# Stiff-person syndrome--DEEPER lOOK

**Contributors**

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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" (Ornsteen 1935).GAD) antibodies and evidence of other autoimmune disease; it responds to pharmacotherapy with myoclonus progresses to death within months and may be associated with grossly abnormal cerebrospinal fluid (Barker et al 1998). The latter syndrome is often a paraneoplastic syndrome and may be associated with antibodies to glutamic acid decarboxylase, amphiphysin I, geophysin, or Ri antibodies (Butler et al 2000; Dalakas et al 2000; Wessig et al 2003; McCabe et al 2004; Grant and Graus 2009; Mehta et al 2009; Graus et al 2010).

Currently accepted clinical criteria for the diagnosis of stiff-person syndrome include: (1) insidious onset of muscular rigidity with difficulty turning or bending, with rigidity most prominent in the limbs and axial muscles, especially abdominal and thoracolumbar; (2) co-contraction of agonist and antagonist muscles, confirmed clinically and electrophysiologically; (3) episodic spasms superimposed on the underlying rigidity, precipitated by noise, tactile stimuli, or emotional upset; and (4) absence of other neurologic or other diseases that could explain the symptoms (Dalakas 1999).

Early studies noted a relationship between stiff-person syndrome and type I diabetes mellitus in as many as 60% of patients (Dalakas et al 2000). Other autoimmune disorders, including thyroiditis (Gorin et al 1990), and autoimmune retinopathy have been described (Steffen et al 1999). Antibodies to GAD can be detected in up to 85% of patients with stiff-person syndrome using immunocytochemistry or radioimmunoassay. GAD antibodies are not specific for the diagnosis of stiff-person syndrome, but titers are higher than in other patients with GAD antibodies, including those with type I diabetes mellitus (Daw et al 1996). Among stiff-person syndrome patients with GAD antibodies, other autoantibodies were common (Dalakas et al 2000).

Jerking stiff-man syndrome resembles stiff-person syndrome; in addition to the chronic muscle spasm, though, there are rapid, violent, nocturnal, or 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 CAD65 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, opsoclonus, 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 Intravenous immune globulin has been reported to have benefited 6 patients in open trials at 2 centers (Amato et al 1994; Karlson et al 1994) and in anecdotal cases (Khanlou and Eiger 1999; Souza-Lima et al 2000). Dalakas and colleagues conducted a randomized, double-blind, placebo-controlled crossover study of intravenous immune globulin (2 g/kg per month administered as sequential doses of 1 g/intrathecal baclofen in 3 patients, all showed improvement in GAD antibodies were detected in amniotic fluid and blood of the infants, but there were no signs of stiff-person syndrome in the infants (Nemni et al 2004). GAD65 antibodies may be seen in the serum of infants of mothers with stiff-person syndrome, but the infants do not themselves necessarily show evidence of the disorder.

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## Anesthesia

A syndrome resembling stiff-person syndrome has been reported with the use of sufentanil during cardiac, abdominal, or vascular surgery. There was no confirmation of continuous muscle firing by electromyography in these 3 cases, in which symptoms resolved within 12 hours (Gust and Bohrer 1995). Prolonged weakness following general anesthesia, including the use of nondepolarizing muscle relaxants, has also been reported in stiff-person syndrome (Johnson and Miller 1995; Bouw et al 2003).

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## ICD codes

ICD-9:
Other and unspecified extrapyramidal diseases and abnormal movement disorders: 333.91
ICD-10:
Other specified extrapyramidal and movement disorders: G25.8

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## Associated disorders

Myasthenia gravis
Pernicious anemia
Type 1 diabetes mellitus
Vitiligo

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## Related summaries

Diazepam
Paraneoplastic syndromes
extrapyramidal disorders
early tetanus
neuropathic disorders
myopathic disorders

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## Demographics

For more specific demographic information, see the Epidemiology, Etiology, and Pathogenesis and pathophysiology sections of this clinical summary.

**Age**

13-18 years

19-44 years
45-64 years
65+ years

**Population**

None selectively affected.

**Occupation**

None selectively affected.

**Sex**

male=female

**Family history**

None

**Heredity**

None

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