Nervous system disorders

<div style="text-align: right">**8**</div>

Disorders of the nervous system are common in patients with Sjögren's syndrome. These usually concern *sensory peripheral neuropathies* (see further) that are often mild. However, this type of neuropathy has many other possible causes and it may be difficult or even impossible to prove whether it is related to Sjögren's syndrome or not (table 8.1).

Disorders of the *central nervous system* may also occur in patients with Sjögren's syndrome (table 8.2), but it is not always certain that these are related to Sjögren's syndrome.

Relatively rare but clinically important are *paraneoplastic neurological disorders* (*e.g.* paraneoplastic subacute sensory neuronopathy, sensory ataxia, limbic encephalitis). These are believed to be remote immunologically mediated effects of a neoplastic (malignant) process, *e.g.* a small cell lung carcinoma.

Table 8.1 Some causes of peripheral neuropathy

inflammatory diseases
  Guillain-Barré syndrome, SLE, Sjögren's syndrome, leprosy

metabolic and endocrine
  diabetes mellitus, renal failure, porphyria, amyloidosis, liver failure, hypothyroidism

intoxication
  alcoholism, drugs (vincristine, phenytoin, isoniazid, thalidomide), metals

vitamin deficiency
  vitamins B1, B12, A, E

genetic disease
  Friedreich's ataxia, Charcot-Marie-Tooth syndrome

paraneoplastic
  mainly small-cell lung cancer, but also prostate, breast, pancreatic, neuroendocrine, bladder and ovarian cancer

various
  malignancy, AIDS, radiation

Table 8.2 Neurological disorders reported in patients with Sjögren's syndrome, not implying a causal relationship

- acute transverse myelopathy [35]
- amyotrophic lateral sclerosis [37]
- aseptic meningoencephalomyelitis [33]
- brain-SPECT abnormalities [43]
- cerebellar ataxia [34]
- cerebral white matter lesions [36,44]
- chorea [31,40]
- dementia [30]
- Devic's disease (optic neuritis and longitudinally extensive transverse myelitis (LETM) [46]
- hemiparkinsonism [28]
- large tumefactive brain lesion [41]
- limbic encephalitis [47]
- multifocal leukoencephalopathy [27]
- multiple sclerosis [29]
- optic neuropathy (bilateral sequential) [26]
- Parkinsonsism [32]
- subacute inflammatory polyradiculopathy [45]

Typically, the neuropathy predates the discovery of the malignancy 3-8 months.[39] Some neurological disorders will be discussed here, without attempting to be fully comprehensive.

NERVOUS SYSTEM

The nervous system is usually anatomically divided in the *central nervous system* (CNS) consisting of the brain and spinal cord, and the *peripheral nervous system* consisting of the nerves between the CNS and the organs.

A functional division also exists: the *somatic* nervous system and the *autonomic* nervous system. The autonomic nervous system is further divided in *sympathetic* and *parasympathetic* nervous system (see also figure 8.2).

Various other disorders are also discussed such as migraine and myasthenia gravis.

A. CENTRAL NERVOUS SYSTEM DISORDERS

The spectrum of suggested CNS involvement

includes focal (sensorial and motor deficits, brain stem, chorea, cerebellar lesions, epilepsy, migraine), non-focal (encephalomyelitis, aseptic meningitis, neuropsychiatric dysfunctions, cognitive deficits, Parkinson disease), spinal cord (myelopathy, transverse myelitis, motor neuron disease) findings or multiple sclerosis-like illness, optic neuritis and Devic's disease (table 8.1).[19,22,42,46]

Vascular disorders: vasculitis and thrombosis

Vasculitis and thrombosis (*e.g.* as part of the anti-phospholipid syndrome) are generally accepted as possible related causes of (secondary) CNS disorders in patients with Sjögren's syndrome.

Non-vascular disorders

There is no consensus on the background of CNS disorders in Sjögren's syndrome without vasculitis or thrombosis. Prevalence figures lie between 0 and 20%.[6-11,18,20] It is quite well possible, however, that CNS disorders in Sjögren's syndrome merely reflect the normal prevalence in the general population.

Generalized chorea caused by Sjögren's syndrome or an unrelated CNS vasculitis?

Min *et al* [40] described a case of a 72-yr old man who presented with generalized chorea. MRI demonstrated bilateral basal ganglia lesions.
He could also be newly diagnosed with primary Sjögren's syndrome and no other diseases could be found.

