Sjogren syndrome: neurologic complications

By Gustavo C Roman MD (Dr. Roman, Director of the Alzheimer Center of Excellence at the Methodist Neurological Institute in Houston, Texas, has no relevant financial relationships to disclose.)

Pedro J Ruiz MD (Dr. Ruiz of the California Pacific Medical Center in San Francisco, California, has no relevant financial relationships to disclose.)

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Introduction

This article includes discussion of the neurologic complications of Sjogren syndrome, Gougerot-Sjögren syndrome, and Sicca complex. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Neurologic manifestations occur in 20% to 27% of patients with Sjögren syndrome, often preceding the diagnosis of this systemic autoimmune disease. The peripheral nervous system, skeletal muscles, and central nervous system may be involved. Sjögren syndrome can mimic the symptoms of multiple sclerosis, particularly neuromyelitis optica with positive serum aquaporin autoantibody. HTLV-1 infection and vitamin B12 deficiency can complicate Sjögren myeloneuropathies. In this article, the authors review the clinical presentations and postulated pathogenesis of these complications and offer current treatment recommendations.

Key points

- Sjögren syndrome is a common autoimmune disease, particularly among postmenopausal women, and it is manifested by dry mouth, dry eyes, fatigue, and arthralgias.
- Neurologic symptoms occur in 20% to 27% of patients with Sjögren syndrome due to involvement of cranial nerves (Bell palsy, trigeminal neuralgia, diplopia), peripheral nerves (sensorimotor neuropathies), skeletal muscles (fibromyalgia, polymyositis), and the central nervous system.
- Sjögren syndrome can mimic the symptoms of multiple sclerosis, particularly neuromyelitis optica with positive serum aquaporin autoantibody.
- HTLV-1 infection and vitamin B12 deficiency can complicate Sjögren myeloneuropathies.
- A high index of suspicion is required given the pleomorphic manifestations and the fact that neurologic symptoms often precede the clinical diagnosis of Sjögren syndrome.

Historical note and terminology

In 1933, Henrik Sjögren described the association of keratoconjunctivitis sicca (filamentary keratitis) with arthritis (Sjogren 1933). Morgan and Castleman noted the histopathological commonality between the keratitis described by Sjögren and the glandular enlargement described by Mikulicz (Morgan and Castleman 1953; Mikulicz 1892). By 1973, the term “Sjögren syndrome” became widely accepted as these disorders were considered variants of the same process (Mason et al 1973). The name Gougerot-Sjögren syndrome is commonly used in the French literature (de Seze et al 2005) given that Henry Gougerot first reported, in Paris, the typical symptoms of xerostomia and xerophthalmia due to atrophy of salivary and lachrymal glands (Gougerot 1925).

Clinical manifestations

Presentation and course

Sjögren syndrome is a chronic, multisystem autoimmune disorder. Primary Sjögren syndrome presents as dry eye and dry mouth secondary to autoimmune dysfunction of the exocrine glands. In secondary Sjögren syndrome, these manifestations occur in the presence of another autoimmune disease. Overall, there is no increased mortality in patients with primary Sjögren syndrome (Martens et al 1999).
Systemic involvement in Sjögren syndrome includes chronic fatigue affecting as many as 50% of patients; arthralgias present in 53%; esophageal dysmotility in 36%; hematological abnormalities, including anemia and leucopenia (33%), increased erythrocyte sedimentation rate (22%), and hypergammaglobulinemia (22%); inflammatory myalgias (22%); and skin lesions, such as “burning skin” (18%), cutaneous vasculitis (10%), alopecia, vitiligo, papular lesions, and annular erythema (Kassan and Moutsopoulos 2004; Ramos-Casals et al 2005b). Lymphoma may develop in 5% to 7% of patients with primary Sjögren syndrome, often associated with cutaneous purpura (Voulgarelis et al 1999). Less common lesions include lung involvement with lymphocytic alveolitis, lymphocytic interstitial pneumonitis, fibrosis, pulmonary pseudolymphoma, pulmonary hypertension, and pericarditis; vascular lesions manifested by Raynaud phenomenon; renal tubular lesions, interstitial nephritis, and glomerulonephritis; malabsorption due to lymphocytic infiltrates of the intestine; as well as mild pancreatitis and hepatitis. Exclusions to the diagnosis include infections with HIV, HTLV-1, or hepatitis C virus (Ramos-Casals et al 2005a). Table 1 summarizes the current consensus criteria for the diagnosis of Sjögren syndrome:

**Table 1a. Revised International Classification Criteria for Sjögren Syndrome**

**I. Ocular symptoms:** A positive response to at least 1 of 3 validated questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

**II. Oral symptoms:** A positive response to at least 1 of 3 validated questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrent or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry foods?

**III. Ocular signs:** Objective evidence of ocular involvement defined as a positive result to at least 1 of the following 2 tests:
1. Schirmer's test, performed without anesthesia (5 mm in 5 min)
2. Rose Bengal score or other ocular dye score (4 according to van Bijsterveld's scoring system)

**IV. Histopathology:** In minor salivary glands focal lymphocytic sialoadenitis, with a focus score of 1.

**V. Salivary gland involvement:** Objective evidence of salivary gland involvement defined by a positive result to at least 1 of the following diagnostic tests:
1. Unstimulated whole salivary flow (1.5 mL in 15 min)
2. Parotid sialography
3. Salivary scintigraphy

**VI. Autoantibodies - presence in the serum of the following autoantibodies:**
1. Antibodies to Ro/SS-A or La/SS-B antigens, or both

**Table 1b. Revised Rules for Classification**

**Exclusion criteria**
- Past head and neck radiation treatment
- Hepatitis C infection
- AIDS
- Preexisting lymphoma
- Sarcoidosis
- Graft-versus-host disease
- Use of anticholinergic drugs

**For Primary Sjögren syndrome**
- a. Any 4 of the 6 items, as long as item IV (histopathology) or VI (serology) is positive
b. Any 3 of the 4 objective criteria items (items III, IV, V, VI).

