Neurological Involvement in Sjögren's Syndrome

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Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by xerophthalmia and xerostomia. Besides sicca syndrome, neurological manifestations involving both the central nervous system (CNS) and the peripheral nervous system (PNS) may be present in SS.

25.1 Epidemiology of Neurological Involvement in SS

The prevalence of neurological manifestations ranges from 10 to 70 % [1].

The wide spectrum of prevalence data is related to several factors: the different diagnostic criteria that were used before and after 2002, definition of the disease, differences in study populations, and definition and method of detection of neurological involvement [2, 3]. Central nervous system involvement is far less common and varies from 2 to 25 % [2]. The male/female ratio of patients with neurological manifestations of SS ranges from 3.8 to 31 [2]. Neurological involvement may precede the development of sicca syndrome in 25–65 % of cases [4]. Disability is more frequent in cases of CNS involvement than in cases of PNS involvement [1].

25.2 Pathophysiology of Neurological Involvement in SS

The pathogenetic mechanisms responsible for neurological manifestations of SS are still unknown.

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Many hypotheses have been put forth to explain the wide range of neurological disorders. As far as PNS involvement is concerned, ganglionitis has been hypothesized in sensory ataxic, autonomic, painful, and trigeminal neuropathy, whereas vasculitis is the cause of multiple mononeuropathies and multiple cranial neuropathies [2]. Cryoglobulins may play a pathogenetic role in sensory-motor neuropathy [1].

Several studies have suggested that there is an ischemic mechanism in CNS involvement [3]. However, multiple sclerosis-like manifestations are not consistent with this explanation. Mononuclear cell infiltration of the CNS is another hypothesis. Other mechanisms, such as immunologically mediated vascular damage, the action of antineural antibodies, or a direct role of anti-SSA antibodies, have also been suggested [1].

25.3 Diagnosis

The typical autoantibodies associated with SS (anti-SSA and anti-SSB) are observed in only 40 % of patients with neurological involvement, whereas positivity may be as high as 60 % in patients without neurological involvement [3].

Some autoantibodies (anti-GW182, anti-alpha-fodrin, anti-3 muscarinic receptor) have been described as potential serological markers, but their usefulness is uncertain [3].

Schirmer's test is positive in 56–89 % of patients with SS-associated neuropathy, and Rose Bengal testing is also positive in 69–92 % of patients with SS-associated neuropathy [4].

Biopsy of the minor salivary glands of the lip may be diagnostic in 37–75 % of patients with PNS involvement in SS [4].

Non-serological ancillary testing is more sensitive than autoantibodies in neurological involvement in SS [4].

25.4 Peripheral Nervous System Involvement

Various neuropathy subtypes have been reported in SS patients. Sensory neuropathies are the most common manifestations (e.g., small fiber involvement and sensory ataxic neuropathy), but other subtypes like multiple mononeuropathy, polyradiculopathy, sensory-motor neuropathy, cranial neuropathy, and autonomic neuropathy have been described [2, 3].

The course of the disease can be subacute or chronic; in some cases it may be indolent for many years [2].

The onset of neuropathy can precede the diagnosis of SS by several years. This chronological pattern is more characteristic of ganglionitis-related neuropathies, suggesting that, as well as salivary and lacrimal glands, neural tissues, especially sensory dorsal root ganglion cells and autonomic ganglion cells, are the primary targets in SS.

25.4.1 Sensory Neuropathies

25.4.1.1 Sensory Ataxic Neuronopathy/Sensory Ganglionopathy

Sensory ataxic neuronopathy is due to posterior spinal root involvement with lymphocytic infiltration without vasculitis of the dorsal root ganglia [2, 3, 5].

This neuropathy is characterized by sensory ataxia without substantial motor symptoms. Distal, asymmetrical paresthesias are the heralding symptom. Onset of the symptoms ranges from subacute to chronic. Impaired proprioception can go from gait instability to severe incapacitation and wheelchair confinement. Pseudoathetosis may be present. Autonomic symptoms have been reported [5].

Conduction studies indicate axonal damage with reduced amplitude or absent sensory nerve action potentials with preservation of compound motor action potentials [5]. In some patients a posterior column high-intensity signal on T2-weighted MRI is observed due to retrograde degeneration of the large afferent fibers in the posterior columns [5].

