GAD is found in the pancreatic beta islet cell, fallopian tube epithelium, and spermatozoa (Solimena and DeCamilli 1991). GAD is localized at the cytoplasmic surface of synaptic vesicles in GABA-ergic nerve terminals and in pancreatic beta islet cells (Solimena et al 1990; Solimena and DeCamilli 1991). Glutamic acid decarboxylase exists in 2 isoforms, 65-kd and 67-kd, which are the products of 2 different genes. Analysis of the binding specificity of GAD65 antibodies in stiff-person syndrome suggests differences in epitope specificity of plasma and CSF GAD65 antibodies, supporting intrathecal synthesis of the antibody. The antibodies inhibit GAD65 activity, preventing GABA synthesis (Raju et al 2005). Detailed immunologic study has shown that T-cells of persons with stiff-person syndrome target epitopes in the middle of GAD65, whereas T-cells of persons with type 1 diabetes target different epitopes in the middle and at the C-terminal end of GAD65 (Lohmann 2003; Burbelo et al 2008). The patients show differences in GAD antibodies as well, with IgG4 and epilepsy, non-IgG to rats induces a characteristic syndrome of muscle stiffness with spasms, supporting a direct role of amphiphysin antibodies in paraneoplastic stiff-person syndrome (Sommer et al 2005). Purified IgG from patients with stiff-person syndrome and anti-GAD antibodies infused directly into the rat cerebellum blocked the enhancement of the corticomotor response caused by repetitive stimulation of the sciatic nerve. Paraspinal administration of the purified IgG induced continuous motor activity in the gastrocnemius muscle (Manto et al 2007).

Neuropharmacologic studies have shown that the muscle spasm of stiff-person syndrome decreases following the administration of valproic acid, EMG shows continuous motor unit activity, and may show fibrillations and fasciculations. Persistence of the muscle contraction during sleep and general anesthesia as well as proximal nerve block distinguish these disorders from stiff-person syndrome, as does the response of these symptoms to Extrapyramidal disorders may present with dystonia. Chronic

encephalomyelitis with rigidity and structural lesions of the nervous system. [autoantibodies](#), such as smooth muscle, mitochondrial, and nuclear antibodies, as well as organ specific autoantibodies including thyroid-microsomal, thyroglobulin, and parietal cell antibodies ([Gorin et al 1990](#); [Darnell et al 1993](#); [Grimaldi et al 1993](#)). Although not needed for diagnosis, in settings where assays for CSF and serum glutamic acid decarboxylase antibodies are available, these may be useful in the confirmation of diagnosis. An evaluation for underlying malignancy is important, particularly in patients with predominant upper body stiffness and sparing of the lumbar and abdominal musculature, or when other neurologic deficits such as encephalopathy, opsochonus, or rigidity and spasm. [valproic acid](#), clonidine, [levetiracetam](#) ([Spehlmann et al 1981](#); [Lorish et al 1989](#); [McEvoy 1991a](#); [Prevett et al 1997](#); [Murinson and Rizzo 2001](#); [Riegg et al 2004](#)). The rarity of stiff-person syndrome has precluded any controlled trials of either symptomatic treatments or strategies to treat the presumed autoimmune basis of the condition.

Anecdotal reports of the effectiveness of [km](#) over successive days) in 16 patients with stiff-person syndrome. Each treatment was given over 3 months. There were significant improvements in the intravenous immune globulin treatment group in stiffness score and in the heightened-sensitivity scale. Anti-GAD65 antibody titers declined during the active treatment phase ([Dalakas et al 2001a](#)). Intravenous immune globulin treatment improves quality of life in stiff-person syndrome ([Gerschlager and Brown 2002b](#)). An evidence-based review suggested intravenous immunoglobulin was useful as second-line therapy in stiff-person syndrome ([Dalakas 2004](#)).

There are anecdotal reports of response to rituximab in a patient refractory to conventional treatment and cytotoxic agents ([Baker et al 2005](#)). A clinical trial of rituximab for stiff-person syndrome has been completed, but there are no published results (see [EMG activity](#), but only 1 patient had significant clinical improvements ([Silbert et al 1995](#)).

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## **Pregnancy**

In isolated cases, stiff-person syndrome symptoms in women have begun during pregnancy or in the peripartum period ([Trethowan et al 1960](#); [George et al 1984](#)). Pregnancy in a woman with established stiff-person syndrome has been described. The pregnancy itself was unremarkable. Indeed, stiffness and spasm improved, allowing reductions in the patient's requirement for [epidural](#) analgesia. Following delivery, the baby did well, though the mother was required to once again increase her medication doses ([Weatherby et al 2004](#)). In another woman who had 2 successful pregnancies,

[Dysarthria](#)

[Graves disease](#)

[Hashimoto thyroiditis](#)

[Botulinum toxin treatment of neurologic disorders](#)

[Intrathecal baclofen](#)

[spasticity](#)

[dystonia](#)

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