**For Secondary Sjögren syndrome**

In patients with a potentially associated disease (eg, another well-defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary Sjögren syndrome.

From: (Vitali et al 2002)

A number of neurologic manifestations have been reported traditionally in about 20% of patients with Sjögren syndrome (range 6% to 70%) (Lafitte et al 2001; Delalande et al 2004; de Seze et al 2005; Mori et al 2005); in most cases, neurologic symptoms precede the diagnosis of Sjögren syndrome (Barendregt et al 2001; Mori et al 2005). The most common include involvement of the peripheral nervous system and skeletal muscles. More recent reports emphasize the involvement of the central nervous system, often mimicking the clinical symptoms of primary progressive or relapsing-remitting multiple sclerosis. Sjögren syndrome appears to be a great imitator of multiple sclerosis, involving the central nervous system more often than previously recognized. Table 2 lists some of the most common neurologic manifestations of primary Sjögren syndrome.

**Peripheral nervous system.** Mori and colleagues reviewed 92 patients (86% women, mean age 60 years) with Sjögren syndrome and found the following varieties of neuropathy: sensory ataxia (39%); sensory painful neuropathy (20%); trigeminal neuropathy (17%); multiple mononeuropathy (12%); multiple cranial neuropathies (5%); autonomic neuropathy (3%); and radiculoneuropathy (4%) (Mori et al 2005).

Dyck described the following nerve fiber lesions in these cases (Dyck 2005). In the ataxic variety, large primary afferent neurons or fibers are selectively affected as suggested by inflammatory infiltrates found in spinal ganglia. In trigeminal neuropathy, all classes of sensory neurons or fibers are involved. In sensory and autonomic neuropathy affecting limb or trunk, all classes of sensory neurons or fibers are affected, but symptoms suggest predominant small fiber sensory involvement with either tactile (allodynia) or thermal hypersensitivity (hyperalgesia), as well as sudomotor abnormalities such as decreased sweating in toes and feet or in an asymmetrical quasiradicular distribution. These sensory and autonomic neuropathies may occur with minimal or no evidence of sicca symptoms (Dyck 2005).

**Axonal neuropathies.** Between 17% and 39% of patients with Sjögren syndrome have minor symptoms of peripheral neuropathy (Barendregt et al 2001; Dyck 2005). The most common axonal forms are symmetrical sensory neuropathy and sensorimotor neuropathy (Barendregt et al 2001; Lafitte et al 2001; Delalande et al 2004; Dyck 2005; Mori et al 2005). Vibration perception threshold and thermal perception are sensitive and useful methods of monitoring peripheral nerve function in these patients (Barendregt et al 2001). The course is generally slowly progressive.

**Autonomic symptoms** are rare. A common complication is carpal tunnel syndrome. Motor and sensory action potentials in the involved nerves are markedly reduced. Sural nerve biopsies have shown vasculitis of vasa nervorum, perivascular cellular infiltration, and necrotizing vasculitis, along with focal or multifocal axonal degeneration of large and small myelinated fibers and minor demyelination.

**Sensory ataxic ganglionopathy with antiganglion neuron antibodies.** This is a distinctive type of sensory neuronopathy with a reported association with antiganglion neuron antibodies characterized by lesions of the dorsal root ganglia with presence of mononuclear cell infiltrates (ganglionitis) but without vasculitis (Griffin et al 1990; Murata et al 2005). Clinically it is characterized by a profound loss of proprioception and vibratory perception leading to sensory ataxia, with a positive Romberg sign, global areflexia, and no motor involvement. The sensory symptoms are mostly asymmetrical, segmental, or multifocal, including trigeminal nerve involvement (Mori et al 2005).

There is usually autonomic involvement manifested by abnormal pupillary responses including Adie pupils, anisocoria and oval pupils; orthostatic hypotension, decreases in 123I-MIBG cardiac uptake, hypohidrosis, and segmental anhidrosis of the trunk. Sensory potentials are absent, contrasting with normal motor potentials and normal peripheral nerve conduction velocities. Somatosensory evoked potentials are usually absent. Sural nerve biopsies show a selective loss of large myelinated fibers, with minimal inflammation or vasculitis. Cervical spinal cord MRI may show hyperintensity of T2-weighted signals corresponding to involvement of the fasciculus cuneatus and fasciculus gracilis in the dorsal columns, proportional to the severity of the damage (Mori et al 2001). This form of neuropathy is chronic.
and progressive and responds occasionally to treatment with **IVIG** (0.4 g/kg for 5 days). Yamada and colleagues reported excellent results with interferon alpha (IFN-alpha) treatment (3 MIU/day, 3 times weekly), resulting also in marked improvement of the clinical and laboratory manifestations of Sjögren syndrome (Yamada et al 2005).

**Painful sensory neuropathy (without sensory ataxia).** According to Mori and colleagues, this is a relatively common form of neuropathy with acute or subacute onset of painful dysesthesias in toes, feet, or hands, usually in the limbs on 1 side, or over the entire body, including the trunk and the face (Mori et al 2005). Dysautonomic signs may also be present, but there is no evidence of dorsal column involvement. Sural nerve biopsies show small-fiber loss suggesting predominant impairment of small sensory neurons with preservation of large-diameter sensory neurons (Chai et al 2005). The measurements of intraepidermal nerve fiber densities in skin punch biopsy specimens show less than 3.4 fibers/mm, which is consistent with the morphological criteria for small-diameter nerve fiber neuropathy (Goransson et al 2006).

**Multiple cranial neuropathy.** The most common forms of cranial nerve involvement include **Bell palsy**, often bilateral; recurrent **diplopia** due to III and VI cranial nerve involvement; swallowing problems due to compromise of V, IX, and X nerves, and less commonly simultaneous lesions of V, VII, IX, X, and XII cranial nerves (Mori et al 2005). **Neurosarcoidosis** should be included in the differential diagnosis in patients with multiple cranial nerve involvement (Tuisku et al 2004).