Treatment was started with oral prednisolone 60 mg/day and haloperidol 1.5-2.5 mg/day. After 2 months, his symptoms completely resolved and the follow-up MRI revealed the disappearance of previous lesions.

The underlying mechanism is unknown but the mild leukocytosis at presentation and the excellent response to corticosteroid treatment suggest giant cell arteritis as the underlying vasculitis.

Despite the fact that Sjögren's syndrome was diagnosed according to the American-European criteria, the disease was only suspected and diagnosed after laboratory abnormalities suggested Sjögren's syndrome. Therefore, the relationship between the probable CNS vasculitis and the hitherto subclinical Sjögren's syndrome is uncertain. The CNS vasculitis could also be due to an unrelated vasculitis such as isolated CNS vasculitis or giant cell arteritis.

Brain-SPECT abnormalities

Le Guern *et al* [43] assessed subclinical CNS involvement in Sjögren's syndrome by comparing standard brain MRI, in-depth neuropsychological testing and ^{99m}Tc-ECD brain SPECT of patients to matched controls. Brain-SPECT abnormalities were significantly more frequent in Sjögren's patients than controls. Cognitive dysfunctions, mainly expressed as executive and visuospatial disorders, were also significantly more frequent in Sjögren's patients. A correlation was found between neuropsychological assessment and brain-SPECT abnormalities in Sjögren's patients. MRI abnormalities in patients and controls did not differ. It should be noted, however, that 8 out of 10 Sjögren's patients had hematological complications: MALT lymphoma (n=3), vasculitis (n=2), cryoglobulinemia (n=4, two of which had MALT lymphoma) and antiphospholipid syndrome (n=1). One of the remaining two patients had active peripheral neuropathy. These data suggest an organic etiology of cognitive CNS dysfunction in this subgroup of patients with Sjögren's syndrome. This is possibly not directly related to Sjögren's syndrome but due to vascular-mediated cerebral damage.

Cerebral white matter hyperintensities

Harboe *et al* [44] compared cerebral white matter hyperintensities (WMHs) in 68 unselected patients with Sjögren's syndrome and 68 age and sex matched healthy subjects (HS). Among the 68 Sjögren's patients, 50% had normal cognitive function, 24% had mild, 21% had moderate, and 6% had severe cognitive dysfunction. The Sjögren's patients with cognitive dysfunction had higher total WMH scores than those without cognitive dysfunction but this is in accordance with population-based studies of elderly people. The present study, however, showed no differences in WMH scores between Sjögren's patients and HS. It appears that cognitive dysfunction correlate with WMHs in both Sjögren's patients and HS.

White matter hyperintensities

White matter hyperintensities (WHMs) are areas of abnormal signal in the cerebral white matter detected by MRI T2-weighted sequences of fluid-attenuated inversion recovery. WHMs frequency increases with advancing age and in subjects with cerebrovascular risk factors. WHMs are typical features of multiple sclerosis but also appear more frequently in SLE and are reported in other autoimmune diseases such as the antiphospholipid syndrome and Behçets disease. Both groups showed a significant association between age and total WMH score.

Screening for Sjögren's syndrome should be systematically performed in cases of acute or chronic myelopathy, axonal sensorimotor neuropathy, or cranial nerve involvement.

Delalande et al (2004) [11]

Demyelinating spinal cord lesion

Yamout *et al* described a 47-year-old female with Sjögren's syndrome and severe weakness in her legs. An MRI of the brain and spine revealed a longitudinally extensive demyelinating lesion with oedema extending from Th7 to Th10. She had been initially treated with corticosteroids and intravenous cyclophosphamide with significant improvement but then deteriorated. The patient responded within a few days on a weekly dose of rituximab (375 mg/m^2) for four consecutive weeks and the improvement sustained at least eight months after her last dose.[42]

Devic's disease

Devic's disease, also known as *neuromyelitis optica* (NMO), is diagnosed on the basis of the presence of *optic neuritis*, a *myelopathy* spanning more than three vertebral segments of the cord and the presence of NMO IgG, a recently characterised *autoantibody* to the aquaporin-4 (AQ4) water-pump channel antigen.

MRI characteristics of myelitis in Devic's disease differ from myelitis seen in MS.[46] In Devic's disease spinal lesions tend to be symmetrical and span multiple vertebral segments. These lesions have been described as *longitudinally extensive transverse myelitis* (LETM). Javed *et al* [46] evaluated 16 patients with Devic's disease and 9 with LETM. They report that 4 out of these 25 patients satisfied the criteria for Sjögren's syndrome. No information is given on oral symptoms. It is remarkable that 10 of 15 patients with Devic's disease and 3 of 9 with LETM were African-Americans.

