

# Nervous system involvement in Sjögren's syndrome

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## History

The first report of neurological manifestations in Sjögren's syndrome (SS) is attributed to Henrik Sjögren himself, who in his monograph described a patient with bilateral facial paresis and transient sensory changes of the cornea and skin of the face indicating the involvement of both the seventh and the fifth cranial nerves (1). Due to the lack of other signs of brain stem involvement, these neurological symptoms and signs were most likely secondary to the involvement of the peripheral nervous system (PNS), but a central etiology can not be excluded. The first definite case of central nervous system (CNS) SS was described in 1938 by Sheldon (2) whose patient suffered from mental changes of delusional type and epileptic seizures.

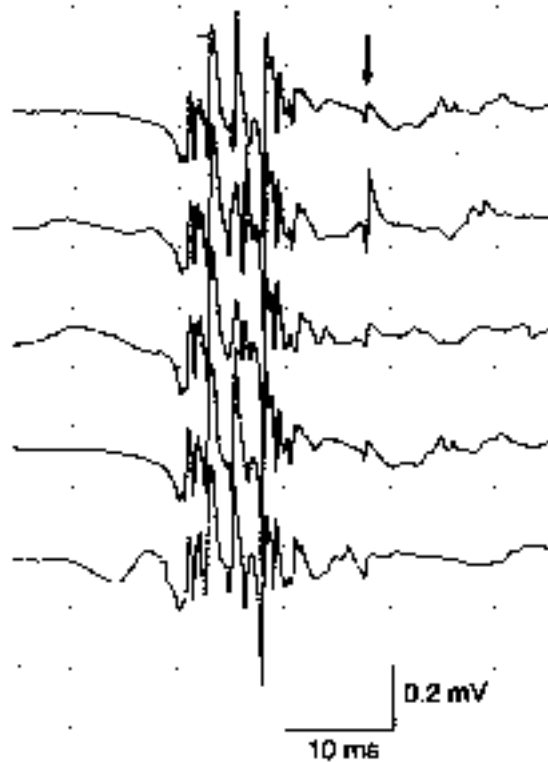
## Peripheral nervous system involvement

The prevalence of peripheral neuropathy in SS ranges from 10% to 50% (3). This wide range may have several explanations. First, distinction has not always been made between clinically manifest peripheral neuropathy and minimal electrophysiological alterations in the absence of clinical symptoms. Second, confounding variables, i.e. clinical conditions or accompanying diseases, which may contribute to neuropathy, have usually not been identified. The existence of many diagnostic criteria for SS makes the comparative assessment of the exact prevalence of PNS complications in SS difficult (3). Finally, the racial and immunogenetic background of the patient may affect her susceptibility to PNS manifestations (4).

The clinical spectrum of PNS involvement is diverse. It includes *distal symmetric polyneuropathy*, *sensory neuronopathy*, *mononeuropathy (multiplex)*, *autonomic neuropathy* and various combinations of these disorders. The existence of different types of neuropathies indicates that different underlying pathogenic mechanisms may be of importance.

Patients with *distal symmetric neuropathy* may have distal sensory or sensorimotor polyneuropathies (3,5). The distal sensory and symmetrical neuropathy is the most common peripheral neuropathy in SS (6). In most of the patients this neuropathy begins with sensory symptoms such as paresthesia ("asleep or prickling numbness") of the feet. The onset is typically insidious and the course slowly progressive, leading to mild to moderate degrees of symptoms and deficits. Neurophysiological studies show distal symmetrical loss of sensory axons and, to a lesser extent, motor fibres (Figure 1). In 15% of cases, exclusively sensory asymmetrical axonal loss may occur (6). Symptomatic treatment includes the use of tricyclic antidepressants. In SS venlafaxine may be more appropriate than amitriptyline, because it has less anticholinergic side effects.