**Trigeminal neuralgia.** A common form of pure sensory trigeminal neuropathy in Sjögren syndrome is trigeminal neuralgia, often with bilateral involvement. There is facial numbness, decreased corneal reflexes, and loss of pin prick and soft touch perception in the trigeminal nerve distribution, without motor trigeminal nerve involvement. Immunemediated involvement of Gasserian ganglion neurons is suspected. Simultaneous sensory neuropathy of the trigeminal, glossopharyngeal, and vagus nerves has been reported (Urban et al 2001).

**Hearing loss.** Sensorineural hearing loss, due to lesion of the VIII cranial nerve, manifested by sudden or progressive deafness has been reported in Sjögren syndrome. In some cases, hearing loss was associated with the presence of **antiphospholipid antibodies** (Mouadeb and Ruckenstein 2005), suggesting an underlying autoimmune cause.

**Autonomic neuropathy.** The peripheral sympathetic nervous system is severely involved in this form of neuropathy. These patients commonly present with sicca syndrome, orthostatic hypotension and **syncope**, anhidrosis, Adie pupil, neurogenic bladder, as well as gastrointestinal symptoms such as abdominal pain, constipation or diarrhea (Delalande et al 2004; Dyck 2005; Mori et al 2005). In addition to the above, examination reveals reduced cardiac 123I-MIBG uptake, no plasma norepinephrine response after standing, and hypertensive response to minimal doses of norepinephrine (Mori et al 2005). These patients usually have elevated titers of ganglionic acetylcholine receptor autoantibody, a putative effector of autoimmune cholinergic dysautonomia (Sandroni et al 2004).

**Radiculoneuropathy.** A demyelinating **polyradiculoneuropathy** sometimes develops in patients with Sjögren syndrome. Patients present with progressive sensory disturbances in a glove-and-stocking distribution, muscle weakness, and sensory ataxia but without autonomic symptoms. **CSF** protein is elevated and nerve conduction studies show reduced conduction velocities and temporal dispersion. Biopsies show histopathological evidence of remyelination. According to Mori and colleagues, the primary lesion in these patients is an inflammatory radiculoneuropathy (Mori et al 2005). Yamada and colleagues reported good results with IFN-alpha treatment of this form of neuropathy (Yamada et al 2005).

**Skeletal muscle.**

**Inflammatory myositis.** Myalgias, without elevation of muscle enzymes or electromyographic changes, have been reported in 30% to 44% of patients with Sjögren syndrome (Lindvall et al 2002); many of them fulfill criteria for fibromyalgia. Findings on muscle biopsies show signs of inflammation in 50% to 72%, and evidence of polymyositis (inflammation combined with degeneration and regeneration of muscle fibers) in 47% (Derk et al 2003). Some cases have symmetrical inclusion body myositis diagnosed by electron microscopy (Lindvall et al 2002; Derk et al 2003). Myopathy due to medications such as steroids must be considered in the differential diagnosis.

**Central nervous system.**

**Multiple sclerosis-like manifestations.** Alexander and colleagues first reported the frequent occurrence of a syndrome resembling multiple sclerosis associated with cutaneous vasculitis in patients with Sjögren syndrome (Alexander et al...
Many of these cases presented a combination of optic neuropathy and chronic myelopathy that could be confused with Devic disease or spinal forms of multiple sclerosis. The occurrence of Sjögren syndrome in patients with confirmed multiple sclerosis ranges from no cases among 192 patients (Noseworthy et al 1989) to about 5% (3/64 cases) (Miro et al 1990). In some geographic areas, a chronic myelitis due to infection with the human T-lymphotropic virus type 1 (HTLV-1) has been also associated with sicca syndrome (Nakamura et al 2000; Seguchi et al 2006).

Table 2. Neurologic Manifestations of Primary Sjögren Syndrome

PNS manifestations

Isolated neuropathies
- Painful sensory neuropathy
- Sensorimotor (axonal) polyneuropathy
- Sensory ataxic ganglionopathy with antiganglion neuron antibodies
- Radiculoneuropathy (demyelinating polyradiculoneuropathy)
- Vasculitic neuropathy
- Mononeuritis multiplex
- Entrapment neuropathies
- Multiple cranial neuropathy: diplopia, trigeminal, facial (Bell palsy), cochlear
- Sensorineural hearing loss
- Autonomic neuropathy (dysautonomia, bladder, cardiovascular)

CNS manifestations
Focal symptoms

- **Stroke** with motor or sensory deficits, associated with CNS vasculitis
- Aphasia or **dysarthria**
- Seizure disorders
- CNS **T-cell** lymphoma

Movement disorders and cerebellar syndromes

- Parkinsonism
- **Chorea**
- Brainstem syndromes
  - **Central pontine myelinolysis**
  - Painful tonic or dystonic spasms
- Cerebellar atrophy
- Cerebellar ataxia with **antineuronal antibodies**, **perivenous demyelination**, **angiitis**

Diffuse nonfocal symptoms

- Acute or subacute encephalopathy
- MRI: White matter abnormalities
- Aseptic **meningoencephalitis** (often recurrent)
- Cognitive dysfunction or dementia
- Psychiatric abnormalities

Spinal cord involvement

- **Transverse myelitis**
- Chronic progressive myelitis
- **Brown-Sequard syndrome**
- Neurogenic bladder
- Lower motor neuron disease
- HTLV-1 myelitis
- Subacute combined degeneration (vitamin B12 deficiency)

Multiple sclerosis-like syndromes

- Optic neuropathy
- Myelopathy
- **Neuromyelitis optica** (aquaporin autoantibody positive)
- Multiple sclerosis-like relapsing-remitting syndromes
- Mood disorders (depression, anxiety, chronic fatigue)

Muscle manifestations

- Subclinical myositis
- Myalgias

**Focal encephalic manifestations.** Focal manifestations may present acutely, with stroke-like features such as aphasia, hemiplegia, or **hypesthesia**, consistent with a focal vasculitis (Delalande et al 2004). Intracerebral or **subarachnoid hemorrhage** may signal the presence of vasculitis. Recurrent or relapsing forms may mimic multiple sclerosis.

