

## Stiff-Person Syndrome

<http://www.pnseuronet.org/stiffman.php>

### Clinical Features

Stiff-Person Syndrome (SPS) is a rare neurological disorder first described by Moersch and Woltmann in 1956. The syndrome affects both sexes equally and is of insidious onset, usually in the fourth or fifth decades and is characterised by stiffness, more prominent in axial muscles, with co-contraction of agonist and antagonist and painful spasms precipitated by sensitive stimuli. The disease can progress to involve the proximal and distal part of the limbs and patients sometimes show symmetric spine deformity, typically lordosis. Electromyography reveals the existence of continuous motor unit activity in the affected muscles at rest. The physiopathology of this syndrome is regarded as a disequilibrium between catecholaminergic excitatory and GABAergic inhibitory pathways in spinal cord and central nervous system. Detection of autoantibodies to glutamic acid decarboxylase (anti-GAD antibodies) in the serum of 60-70% of patients suggest an autoimmune mechanism of damage in a subgroup of patients; this is also supported by detection of oligoclonal bands and intrathecal synthesis of IgG.

Several variants have recently been characterised according to the relative distribution of clinical signs. "Encephalomyelitis with rigidity" is characterised by a subacute course leading to death within three years; "jerking stiff person syndrome" presents a predominant brainstem involvement and "stiff limb syndrome" is a focal form with predominant involvement of the spinal cord.

A paraneoplastic variant has been described in association with breast cancer in women harbouring anti-amphiphysin antibodies. In those patients the onset of stiffness in upper limbs is suggestive of a paraneoplastic aetiology. Autoimmunity to gephyrin, a cytosolic protein at post-synaptic inhibitory synapses, has been described in association with undifferentiated mediastinal tumour. SPS has also been reported in association with neoplasia of the colon and lung, Hodgkin's disease, thymoma.

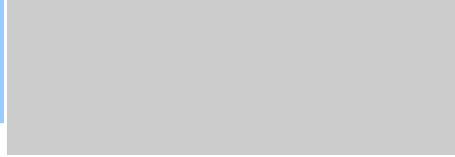
### Associated antibodies

*Anti-GAD antibodies* (figure 1) are present in 60% of patients and stain the axon hillocks of Purkinje cells and diffuse nerve terminals in the molecular and granular layers of cerebellum. In addition, antibodies to pancreatic islet cells, gastric parietal cells, thyroid microsomes, and thyroglobulin are frequently found in patients positive for anti-GAD antibodies. The relationship of autoantibodies to the pathogenesis of the disease remains to be determined. Anti-GAD antibodies are also present in patients with insulin dependent diabetes mellitus and autoimmune polyendocrine syndrome but the anti-GAD level in these syndromes is usually much lower than in SPS.

Figure 1. Immunohistochemistry on frozen

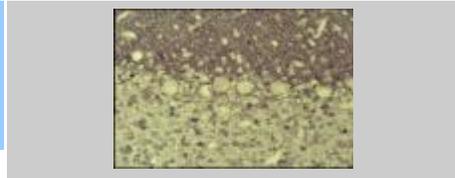


sections of rat cerebellum. Anti-GAD antibodies positive sera recognise the axon hillocks of Purkinje cells and diffuse nerve terminals in the molecular and granular layer of cerebellum.



[Anti-amphiphysin antibodies](#): (figure 2) are directed to a 128 kd neuronal protein concentrated in nerve terminals. Rare paraneoplastic SPS present anti-GAD antibodies alone or associated with anti-amphiphysin antibodies.

**Figure 2.** Immunohistochemistry on paraffin-section of rat cerebellum. Anti-amphiphysin antibodies positive sera stain diffusely the synaptic terminals in molecular layer and granular glomeruli. In addition they recognise the membrane of Purkinje cells.



## Treatment

Benzodiazepines are an effective therapy for SPS because they modulate the levels and activity of GABA. A similar mode of action has been proposed for baclofen, which can be administered orally or via an intrathecal route. Sodium valproate and vigabatrin are found to be effective therapies for a few patients; the mechanism of action may be to potentiate GABAergic synaptic transmission. Immunosuppressive agents such as steroids, azathioprine; plasmapheresis and intravenous immunoglobulin are also effective.

## Selected references

1. Helfgott SM. Stiff-man syndrome. From the bedside to the bench. *Arthritis & Rheumatism* 1999; 42: 1312-1320
2. Brown P, Marsden CD. The stiff man syndrome and stiff man plus syndromes. *J Neurol* 1999; 246: 648-652
3. Dalakas MC, Li M, Fujii M, Jacobowitz D. Stiff person syndrome. Quantification, specificity and intrathecal synthesis of GAD65 antibodies. *Neurology* 2001; 57: 780-784
4. Solimena M, Folli F, Denis-Domini S, et al. Autoantibodies to glutamic acid decarboxylase in a patient with Stiff-Man Syndrome, epilepsy, and type I diabetes mellitus. *N Engl J Med* 1988; 318: 1012-20
5. De Camilli P, Thomas A, Cofield R, et al. The synaptic vesicle-associated protein amphiphysin is the 128-kD autoantigen of Stiff-Man Syndrome with breast cancer. *J Exp Med* 1993; 178: 2219-2223
6. Dalakas MC, Fujii M, Li M, et al. High-dose intravenous immune globulin for stiff-person syndrome. *New Engl J Med* 2001; 345: 1870-1876