Vasculitis may be the most common cause for the mild distal axonal polyneuropathy in SS because up to one third of the cases with cutaneous vasculitis develop at least mild axonal polyneuropathic changes. This has been supported by Mellgren *et al* (6), who found vasculitic changes in sural nerve biopsies from such patients. True necrotising vasculitis seems to be rare, but small vessels in the endoneurium show microangiopathic changes and perivascular inflammation (3). Patients with subacute distal symmetrical polyneuropathy should not be given immunosuppressive treatment until vasculitis has been confirmed, usually with a biopsy (5). The initial symptoms suggesting vasculitic neuropathy include acute proximal deep aching pain that typically is poorly localized. Burning cutaneous pain or tingling sensations are also common, but these symptoms as well as numbness and weakness typically develop over several hours or days (5).

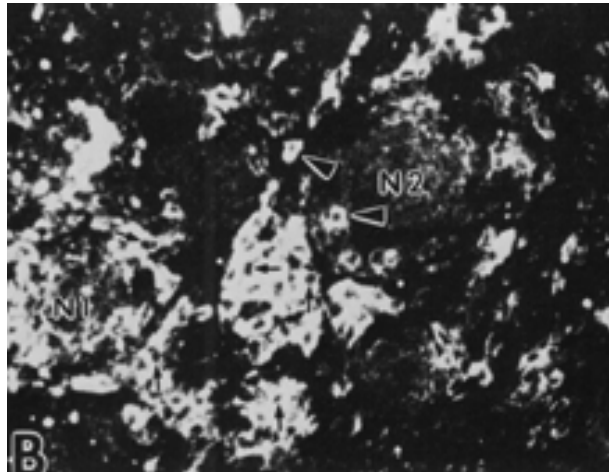


**Figure 1.** This electroneuromyograph demonstrates a polyphasic motor unit potential with a satellite potential (marked with an arrow) indicating regenerated axonal damage.

SS is the only connective tissue disease associated with *sensory neuronopathy* or *pure sensory neuropathy* (3,5,7,8). This is also the best-characterized paraneoplastic peripheral nerve disorder, usually associated with the small cell carcinoma of the lung. The symptoms in SS patients are dominated by loss of kinesthetic sensibility with gait ataxia, pseudoathetosis and dramatic difficulties in position sense and ability to locate the limbs in space (8). It is frequently associated with Adie syndrome (8,9) (tonic pupil), trigeminal nerve involvement and autonomic neuropathy. The sensory involvement may be symmetric or asymmetric. In some cases there is a discrepancy in the distribution of symptoms between arms and legs. On examination, the signs are predominantly related to the loss of large sensory fiber function, with a decreased appreciation of vibration and joint position. Alterations in pain and temperature sensation are less prominent. Reflexes are generally absent or depressed in affected limbs. Muscle strength is always normal unless impaired by sensory ataxia. The clinical course is variable: the onset is commonly indolent but may be acute and the condition may stabilize or even improve over time. Nerve conduction studies reveal low-amplitude or absent sensory nerve action potentials with normal conduction in the motor nerves. Unlike carcinomatous sensory neuronopathy, where the cerebrospinal fluid (CSF) analysis usually shows elevation of protein and pleocytosis, CSF in sensory neuronopathy associated with SS is normal (8). Immunosuppressive treatment is often used although the benefit of such therapy has not been established (5). Cessation of progression and functional improvement can occur in patients, who do not receive any drug therapy.

Sensory neuronopathy in SS seems to be caused by a dorsal root ganglionitis. Biopsies of dorsal root ganglia have revealed lymphocytic T-cell infiltrates with degeneration and loss of dorsal root ganglion neurons (8) (Figure 2). Electrophysiological studies of the trigeminofacial and trigemino-trigeminal reflexes in patients with trigeminal nerve involvement suggest that the lesion involves damage to the neurons of the gasserian ganglia rather than the trigeminal axons (10). Because of the

close association of Adie syndrome with sensory neuronopathy, the ciliary ganglion is probably also involved in the pathogenesis (9). The presence of anti-dorsal root ganglion neuron antibodies in a Japanese SS patient with dorsal root ganglionitis (11) and the detection of antineuronal antibodies in the sera of 6 of 11 SS patients with major neurologic complications (12) suggests that this disorder may also be mediated by humoral autoimmunity.