Sural nerve biopsy predominantly demonstrates large fiber loss [5].

Several treatments have been reported, but randomized controlled trials are lacking. There are reports of the use of intravenous immunoglobulins, plasmapheresis, D-penicillamine, infliximab, interferon alpha, and rituximab [5].

25.4.2 Painful Small Fiber Neuropathy

It is a painful, sensory neuropathy affecting the nociceptive A-alpha and unmyelinated C-fibers that relay nociceptive and temperature stimuli [5]. A burning sensation in the feet is the typical symptom, but some patients present patchy burning paresthesias in the thighs and legs. This fact suggests a small fiber sensory neuronopathy, rather than a dying-back sensory axonopathy [5].

Impairment of the superficial sensation of pain, temperature, and light touch is associated with pain or painful dysesthesia. Deep sensation is well preserved, as is motor function. Nerve conduction studies are normal. Sural nerve biopsy shows small fiber loss, but skin biopsy is the standard tool for recognizing painful, small fiber neuropathy by demonstrating the decrease of intraepidermal nerve fiber density [2, 4, 5].

Treatment is generally symptomatic using antiepileptic agents or tricyclic antidepressants and avoiding agents with more anticholinergic side effects. A small, uncontrolled trial showed an improvement in neuropathic pain with the use of intravenous immunoglobulins [5].

25.4.3 Sensory Axonal Polyneuropathy

This neuropathy presents with distal, symmetric sensory deficits of chronic or subacute onset in a glove and stocking distribution [5]. It is the most characteristic peripheral involvement in SS and mainly affects the lower limbs [3], though the

upper limbs may be affected in 20 % of cases [5]. Electrophysiological studies show axonal impairment of the sensory nerves. Sural nerve biopsy reveals a varying degree of reduction of fiber density, mainly a dying-back axonal degeneration of thinly myelinated fibers without vasculitis [3]. Treatment is symptomatic with antiepileptic agents or tricyclic antidepressants [5].

25.4.4 Sensory-Motor Neuropathies

25.4.4.1 Sensory-Motor Polyneuropathy/Polyradiculoneuropathy

There is a wide range in the reported prevalence of sensory-motor polyneuropathy in SS patients (6–68 %) depending on whether subclinical motor abnormalities are taken into consideration or not. Large-diameter fibers are involved [2].

Some patients show a chronic inflammatory demyelinating polyneuropathy pattern in electrophysiological studies. Muscle weakness and sensory symptoms are present.

Sensory-motor polyneuropathy may be accompanied by palpable purpura, low C4 complement factor and cryoglobulinemia, and an increased risk of developing lymphoma [5].

Polyradiculoneuropathy has an average prevalence of 4–15 % in patients with SS neuropathy [2]. F-wave prolongation with abnormal motor distal latencies is a common finding in nerve conduction studies. Selective abnormal gadolinium enhancement of the dorsal spinal roots and cauda equina are found in the MRI of the lumbar spine [2].

Cerebrospinal fluid protein concentration is raised. Sural nerve biopsy shows demyelinating changes [2]. Symptomatic treatment is administered for positive sensory symptoms. Remission of neuropathic manifestations has been reported in patients with lymphoma who were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and/or rituximab [5].

25.4.5 Multiple Mononeuropathy

Although relatively uncommon, the prevalence of multiple mononeuropathy in SS patients is reportedly between 6 and 12 % [2].

Typically, onset is acute or subacute with asymmetric multifocal paresthesias or dysesthesias and weakness in the distal limbs [2].

Trigeminal and autonomic fibers may be involved as well. Electrophysiological studies demonstrate a marked reduction of compound motor action potentials and sensory nerve action potentials. Sural nerve biopsy shows a depletion of both large and small myelinated fibers along with axonal degeneration and typical vasculitic lesions with perivascular cellular invasion [6].

Rapid immunosuppressive treatment is needed to prevent permanent axonal damage due to ischemic nerve insult in vasculitis [5].

Along with corticosteroids, cyclophosphamide is the mainstay of treatment. Rituximab has been reported as being an effective alternative treatment [5].