Spinal cord and optic nerves express high levels of AQ-4 (aquaporin-4). Salivary glands express high levels of AQ-5.[46] A possible explanation for the association between Devic's disease and Sjögren's syndrome, therefore, could be cross-reacting or co-occurring autoantibodies to AQ-4 and AQ-5.

Large tumefactive brain lesion

Sanahuja *et al* described a 50-year-old woman with recurrent neurologic deficits. MR imaging revealed a large brain lesion. A diagnosis of primary Sjögren's syndrome was made. The patient was treated with oral prednisone with good response. The authors suggest that large tumefactive brain lesions are a complication of primary Sjögren's syndrome.[41]

Limbic encephalitis

Limbic encephalitis, inflammation in the limbic system, is divided into two broad categories: *infectious* encephalitis and *autoimmune* encephalitis.

Limbic encephalitis is characterized by a severe impairment of short-term memory. Anterograde amnesia (a loss of the ability to memorise new events) is often associated with behavioural and psychiatric symptoms such as anxiety, depression, irritability, personality change, acute confusional state, hallucinations and complex partial and secondary generalised seizures. The symptoms typically develop over a few weeks or months, but they may evolve over a few days.[49]

Infectious limbic encephalitis

Infectious limbic encephalitis is caused by invasion of the brain by an infectious agent, usually a virus (*e.g.* herpes simplex virus).

Autoimmune limbic encephalitis

Autoimmune limbic encephalitis is caused by the immune system. There are two forms: *paraneoplastic limbic encephalitis* (PLE) and *non-paraneoplastic limbic encephalitis* (NPLE).

Paraneoplastic limbic encephalitis

Paraneoplastic limbic encephalitis (PLE) occurs in a small proportion of people with cancers, mainly cancer of the lung, thymus gland, the breast or the testis. In many cases, PLE can be diagnosed by testing for one of a group of *paraneoplastic autoantibodies* in the patient's blood.

Neurological symptoms precede the diagnosis of the malignancy in 60-75% of the patients.[49] The condition may improve or stabilise if the cancer is treated effectively, but unfortunately in many cases the tumour proves difficult to identify or the treatment does not cure the patient's neurological symptoms.[47]

Non-paraneoplastic limbic encephalitis

Non-paraneoplastic limbic encephalitis (NPLE)

The limbic brain

The limbic brain includes the hippocampus, thalamus, hypothalamus and amygdala which are involved in memory and much of the behaviour related to sex, hormones, food, fight or flight responses, the perception of pleasure and competition with others. The limbic brain is the seat of higher emotions including the protection of the young and feelings such as love, sadness and jealousy.[48]

> ### Voltage-gated potassium channel antibodies
>
> Voltage-gated potassium channel (VGKC) antibodies cause a reduction in the number of potassium channels, decreasing the control over electrical signals operating in the brain.
>
> Potassium channels are proteins that lie in the surrounding membrane of nerve cells in the brain and in the nerves that lead to the muscles of the skeleton, the gut and the heart. They are particularly common in the hippocampus and other limbic areas of the brain.[48]
>
> See also *Lambert-Eaton myasthenic syndrome* at the end of this chapter.

has only been clearly recognised recently. Doctors began to identify patients who had the symptoms of paraneoplastic limbic encephalitis but who did not

have any of the marker paraneoplastic antibodies in their blood and never developed a tumour. Moreover, some of these patients got better if they were treated with drugs that suppress the immune system.

Antineuronal antibodies
In many patients with auto-immune limbic encephalitis (PLE and NPLE), one or more antineuronal antibodies can be identified. Examples are anti-Hu, anti-Yo, anti-Ma2, CRMP-5 (collapsin response-mediator protein-5), amphiphysin, VGKC (voltage-gated potassium channel), VGCC (voltage-gated calcium channel), NMDAR (*N*-methyl-D-aspartate receptor) or neuropil antibodies. These antibodies show more or less associations with the kind of tumour, clinical features in addition to the limbic symptoms, and the response to treatment (see table 8.3).[49-51]