**Figure 2.** A thoracic dorsal root ganglion, which showed loss of neurons and clusters of mononuclear cells in routine haematoxylin-eosin stained section (not shown), has in this section been stained with immunofluorescence method for T lymphocytes (Leu-4, pan-T). T lymphocytes form small infiltrates. Some individual T lymphocytes in such infiltrates have been marked with black arrows. These T lymphocytes are in close contact with local dorsal root ganglion neurons, two of which have been marked (N1 and N2). (From: Griffin JW, Cornblath DR, Alexander E, Campbell J, Low PA, Bird S, Feldman EL: Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjögren's syndrome. *Ann Neurol* 27:304-315, 1990).

*Mononeuropathy* includes patients with cranial neuropathies, mononeuropathy multiplex and compression neuropathies. The best known cranial neuropathy in SS and other connective tissue disorders is trigeminal sensory neuropathy, which is characterized by slowly progressive unilateral or bilateral numbness of the face, often associated with paresthesias and pain. In a recent Japanese study of 21 primary SS patients, trigeminal neuropathy was observed in 8 (38%) (4). In a Finnish study of 48 primary SS patients only 2 (4%) were found to have trigeminal neuropathy (13). None of 46 SS patients reported by Gemignani et al (3) from Italy had any cranial neuropathy or mononeuropathy multiplex. Trigeminal sensory neuropathy does not generally indicate the need to initiate immunosuppressive therapy (5). The other cranial neuropathies reported in SS include optic neuropathy (13,14), facial paresis (1) and eighth nerve disorder (15). A study of 30 SS patients by Tumiatì *et al* (15) demonstrated a sensorineural hearing loss in 14 patients (46%). Nine of the 14 patients who had SS and sensorineural hearing loss (64%) had anticardiolipin antibodies compared with only 3 controls, suggesting that disturbances of humoral immunity may be associated with eighth nerve disorder in SS.

Mononeuropathy multiplex is usually considered to be rare in SS (3). In a study by Tajima et al., however, it was reported to occur in 24% of patients (4). It may affect peroneal, sural, tibial, ulnar, median or radial nerve. Also multiple cranial neuropathies have been described in SS (16). It is important to diagnose mononeuropathy multiplex, because it is usually caused by vasculitis in a patient with known SS. If electroneuromyography (ENMG) verifies a multifocal axon loss, a presumptive diagnosis of vasculitic neuropathy can be made confidently enough without nerve biopsy to commence immunosuppressive treatment (5).

Up to 20% of patients with SS may have a compression neuropathy, usually the carpal tunnel syndrome (5). In ENMG, the sensory and motor latencies are prolonged, which contrasts to the findings of axon loss in neuropathies caused by vasculitis.

*Autonomic neuropathy* has been reported as an isolated neurological manifestation of SS (17) and as an additional feature in patients with sensory neuronopathy (8,15). In a Japanese study of 21 primary SS patients, pandysautonomy was recognized in 2 (4). Mandl et al. showed in their study of 19 patients that the disturbances of parasympathetic nerves are associated with primary SS (18). It is possible that in some cases only vagal (tenth cranial) nerve is affected. Especially in association with sensory neuronopathy, a parasympathetic ganglionitis can be tentatively suggested as a pathogenetic mechanism in this disorder.

The recent report by Grant et al. from Mayo Clinic suggests that peripheral neuropathy and isolated sicca complex form a distinctive syndrome in which neuropathy is the presenting feature and the clinical features of rheumatologic disease are usually absent (7). Their report was based on retrospective study of 54 patients with peripheral neuropathy and sicca complex. The neuropathy was usually chronic and sensory, with variable large- and small-fiber deficits, and due to inflammatory polyganglionopathy in a significant proportion. Subclinical autonomic dysfunction was also common in these patients. Furthermore, some patients presented with a clinical picture of chronic inflammatory demyelinating polyneuropathy. Of note was also the exceptionally low rate of serologic abnormalities, such as polyclonal hypergammaglobulinemia and autoantibodies to SS-A/Ro and SS-B/La, compared with published series of SS. This study was supported by the findings of van Dijk et al. who found SS in 3 out of 65 patients with chronic idiopathic axonal polyneuropathy (19). Both of these studies broaden the spectrum of SS and prompt the exclusion of SS in patients with idiopathic axonal polyneuropathy.