Occurrences of subacute development of cerebellar ataxia and tremor may be produced by demyelination. In 1 patient, the MRI showed T2-hyperintensities in the cerebellar white matter and the pons; severe necrotic lesions were found in the cerebellar white matter bilaterally, with several foci of perivenous demyelination in the periphery of the lesions and similar demyelinated areas in the pons; there was minimal granulomatous angiitis (Ichikawa et al 2004).

Other focal neurologic manifestations described in Sjögren syndrome include: internuclear ophthalmoplegia, **nystagmus**, **dystonia**, athetosis, and intention tremor; or **aseptic meningitis** with confusion, cerebellar involvement, and spastic tetraparesis (Moutaoukil et al 2005). A rigid form of parkinsonism with preponderant **akinesia** but without tremor and resistance to L-DOPA treatment has been described (Walker et al 1999). There are also rare cases of generalized chorea (Vanegas Fanchke et al 2005). Focal and **generalized seizures** may occur during relapses of cerebral vasculitis.
**Meningoencephalitis.** Meningoencephalitis is a relatively common neurologic complication of Sjögren syndrome (Delalande et al 2004). It begins with headache, myalgias, confusion, and meningeal signs but without fever (Rossi and Valeria Saddi 2006); in some cases, sensorineural deafness may occur. Focal neurologic signs may be present; brain MRI shows hyperintense inflammatory changes in the cerebral white matter and cortex. The CSF profile is consistent with an aseptic lymphocytic meningitis, with up to 900 cells/mm³. Recurrences occur, and changes associated with vasculitis may be demonstrated by angiography.

**Psychiatric and cognitive disorders.** In many patients, symptoms of depression and anxiety may precede the diagnosis of Sjögren syndrome or become chronic accompaniments of the disease (Utset et al 1994). Also common are cognitive changes with poor concentration and memory and abnormalities in neuropsychometric testing, including executive dysfunction and frontal lobe deficits. The pathogenesis of these changes is not clearly understood, but it may be part of the so-called “vascular depression-vascular cognitive disorder,” resulting from ischemic interruption of prefrontal circuits important for mood and behavior (Roman et al 2004).

**Optic neuropathy.** Patients with Sjögren syndrome can present with bilateral visual loss secondary to retrobulbar optic neuropathy (Alexander et al 1986; Delalande et al 2004). In some cases, blindness secondary to bilateral optic neuropathy was the first manifestation of Sjögren syndrome (Trojet et al 2003; Pournaras et al 2007; Bejot et al 2008). In about 12% to 15% of patients, the diagnosis was revealed by abnormal visual evoked potentials (Delalande et al 2004). The pathogenesis of optic nerve involvement in Sjögren syndrome is postulated to result from a combination of ischemic vasculitis and demyelination. The differential diagnosis should include multiple sclerosis.

**Neuromyelitis optica.** The combination of optic neuritis with concurrent myelitis has been designated Devic disease (Sofat and Venables 2008) or neuromyelitis optica, a variant of multiple sclerosis. More than 95% of neuromyelitis optica cases test positive to the disease-specific serum aquaporin autoantibody (Wingerchuk et al 2006). Autoantibodies or autoimmune diseases are often found in patients with neuromyelitis optica, including Sjögren syndrome (Pittock et al 2008), and 7.7% to 12% of patients with neuromyelitis optica have anti-Ro/SS-A or anti-La/SS-B antibodies (Hayakawa et al 2008). In Korea, Kim and colleagues studied 8 patients with Sjögren myelopathy and demonstrated that most of them exhibited clinical, radiological, and immunological characteristics of neuromyelitis optica, including positive results from aquaporin autoantibody testing (Kim et al 2009). Also in Korea, Min and colleagues studied 12 women with primary Sjögren syndrome and recurrent cerebral manifestations (Min et al 2009). MRI showed characteristic neuromyelitis optica lesions in the third and fourth ventricles and in the posterior limb of the internal capsule, along with cerebral or cerebellar lesions larger than 3 cm in size and with cavity-like formations. Aquaporin autoantibody was positive in 6 of 8 patients tested, and all the seropositive patients showed lesions with increased MRI diffusion, suggestive of vasogenic edema. These authors recommend testing for aquaporin autoantibody in all patients with Sjögren myelitis, followed by early aggressive immune therapies in these patients irrespective of the presence or absence of optic neuritis.

**Spinal cord involvement.** Following an initial report (Williams et al 2001), at least 57 cases of spinal cord involvement in Sjögren syndrome have been reported, indicating that this neurologic complication is not uncommon (Kompoliti et al 1996; Wright et al 1999; Arai et al 2002; Hawley and Hendricks 2002; Hermisson et al 2002; Thong and Venketasubramanian 2002; Anantharaju et al 2003; Pericot et al 2003; Vincent et al 2003; Fushimi et al 2004; de Seze et al 2006; Pot et al 2006; Taguchi et al 2006; Tristan 2006; Sofat and Venables 2008; Kato et al 2009; Kim et al 2009). Furthermore, a study in France on the prevalence of Sjögren syndrome in patients with primary progressive multiple sclerosis showed that the prevalence of Sjögren syndrome (16.6%) in multiple sclerosis is much higher than expected in the general population (1% to 5%) (de Seze et al 2001).

Acute transverse myelitis is the most frequent form of spinal cord involvement in Sjögren syndrome (Williams et al 2001). The symptoms of acute transverse myelitis develop abruptly usually with severe neck and interscapular pain followed by sensory and motor deficits below the thoracic level of the lesion. In Sjögren syndrome, this form of myelopathy is probably due to vasculitis and carries a high mortality.

Spinal cord involvement may present also as a progressive myelitis, Brown-Sequard syndrome, neurogenic bladder or lower motor neuron disease. As mentioned before, optic nerve involvement frequently accompanies spinal cord involvement. The subacute or chronic form of myelopathy usually develops with sensory symptoms, sphincter incontinence, and difficulty walking progressing to spastic paraplegia.