Table 8.3 Antineuronal antibodies associated with limbic encephalitis [49-51]			
antibody to	**main tumours**	**additional clinical features**	**response to treatment** [a]
Hu	SCLC	sensory neuronopathy brain stem, cerebellar signs motor neuronopathy autonomic neuropathy multifocal encephalomyelitis	poor
Yo	breast, ovary	cerebellar ataxia, nystagmus	poor to moderate
Ma2	testis	hypothalamic dysfunction rostral brain stem dysfunction atypical Parkinsonism	30% improve
CRMP-5	SCLC, thymoma	cerebellar ataxia encephalomyelitis chorea, parkinsonism uveitis, retinopathy neuropathy	poor
amphiphysin	breast, SCLC	stiff person syndrome multifocal disease	poor
VGKC	nil	REM sleep behaviour disorder hyponatraemia temporal lobe epilepsy	good
VGCC	SCLC	Lambert-Eaton myasthenic syndrome	
GAD65	nil	temporal lobe epilepsy stiff person syndrome	poor
NMDAR	ovarian teratoma	psychiatric symptoms dystonia depressed consciousness hypoventilation	good
neuropil	SCLC, thymoma	multiple	good

CRMP-5 = collapsin response-mediator protein-5; NMDAR = N-methyl-D-aspartate receptor; GAD = glutamic acid decarboxylase-65; SCLC = small cell lung carcinoma; VGKC = voltage-gated potassium channel; VGCC = voltage-gated calcium channel; REM = rapid eye movement.
[a] Treatment of tumour, immunotherapy, or both.

Limbic encephalitis in Sjögren's syndrome
In *paraneoplastic* limbic encephalitis, dermatomyositis is the only autoimmune disease with an increased prevalence. Dermatomyositis is a rare disease that may also be paraneoplastic.

Very few patients (<10) with *non-paraneoplastic* limbic encephalitis and Sjögren's syndrome have been described to date.[47] This is remarkable as Sjögren's syndrome is one of the most prevalent autoimmune diseases. Therefore, the rarity of reports on patients with limbic encephalitis and Sjögren's syndrome suggests that limbic encephalitis is not part of Sjögren's syndrome but rather an example of an autoimmune disease with similar prevalences in Sjögren's syndrome and the normal population (such as Graves'disease).

Autoimmune limbic encephalitis is rare but probably under-recognised. The detection of antineuronal antibodies, therefore, may be helpful for a correct diagnosis in patients with a puzzling clinical picture.

Multiple sclerosis
In a recent study, the prevalence of multiple sclerosis (MS) in the population has been found to be 357.6/100,000 in 2004. The female:male ratio was 2.6:1 implying a prevalence of MS in women of 0.5%.[21] The prevalence of epilepsy in the population may even be as high as 1-2%.[23]

Associations between Sjögren's syndrome and multiple sclerosis are suggested in several case reports. It is clear, however, that this is not evidence of an association as both disease are common and prone to diagnostic errors.

B. PERIPHERAL NERVOUS SYSTEM DISORDERS
Disorders of peripheral nerves are usually divided on the basis of the number of involved nerves. In mononeuritis one (*mononeuritis simplex*) or a few nerves (*mononeuropathy multiplex*) are involved, while in polyneuropathy many nerves are involved. The term neuropathy means disease of a nerve. Neuritis means inflammation of a nerve but this term is broadly used. Mono means single and poly means many. Peripheral refers to the part of the nervous system between the CNS on the one hand and the organs on the other. Cranial nerve neuropathies (see next column) are examples of mononeuritis simplex.

Involvement of few or single peripheral nerves

Mononeuritis multiplex
Mononeuritis multiplex is a painful asymmetric sensory and motor peripheral neuropathy (see further). The damage to the nerves involves destruction of the axon (the long part of the nerve cell) and interferes with signal conduction. Damage results from a lack of oxygen from decreased blood flow. Mononeuritis multiplex can result from many different systemic disorders such as diabetes mellitus, vasculitis of medium-size or large blood vessels, malignancies, Lyme disease, leprosy, and AIDS. It may also occur in (primary) Sjögren's syndrome but this is rare.

Cranial nerve neuropathy
Involvement of the cranial nerves is relatively rare. Cranial nerves go directly from the brain to their target areas and mainly regulate functions in the head.

In particular, there may be involvement of the 5th cranial nerve (trigeminal nerve) and the 7th cranial nerve (facial nerve). Inflammation of the 5th cranial nerve can lead to facial pain or trigeminal neuralgia. Inflammation of the 7th nerve results in Bell's palsy or facial paralysis with one-sided paralysis of facial muscles and one-sided loss of function of the salivary glands under the jaw and under the tongue (the parotid gland, however, is controlled by the 9th cranial nerve and therefore continues to function normally).