### **Central nervous system involvement**

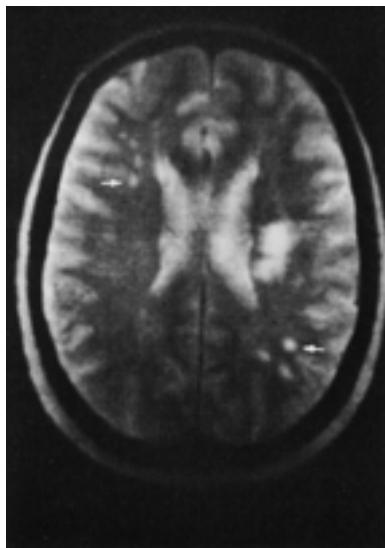
The detailed clinical and immunopathological studies by Alexander et al. from Johns Hopkins have focused the attention to CNS complications in SS. Following the initial discovery of serious progressive focal CNS disease in a small group of SS index patients (20), they have estimated that approximately 20-25% of highly selected SS patients referred to their tertiary referral center have CNS disease(14).

CNS involvement in SS can affect both the brain and spinal cord. Involvement of the brain can cause focal or diffuse neurologic abnormalities. Focal deficits include motor or sensory hemiparesis, aphasia/dysarthria, absence or psychomotor seizures, extrapyramidal disorders or brain stem and cerebellar involvement (14). Diffuse manifestations include subacute or acute encephalopathy, recurrent aseptic meningitis, cognitive dysfunction and dementia (14). Affective disturbances, especially anxiety and panic attacks, are the most common psychiatric abnormalities; psychosis, on the other hand, is rare (14). Spinal cord involvement can manifest as transverse myelitis, chronic progressive myelitis, Brown-Sequard syndrome, neurogenic bladder or lower motor neuron disease (14,21). Of special interest is a multiple sclerosis (MS)-like syndrome, which was originally described in 1961 by Atwood and Poser (16). In these patients, the clinical findings, electrophysiological results, CSF parameters and findings in brain magnetic resonance imaging (MRI) scans are indistinguishable from those observed in MS (Figures 3 and 4). Epidemiological studies, however, have suggested that SS is not more common among patients with MS than in the general population (22).

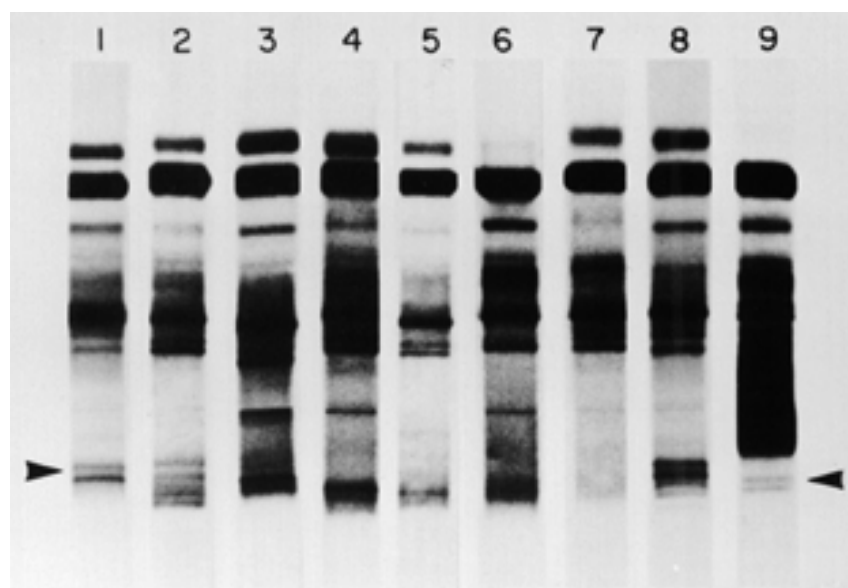
There is not any consensus as to the treatment of CNS manifestations of SS. In SS patients with mild CNS involvement a conservative approach seems to be warranted. For those patients, however, who present with progressive clinical neurologic dysfunction and who have objective findings of active CNS disease (i.e. MRI or CSF abnormalities) more drastic measures are appropriate. Pulse intravenous corticosteroids and intravenous pulse cyclophosphamide therapy have been used with variable success (14). Azathioprine has not been effective in the treatment of CNS-SS. The indica-

tions for the treatment of nonfocal CNS disease, like cognitive dysfunction, are less clear. There are reports of successfully treated dementia in CNS-SS (14).