A diagnosis of Sjögren syndrome myelopathy requires a high index of suspicion and should be considered
predominantly in women over 45 years of age with progressive spastic paraparesis and abnormalities on spinal cord MRI, even with negative anti-extractable nuclear antigen antibodies (Ro/SS-A or La/SS-B) (Pericot et al 2003). The presence of autoantibodies against fodrin also helps in differentiating myelopathy in Sjögren syndrome from primary progressive multiple sclerosis (de Seze et al 2003). A positive test has 70% sensitivity, 86.7% specificity, 63.6% positive predictive value, and 89.6% negative predictive value (de Seze et al 2003).

Less common is the combined involvement of pyramidal tracts and anterior horn cells resembling amytrophic lateral sclerosis. Postmortem study of 2 cases confirmed in 1 patient a lower motor neuron syndrome combined with flaccid bladder and rectum, and in the other patient unilateral hearing loss, sensory neuronopathy, Adie pupils, upper motor neuron signs, and autopsy-proven anterior horn cell degeneration (Katz et al 1999). These cases demonstrate the wide multisystem neuronal involvement that may occur in Sjögren syndrome. A similar syndrome called pseudo-amyotrophic lateral sclerosis has been reported in patients with HTLV-1 infection (Roman et al 1991).

**Prognosis and complications**

Complications are discussed in the clinical manifestations.

**Clinical vignette**

A 63-year-old woman developed paraplegia, urinary frequency, urgency, and incontinence; she had experienced sensory symptoms in her legs for 10 months. Neurologic examination revealed spastic paraparesis, lower limb hyperreflexia, and flexor plantar responses. No sensory level was noted, but she had hypoesthesia to pinprick in her left buttck and posterior thigh. MRI demonstrated abnormal focal signal intensities on T2-weighted images, enhancing with gadolinium on T1-weighted images, at the C5-6 and T8-9 levels and on the conus medullaris and cauda equina. MRI of the brain was noncontributory. CSF showed lymphocytic pleocytosis with 0.011 x10^9 cells/L, few atypical lymphocytes, a mildly elevated protein level (0.85 g/L), a nonreactive VDRL test, and absent oligoclonal bands. A second CSF had 0.006 x10^9 cells/L, a protein level of 0.72 g/L, and normal cytology. Serum and urine protein electrophoresis showed neither monoclonal gammopathy nor elevation of the angiotensin-converting enzyme level; serum B12 levels were normal. Antibodies to HIV and HTLV-1 were nonreactive. Chest x-ray was normal. A gallium body scan demonstrated increased activity in the lachrymal glands, regional lymph nodes, and right paratracheal region; there was no evidence of sarcoidosis.

Over the next 3 months, her paraparesis progressed to near paraplegia associated with a sensory level at the umbilicus and with left arm paresthesias. Antinuclear antibody ratio was 1:640; the erythrocyte sedimentation rate was 41 mm/h. Mild sicca symptoms (xerostomia and keratoconjunctivitis) were found on further questioning. Neurologic examination showed a left afferent pupillary defect, spastic paraplegia with hyperreflexia, crossed adductor responses, ankle clonus, and bilateral Babinski sign. Motor strength was 5/5 (MRC scale) in the upper extremities and 0/5 in the lower extremities, except for 1/5 for ankle dorsiflexors and plantar flexors. A T10 sensory level was found, along with decreased anal sphincter tone. MRI of the cervical, thoracic, and lumbar spine showed multifocal areas of increased T2-signal intensity, enhanced by gadolinium at the C5-7, T3-5, and T8-11 levels and on the conus medullaris. A third CSF sample had 0.035 x10^9 cells/L, a glucose level of 2.9 mmol/L (53 mg/dL), and a protein level of 0.62 g/L. Oligoclonal bands and myelin basic protein were absent, and the IgG index was normal (0.63). A second antinuclear antibody test was positive, with a titer of 1:2560; Ro/SS-A antibody was positive with a speckled pattern. Complement C3 was 1.78 g/L (reference range, 0.86 to 1.84 g/L) and C4, 0.23 g/L (reference range, 0.20 to 0.59 g/L). Visual evoked potentials were prolonged in the left eye. Examination of a minor salivary gland biopsy specimen showed chronic sialadenitis, with a focus score of 3.

The patient was diagnosed as having CNS Sjögren syndrome because of the presence of sicca syndrome, abnormal serological test results, and the salivary gland biopsy results, which fulfilled the San Diego criteria for "definite" Sjögren syndrome. The patient received a pulse dose of intravenous methylprednisolone sodium succinate, 1 g/d for 3 days, followed by oral prednisone, 60 mg/d. Rheumatology consultants recommended treatment with intravenous cyclophosphamide, 0.75 g/m2, followed by equal monthly doses for 6 months, along with oral prednisone, 20 mg/d. With this treatment, the patient experienced marked improvement in the strength of most of the muscles in her lower extremities, going from 0-1/5 to 3/5 (MRC scale). Furthermore, sensory complaints, particularly subjective paresthesias in the left upper extremity, slowly abated during the ensuing several weeks (Williams et al 2001).
Biological basis

Etiology and pathogenesis

Sjögren syndrome is an autoimmune disorder manifested by alterations of B-cell and T-lymphocytes occurring in individuals with a genetic predisposition.

The pathogenesis of Sjögren syndrome has been reviewed by Fox (Fox 2005). The exact mechanisms are still unknown, but the most prominent immunoregulatory alterations are B-cell hyperreactivity and enhanced levels of B-cell-activating factor/B-lymphocyte stimulator. The pathogenesis is multifactorial, where environmental factors activate glandular endothelial or epithelial cells, triggering inflammation in individuals with a genetic predisposition (HLA DR). The inappropriate B-cell activation can follow various stages of evolution, leading in extreme cases to malignant transformation of B-cells to produce lymphoma.