25.4.6 Cranial Neuropathies

Trigeminal neuropathy is present in 17 % of patients with SS, and typically, the sensory branch is involved. The progression of symptoms is indolent [2].

Besides trigeminal neuropathy, recurrence of other cranial nerve neuropathies, mainly facial and cochlear nerve neuropathy, may occur [2].

25.4.7 Autonomic Neuropathy

Autonomic symptoms can occur in up to 50 % of patients with SS-associated neuropathy [2, 5, 6]. However, isolated autonomic involvement is rare (about 3 %). Symptoms range from pupillary constriction abnormalities (Adie's pupils likely caused by neuronitis in the ciliary ganglion cells) to severe postural hypotension and may include anhidrosis and urinary dysfunction [2].

Antibodies against type 3 muscarinic acetylcholine receptors have been described in SS as a partial explanation for the autonomic dysfunction seen in some patients [5].

25.4.8 Myopathy

Muscle pain is common in SS, but symptomatic myopathy is uncommon with prevalence ranging from 2.4 to 14 % of SS patients. It is often subclinical with normal muscle strength and normal serum creatine kinase levels [2].

Muscle biopsy reveals perivascular inflammation with perimysial or endomysial infiltrates [2].

Treatment with steroids and immunosuppressive drugs is similar to inflammatory myopathies not associated with SS.

25.5 Central Nervous System Involvement

CNS involvement in SS is controversial, and its prevalence ranges from 0 to 68 %, depending on the heterogeneity of inclusion criteria of each study [3]. PNS manifestations are present in 30–63 % of patients presenting with CNS involvement [2, 3].

Clinical manifestations can be focal or diffuse [8].

25.5.1 Focal Manifestations

25.5.1.1 Multiple Sclerosis-Like Manifestations

Patients with a syndrome resembling multiple sclerosis have been reported. MRI usually shows white matter lesions in the brain and spinal cord [2, 3]. Oligoclonal bands are present in cerebrospinal fluid analysis [2]. Many patients are seronegative

for anti-SSA and anti-SSB and do not complain of sicca syndrome [8]. The course of the disease may be relapsing-remitting or progressive.

25.5.1.2 Neuromyelitis Optica

There is an emerging relationship between neuromyelitis optica (NMO) and SS. In about 2 % of NMO patients, a diagnosis of SS is also present [4].

NMO is a demyelinating disease with relapsing, longitudinally extended transverse myelitis and recurrent optic neuritis. Characteristically, autoantibodies to aquaporin-4 are present. Brain lesions are distributed in the hypothalamus, brain stem, and periventricular regions, and spinal cord lesions span multiple segments unlike what is observed in multiple sclerosis [4].

Patients affected by NMO and patients affected by NMO and SS have similar features which differ only with regard to age at onset (patients with SS are older than those with NMO alone).

25.5.2 Transverse Myelitis

Transverse myelitis is an inflammatory disorder of the spinal cord that presents acutely or subacutely [4, 8]. The incidence of myelitis in SS is unknown but at least 60 cases have been reported in the literature. Transverse myelitis accompanying SS usually spans more than three levels of the spinal cord [4].

Intravenous corticosteroids are the first-line treatment, and monthly cyclophosphamide can be administered to patients who do not improve with corticosteroids [4, 8].

25.5.3 Focal Encephalic Manifestations

In SS, focal manifestations mainly occur with stroke-like features such as hemiplegia, aphasia, cerebellar ataxia, or internuclear ophthalmoplegia. An ischemic mechanism has been hypothesized [1, 3].

Moreover, dystonia, chorea, parkinsonism, seizures, and spastic tetraparesis have been reported.

25.5.4 Meningoencephalitis

Meningoencephalitis has been reported as a neurological complication of SS. Brain MRI can be normal or may show inflammatory changes both in white and gray matter or vasculitis. CSF analysis reveals aseptic lymphocytic meningitis [3, 8].

25.6 Diffuse Manifestations

Diffuse CNS involvement is considered to be more frequent than focal involvement [7].

Headache, cognitive dysfunction, mood disorders, and fatigue are the symptoms.

Brain MRI is normal in 80 % of cases, but SPECT can show cortical hypoperfusion in the frontal and temporal lobes [7].

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