From a pathogenic point of view, CNS-SS is an inflammatory disorder secondary to a mononuclear small vessel cerebral vasculopathy. Breach of the blood brain barrier by B lymphocytes or plasma cells takes place leading to intrathecal synthesis of IgG. CSF analysis in active CNS-SS may show a reactive pleocytosis, elevated IgG indices and oligoclonal bands (23). Brain MRI scans from these patients have demonstrated multiple small regions of increased signal intensity on T2 and proton density-weighted images in the periventricular or subcortical white matter consistent with demyelination (14). Furthermore, histopathology of cerebral tissue has shown mononuclear perivascular/vascular inflammatory infiltrates suggesting a disruption of the blood brain barrier of small cerebral blood vessels. There is evidence that the up-regulation of tumor necrosis factor  $\alpha$  synthesis by circulating peripheral blood mononuclear cells, which may infiltrate the perivascular spaces and blood vessel walls in CNS-SS, can contribute to the immunopathogenesis of the more severe (i.e. focal) CNS disease in genetically susceptible individuals with HLA-DR3/DR4 (23).



**Figure 3.** Magnetic resonance image of a patient with Sjögren's syndrome, demonstrating enhanced areas of lesions (arrows) in right occipital and periventricular areas and left parietal and frontal areas (from: Alexander E, Provost TT: Sjögren's syndrome. Association of cutaneous vasculitis with central nervous system disease. Arch Dermatol 123:801-810, 1987).



**Figure 4.** Agarose gel electrophoresis of cerebrospinal fluid (CSF) of patients with Sjögren's syndrome. Lane 1, patient with two IgG oligoclonal bands (arrowhead). Lane 2, patient with five IgG oligoclonal bands. Lanes 3-6, effect of corticosteroid therapy on five original IgG oligoclonal bands demonstrated in lane 2. Lane 7, CSF from a normal control. Lane 8 (control), CSF from a patient with multiple sclerosis, demonstrating at least four IgG oligoclonal bands. Lane 9 (control), serum from a patient with multiple myeloma (two IgG oligoclonal bands, arrowheads) (from: Alexander E, Provost TT: Sjögren's syndrome. Association of cutaneous vasculitis with central nervous system disease. *Arch Dermatol* 123:801-810, 1987).

Two studies have demonstrated that patients with either definite or probable SS have an equal frequency of more severe and less severe CNS disease (13,24). Like the report by Grant et al (7) on PNS complications associated with sicca complex, the results of these studies suggest that the severity of involvement of the autoimmune exocrinopathy in SS may not necessarily parallel the presence or severity of neurological complications. These findings warrant the exclusion of SS in case of idiopathic focal or diffuse CNS dysfunction. It is interesting from the pathogenetic point of view that neuronal cells of the PNS and CNS are subjected to autoimmune inflammation. In addition to the above characterized neurological manifestations, the involvement of the neuronal system may have other important consequences for neuronal regulation of the various tissues and organs, their neurotrophic support and disclosure/increased presentation of potential neuronal autoantigens.