Polyclonal B-cell hyperreactivity in Sjögren syndrome accounts for the hypergammaglobulinemia, circulating immune complexes, and multiple autoantibodies directed against both organ- and nonorgan-specific autoantigens. Clinically, the most important and best characterized are the autoantibodies anti-Ro (SS-A) and anti-La (SS-B) directed against cellular heterogeneous ribonucleoprotein complexes consisting of antigenic proteins (Jonsson et al 2000). The antibodies recognize autoantigens, which bind to ribonucleoprotein particles consisting of a 60kD SS-A/Ro RNA binding protein and hY1 RNAs and 48 KD RNA binding protein, which facilitates maturation of RNA polymerase III transcripts, such as precursors to tRNA and 5S-RNA (Konttinen and Kasna-Ronkainen 2002). These antibodies are found in approximately 50% of the patients with Sjögren syndrome and tend to be associated more with severe glandular and extraglandular manifestations (Jonsson et al 2000; Konttinen and Kasna-Ronkainen 2002; Fox 2005).

There are also alterations of cellular immunity in Sjögren syndrome. Mononuclear cells (primarily T-lymphocytes) infiltrate salivary and lachrymal glands with partial destruction of acinar and ductal structures. The T-lymphocytes and also the glandular cells cause the release of cytokines (especially interleukin-1, interleukin-6, and tumor necrosis factor alpha) (Fox 2005). These cytokines, along with autoantibodies and metalloproteinases, cause a decreased release of neurotransmitters and a diminished response of the residual glandular cells to available neurotransmitters, resulting in the symptoms commonly seen in Sjögren syndrome (Fox and Stern 2002). Interaction between constitutional factors (hormones and major histocompatibility complex) and environmental factors (most likely viruses) are thought to be important in the etiology of Sjögren syndrome. Females are affected in a ratio of 9:1 compared to males. Hormones such as estrogens, reactive hypothalamic and hypophyseal peptide hormones and dehydroepiandrosterone may play a role. Sjögren syndrome is associated with HLA-DR 3 and linked genes B8, DQ 2, and the C4 null gene in about 50% of the patients. Postulated infectious agents capable of triggering the immune process include herpes viruses (particularly Epstein Barr virus, cytomegalovirus, and human herpesvirus-6), H pylori and human retroviruses, in particular HTLV-1.

HTLV-1 and Sjögren syndrome. Transgenic mice expressing the HTLV-1 tax gene develop an exocrinopathy similar to that seen in patients with Sjögren syndrome (Green et al 1989). The expression of sequences homologous to the HTLV-1 tax gene has been found in labial salivary glands of patients with Sjögren syndrome (Mariette et al 1993; Sumida et al 1994). Kompoliti and colleagues described a patient with Sjögren syndrome, lymphocytic pneumonitis, and HTLV-1 myelitis (Kompoliti et al 1996). More recently in Japan, Nakamura and colleagues investigated the presence of Sjögren syndrome in patients with HTLV-1-associated myelopathy, including a histological examination of labial salivary glands; definite Sjögren syndrome was found in 65% (13/20) of patients (Nakamura et al 2000). More severe inflammatory cell infiltration in labial salivary glands was found in patients with HTLV-1-seropositive Sjögren syndrome than in seronegative controls. Pot and colleagues reported a spectacular radiological and clinical recovery of a patient with HTLV-1 myelitis and Sjögren syndrome who was treated with combined antiretroviral drugs (lamivudine and tenofovir) plus immunosuppressant therapy with prednisone and mycophenolate mofetil (Pot et al 2006). Based on the aforementioned findings, it is advisable to test for HTLV-1 antibodies in all patients with Sjögren syndrome who develop a myelopathy.

Epidemiology

Population-based studies show that the prevalence of Sjögren syndrome ranges between 0.5% and 5% with most of the cases presenting in postmenopausal women. Although the majority of cases present in midlife, there are reports of Sjögren syndrome in children and the elderly. In Olmstead County, Minnesota, the incidence rate has been estimated...
at 3.9 cases per 100,000 annually (Pillemer et al 2001).

Neurologic manifestations have been reported traditionally in about 20% of patients with Sjögren syndrome (range 6% to 70%) (Lafitte et al 2001; Delalande et al 2004). Recently, Goransson and colleagues performed a population-based study in Sweden and found that 27% of patients with Sjögren syndrome had neuropathy, including 31% with motor neuropathy, 13% with sensory neuropathy, and 11% with sensorimotor neuropathy (Goransson et al 2006).

**Differential diagnosis**

Depending on the form of neurologic presentation, the differential diagnosis of Sjögren syndrome complications includes multiple sclerosis, peripheral neuropathies of other causes, and other multisystemic disorders. The onset of transverse myelitis with interscapular pain and rapid loss of motor function is reminiscent of nucleus pulposus herniation (Toro and Roman 1994). The latter condition can be diagnosed by a typical appearance on spinal MRI (Duprez et al 2005). HTLV-1 myelitis should also be excluded by appropriate tests in serum and CSF. Serum levels of vitamin B12 and methionalalic acid are diagnostic in subacute combined degeneration.

The differential diagnosis of Sjögren syndrome includes a past history of head and neck radiation therapy, hepatitis C infection, AIDS, preexisting lymphoma, sarcoidosis, graft-versus-host disease, and the recent use of anticholinergic drugs.

**Diagnostic workup**

The diagnostic workup of Sjögren syndrome is outlined in Tables 1a and 1b.

**Management**

Treatment of keratoconjunctivitis sicca includes tears replacement and conservative therapy, as well as topical ocular and systemic medications (Pflugfelder et al 2000). Preservative-free preparations of artificial tears are preferred to avoid irritation and allergic reactions. In refractory cases, more concentrated, viscous solutions or hydroxypropyl cellulose pellets inserted under the lower eyelids may be used. Ointments are used only at night. In keratoconjunctivitis sicca, inflammation appears to have a role in the pathogenesis of the ocular surface epithelial disease. Clinical improvement has been observed after therapy with antiinflammatory agents including corticosteroids, cyclosporine, and doxycycline. Cyclosporine A emulsion was approved by the U.S. Food and Drug Administration (FDA) as therapy for dry eyes. Randomized placebo-controlled FDA clinical trials showed that cyclosporine A was superior to vehicle in stimulating aqueous tear production, decreasing corneal punctuate fluorescein staining, reducing symptoms of blurred vision, and decreasing artificial tears use in patients with keratoconjunctivitis sicca. No ocular or systemic toxicity was observed from this medication (Sall et al 2000).

For the treatment of xerostomia, secretagogues such as pilocarpine may increase secretions in patients with sufficient exocrine tissue. Pilocarpine is usually given at a dose of 5 mg orally 4 times a day to a maximum dose of 30 mg (Vivino et al 1999). Adverse effects include feeling hot and flushed, increased perspiration, and increased bowel and bladder motility. Cevimeline is a muscarinic agonist with higher affinity for the M3 receptor site and decreased affinity for M2 receptors, which are found in cardiac tissue, minimizing the likelihood of cardiac stimulation. Cevimeline also has a much longer half-life than pilocarpine. Cevimeline augments not only the salivary flow rate but also the secretion rate of some digestive or defense factors from infections (Suzuki 2005). Daily topical fluoride, antimicrobial mouth rinse, and frequent dental care are important to minimize progression of dental decay in patients with reduced salivary flow (Daniels and Fox 1992). Two phase III studies showed that the use of oral interferon-alpha by patients with Sjögren syndrome, given at low dosage by the oromucosal route can significantly increase unstimulated whole saliva flow in patients with primary Sjögren syndrome, without causing significant adverse events (Cummings et al 2003). Oral dryness could be ameliorated with the use of sugar-free chewing gum or candies, and patients should be counseled on dietary changes and restriction of sugar intake.

**Vitamin B12 (cobalamin) deficiency.** Andres and colleagues documented the common occurrence of vitamin B12 deficiency in 80 patients with primary Sjögren syndrome (Andres et al 2006a). Serum B12 levels below 200 pg/mL were found in 8.8% (7/80) of patients, and 56.2% of patients had B12 levels between 200 and 300 pg/mL, for an overall prevalence of B12 deficiency of 65%. In comparison, they found B12 deficiency in 5.3% of patients in an Internal Medicine clinic. In the general population, B12 deficiency occurs in 15% of people over 60 years of age.
Cobalamin is first released from proteins in food by pepsin and stomach acid; then cobalamin is bound to the salivary vitamin B12 R-binder protein (Kudo et al 1987) before it can be attached to intrinsic factor. Andres and colleagues postulated that B12 deficiency from food-cobalamin malabsorption is the result of a lack of saliva, which is typical of Sjögren syndrome (Andres et al 2000).

Vitamin B12 deficiency causes a number of neurologic manifestations (Roman 2005) that could worsen the neurologic complications of Sjögren syndrome. The most common manifestations of cobalamin deficiency include: peripheral sensory neuropathy; subacute combined degeneration of the spinal cord presenting with sensory ataxia and pyramidal tract involvement with bilateral Babinski sign (Andres et al 2006b); cerebellar syndromes; cranial nerves neuropathies, including optic neuritis and optic atrophy; urinary or fecal incontinence; stroke and atherosclerosis from hyperhomocysteinemia with cognitive decline or dementia (Garcia et al 2004); parkinsonian syndromes; and depression. In practice, it is advisable to exclude and treat B12 (cobalamin) deficiency in patients with Sjögren syndrome and psychiatric or neurologic symptoms, including the several types of neuropathy and myelopathy described.

The treatment of neurologic complications in Sjögren syndrome is dictated by the clinical symptomatology, the clinical course, and the implicated pathogenic mechanism.

**Peripheral nervous system.** The common symmetric, distal axonal sensory and sensorimotor neuropathy is believed to be caused by perivascular cellular infiltration and necrotizing vasculitis. These axonal neuropathies usually follow a slowly progressive and insidious course that needs no separate treatment from the usual symptomatic therapy of Sjögren syndrome (salicylates, nonsteroidal agents, hydroxychloroquine, oral corticosteroids). In cases with mononeuritis multiplex, multiple cranial neuropathies, pseudo-amytrophic lateral sclerosis forms, or with lesions suggestive of severe vasculitis, first-line treatment appears to be intravenous corticosteroid therapy; but when the patient’s course fails to improve or deteriorates, a nonsteroidal immunosuppressant agent should be considered (Mellgren et al 2007). However, the sensory ataxic gangliopathy with antiganglion neuron antibodies and the demyelinating polyradiculoneuropathy of Sjögren syndrome respond poorly to triple treatment with prednisolone, cyclosporine, and cyclophosphamide (Kastrup et al 2005).

There is 1 case report of a patient with sensory neuropathy treated with infliximab (Caroyer et al 2002). There was marked improvement in clinical and neurophysiologic deficits associated with the neuropathy using a dose of 3 mg/kg given at weeks 0, 2, 6, and every 12 weeks thereafter. Plasmapheresis may produce slight improvement, and there is occasional response to treatment with IVIG (0.4 g/kg for 5 days). More recently, Yamada and colleagues reported excellent results with IFN-alpha treatment (3 MIU/day, 3 times weekly), resulting also in marked improvement of the clinical and laboratory manifestations of Sjögren syndrome (Yamada et al 2005). This treatment could potentially be useful also for predominantly autonomic neuropathies with elevated titers of ganglionic acetylcholine receptor autoantibody, trigeminal neuralgia, and for the painful neuropathy without sensory ataxia of Sjögren syndrome.

**Skeletal muscle.** Myalgias in patients with Sjögren syndrome may respond to hydroxychloroquine (6 to 8 mg/kg daily) (Fox 2005). Additional treatments may include corticosteroids, azathioprine, and methotrexate.

**Encephalic manifestations.** Meningoencephalitis, focal manifestations, or seizures consistent with vasculitis, should be treated with intravenous steroids (Hirohata et al 2005). In severe cases, intravenous corticosteroids may be used in conjunction with cyclophosphamide, azathioprine, cyclosporine, or methotrexate (Ozgocmen and Gur 2008). Plasmapheresis, or treatments with IVIG (Canhao et al 2000), are probably indicated, but there are minimal reported data with these therapeutic modalities.