## References

1. Sjögren H. Zur Kenntnis der Keratoconjunctivitis sicca. II. Allgemeine Symptomatologie und Ätiologie. *Act Ophthalmol (Kbh)* 1935; 13: 1-39.
2. Sheldon JH. Sjögren's syndrome associated with pigmentation and scleroderma of the legs. *Proc Roy Soc Med* 1938; 32: 255-256.
3. Gemignani F, Marbini A, Pavesi G et al. Peripheral neuropathy associated with primary Sjögren's syndrome. *J Neurol Neurosurg Psychiatry* 1994; 57: 983-986.
4. Tajima Y, Mito Y, Owada Y et al. Neurological manifestations of primary Sjögren's syndrome in Japanese patients. *Intern Med* 1997; 36: 690-693.
5. Olney RK. Neuropathies associated with connective tissue disease. *Semin Neurol* 1998; 18: 63-72.
6. Mellgren SI, Conn DL, Stevens JC, Dyck PJ. Peripheral neuropathy in primary Sjögren's syndrome. *Neurology* 1989; 39: 390-394.
7. Grant IA, Hunder GG, Homburger HA, Dyck PJ. Peripheral neuropathy associated with sicca complex. *Neurology* 1997; 48: 855-862.
8. Griffin JW, Cornblath DR, Alexander E et al. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjögren's syndrome. *Ann Neurol* 1990; 27: 304-315.
9. Waterschoot MP, Guerit JM, Lambert M, de Barys T. Bilateral tonic pupils in Sjögren's syndrome: a common pathophysiological mechanism? *Eur Neurol* 1991; 31: 114-116.
10. Valls-Sole J, Graus F, Font J et al. Normal proprioceptive trigeminal afferents in patients with Sjögren's syndrome and sensory neuronopathy. *Ann Neurol* 1990; 28: 786-790.
11. Satake M, Yoshimura T, Iwaki T et al. Anti-dorsal root ganglion neuron antibody in a case of dorsal root ganglionitis associated with Sjögren's syndrome. *J Neurol Sci* 1995; 132: 122-125.
12. Moll JWB, Markuse HM, Pijnenburg JJM et al. Antineuronal antibodies in patients with neurologic complications of primary Sjögren's syndrome. *Neurology* 1993; 43: 2574-2581.
13. Hietaharju A, Yli-Kerttula U, Häkkinen V, Frey H. Nervous system manifestations in Sjögren's syndrome. *Acta Neurol Scand* 1990; 81: 144-152.
14. Alexander E. Central nervous system disease in Sjögren's syndrome. New insights into immunopathogenesis. *Rheum Dis Clin North Am* 1992; 18: 637-672.
15. Tumiati B, Casoli P, Parmeggiani A. Hearing loss in the Sjogren syndrome. *Ann Intern Med* 1997; 126: 450-453.
16. Atwood A, Poser C. Neurologic complications of Sjögren's syndrome. *Neurology* 1961; 11: 1034-1041.
17. Andonopoulos AP, Ballas C. Autonomic cardiovascular neuropathy in primary Sjögren's syndrome. *Rheumatol Int* 1995; 15: 127-129.
18. Mandl T, Jacobsson L, Lilja B et al. Disturbances of autonomic nervous function in primary Sjögren's syndrome. *Scand J Rheumatol* 1997; 26: 253-258.
19. van Dijk GW, Notermans NC, Kater AA et al. Sjögren's syndrome in patients with chronic idiopathic axonal polyneuropathy. *J Neurol Neurosurg Psychiatry* 1997; 63: 376-378.
20. Alexander GE, Provost TT, Stevens MB, Alexander EL. Sjögren's syndrome: central nervous system manifestations. *Neurology* 1982; 31: 1391-1396.

21. Konttinen YT, Kinnunen E, von Bonsdorff M et al. Acute transverse myelopathy successfully treated with plasmapheresis and prednisone in a patient with primary Sjögren's syndrome. *Arthritis Rheum* 1987; 30: 339-344.
22. Sandberg-Wollheim M, Axéll T, Hansen BU et al. Primary Sjögren's syndrome in patients with multiple sclerosis. *Neurology* 1992; 42: 845-847.
23. Alexander EL, Plitt JR, Kozachuk W et al. HLA-class II associated tumor necrosis factor  $\alpha$  synthesis in central nervous system disease in Sjögren's syndrome. In: *Sjögren's syndrome - state of the art*, pp. 113-117. Eds. M Homma, S Sugai, T Tojo, N Miyasaka, M Akizuki. 1994, Kugler Publications, Amsterdam/New York.
24. Alexander EL, Kozachuk W, Ranzenbach MR et al. CNS disease in probable, as well as definite, Sjögren's syndrome. In: *Sjögren's syndrome - state of the art*, pp. 413-418. Eds. M Homma, S Sugai, T Tojo, N Miyasaka, M Akizuki. 1994, Kugler Publications, Amsterdam/New York.