**Spinal cord involvement.** Rogers and colleagues have reviewed this topic (Rogers et al 2004), but these data are based on anecdotal reports. Nonetheless, it seems clear that treatment of Sjögren syndrome myelopathy with intravenous steroids alone is not adequate (Williams et al 2002; Rogers et al 2004; de Seze et al 2006). Combination therapy with agents such as cyclophosphamide, azathioprine, cyclosporine, or methotrexate must be considered.

The agent of first choice based on side effect profile and efficacy, appears to be cyclophosphamide, given intravenously in pulse dosing (Williams et al 2001; de Seze et al 2006). Current treatment regimens consist of a monthly intravenous bolus of drug for 6 to 12 months (de Seze et al 2006); then, if needed, every 3 to 6 months for the second year. Doses used are 0.75 to 1.0 gm/m2. Caution is required due to the high frequency of lymphoma in
Sjögren syndrome. The most common severe adverse effects associated with cyclophosphamide are hemorrhagic cystitis and myelosuppression. Hemorrhagic cystitis can be prevented by adequate hydration and use of mercaptoethane sulfonate sodium, a sulfhydryl compound that binds to the toxic metabolite formed by cyclophosphamide, thus, preventing it from binding to the bladder wall and causing damage. Myelosuppression may be dose-limiting, with the white blood cell nadir occurring 7 to 10 days after treatment. Owing to the aforementioned side effects, the use of **mycophenolate mofetil** is being explored as an alternative to cyclophosphamide in the treatment of vasculitis.

Chlorambucil has been used rarely for neurologic complications of Sjögren syndrome. It induces myelosuppression, which is dose-limiting but does not cause hemorrhagic cystitis.

Azathioprine has been used for relapses or intolerance to cyclophosphamide therapy (**Hawley and Hendricks 2002**). In uncomplicated Sjögren syndrome, azathioprine by itself was ineffective in a dose of 1 mg/kg/d for 6 months. The most serious side effects are dose-related myelosuppression, gastrointestinal disturbances, stomatitis, and hepatotoxicity.

Cyclosporine in combination with corticosteroids may be effective in the treatment of optic neuritis. Cyclosporine is a potent immunomodulator that decreases cytokines involved in T-cell activation and has direct effects on B-cells and macrophages. The onset of effect of cyclosporine is 1 to 3 months. It is only available in an oral dosage form. Serious adverse effects are hypertension, hyperglycemia, nephrotoxicity, tremor, gastrointestinal intolerance, hirsutism, and gingival hyperplasia.

Methotrexate at a dose of 0.2 mg/kg/week tends to improve subjective oral and ocular symptoms, without objective changes. It is an antineoplastic and antiinflammatory agent. Serious adverse effects include thrombocytopenia, gastrointestinal intolerance, stomatitis, hepatotoxicity, and pulmonary toxicity.

Other nonsteroidal immunosuppressant agents should be considered, especially when lack of efficacy or intolerance to cyclophosphamide appears. Other symptoms may benefit from concomitant immunosuppressant treatment. In addition, plasmapheresis appears to be useful when acute relief of symptomatology is needed, such as in a patient with rapid deterioration who is waiting for an immunosuppressant to work. IVIG has been successfully used in Sjögren CNS vasculitis (**Canhao et al 2000**). The dose used in the patient was 400 mg/kg/d for 5 days along with corticosteroids, with additional monthly doses of IVIG for 6 months and then every 2 to 5 months as indicated by the patient's neurologic symptoms.

**Special considerations**

**Pregnancy**

In a questionnaire-based study, primary Sjögren syndrome had no impact on pregnancy outcome before disease onset (**Haga et al 2005**). The most important condition associated with primary Sjögren syndrome in anti-SSA-positive mothers was congenital heart block in the offspring. This condition is associated with high morbidity and mortality, and these patients should receive multidisciplinary care in a neonatal intensive care unit (**Picone et al 2006**).

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**References especially recommended by the author or editor for general reading.

**ICD and OMIM codes**

**ICD codes**

ICD-9:
Sjögren (-Gougerot) syndrome or disease (keratoconjunctivitis sicca): 710.2
Sjögren syndrome with lung involvement: 710.2 + 517.8

ICD-10:
Sicca syndrome [Sjögren]: M35.0

**Profile**

**Age range of presentation**

01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance**

female>male, >2:1

**Family history**

none

**Heredity**

heredity may be a factor

**Population groups selectively affected**

none

**Occupation groups selectively affected**

none selectively affected
**Differential diagnosis list**

- multiple sclerosis
- peripheral neuropathies of other causes
- other multisystemic disorders
- nucleus pulposus herniation
- HTLV-1 myelitis
- history of head and neck radiation therapy
- hepatitis C infection
- acquired immunodeficiency syndrome
- preexisting lymphoma
- sarcoidosis
- graft-versus-host disease
- recent use of anticholinergic drugs
- cobalamin (vitamin B12) deficiency
- aquaporin (AQP4) antibody

**Associated disorders**

- Aquaporin autoantibody
- Angiitis
- B12 deficiency
- Brown-Sequard syndrome
- Carpal tunnel syndrome
- Chronic progressive myelitis
- Devic syndrome
- Entrapment neuropathies
- HTLV-1 infection
- Lower motor neuron disease
- Lupus
- Mononeuritis multiplex
- Multiple cranial neuropathy: diplopia, trigeminal, facial (Bell palsy), cochlear
- Multiple-sclerosis like syndromes
- Myopathy
- Neurogenic bladder
- Neuromyelitis optica
- Painful sensory neuropathy
- Pure sensory neuropathy
- Radiculoneuropathy (demyelinating polyradiculoneuropathy)
- Sensorimotor (axonal) polyneuropathy
- Sensorineural hearing loss
- Sensory ataxic ganglionopathy with antiganglion neuron antibodies
- Sicca syndrome
- Subacute combined degeneration
- Transverse myelitis
- Vasculitic neuropathy

**Other topics to consider**

- Sensory ganglionitis

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