Adie's pupil is caused by damage to nerve fibres in the ciliary ganglion of the 3rd cranial nerve. The cause is thought to be inflammation (ganglionitis), for example due to a viral infection or an autoimmune disease, especially Sjögren's syndrome. It may be the first symptom of the disease to be manifested.[13-15] Adie's pupil refers to an enlarged pupil that reacts poorly to light but better to accommodation (*e.g.* focusing on one finger right in front of the nose). Adie's pupil usually occurs in one eye but may eventually affect both eyes in 20-30% of patients. The pupil is often irregular in form. Adie's pupil is mainly found in young women and the knee jerk reflexes are also often absent.

Adie's pupil should not be confused with Horner's syndrome. In Horner's syndrome there is a constricted pupil, a drooping eyelid and an inability to sweat on the affected side of the face. There is also a congenital form, where the colour of the iris differs in the two eyes, and an acquired form. In the latter form, there is a disruption of the sympathetic nerve control of the eye somewhere along its roundabout pathway which passes via the neck and upper chest cavity. This can be caused for example by an accident, sympathectomy for Raynaud phenomenon, dilatation of the aorta or one of its branches to the head, tuberculosis, a malignant tumour in the lung apex or thyroid gland surgery.

The nervous system, transmitters and receptors

The nervous system consists of a central (brain and spinal cord) and a peripheral nervous system (the nerves).

There are somatic (voluntary) and autonomic (involuntary) nerves.

The somatic nerves control the skeletal muscles and run directly from the spinal cord to the muscles and transmit signals very fast.

The autonomic nerves control the smooth muscles (*e.g.* intestines, bladder, blood vessels), the heart and the glands. They do not go directly to these organs but have a transitional station (ganglion) where the signals are communicated from one nerve to a following nerve by means of chemical substances (transmitters) by binding the transmitter to a receptor.

In the autonomic nervous system, a distinction is made between the parasympathetic and sympathetic systems.

The nervous system makes use of different transmitters and receptors (figure 3.3).

Somatic nervous system

The somatic nervous system relays the signal from the nerve to the muscles by means of the transmitter called acetylcholine that can bind to a specific acetylcholine receptor, a nicotinic type II or M-receptor.

Autonomic nervous system

In the parasympathetic nervous system, the transmission of signals also takes place by means of acetylcholine. The receptors for this in the ganglia are nictoninic type I or G-receptors while receptors on the target organ (glands, heart or smooth muscles) are muscarinic receptors. There are five types of muscarinic receptor: M1 to M5. Some organs have mainly one type (*e.g.* the salivary glands have mainly M3 receptors), while others may have several different types.

In the *sympathetic nervous system*, signals in the ganglia are also transmitted by means of acetylcholine to nictoninic type I receptors. The signal from the nerve to the target organ is likewise transmitted via noradrenaline to adrenergic receptors that differ per organ. The different adrenergic receptors are α1, α2, β1, β2 and β3. Medication prescribed to patients may be based on these. Since, for example, β1-receptors mainly occur in the heart, β1-blockers are used to slow down the heartbeat.

Entrapment neuropathy

Entrapment neuropathy refers to nerve dysfunction caused by entrapment of the nerve. A well-known example of this is carpal tunnel syndrome (see figure 8.1). The median nerve passes through a narrow tunnel in the wrist. There are many reasons why the space for the nerve may become too tight, such as an old bone fracture, arthritis or inflammation.
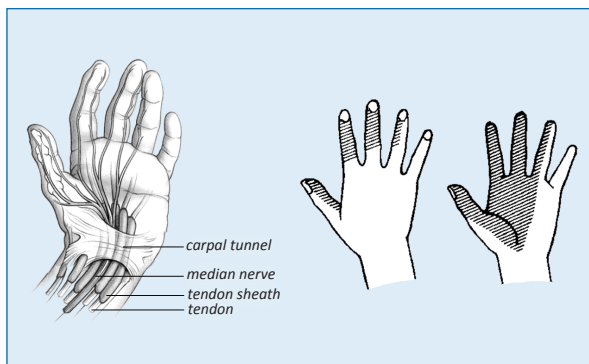

Figure 8.1 The point of entrapment of the median nerve in the wrist in carpal tunnel syndrome (left). The shaded areas indicate the localisation of symptoms (right).

The symptoms may start slowly and gradually worsen over the years and often begin at night. After sleeping for a while, the patient wakes with a hand that feels numb and swollen, with fingers that are painful and difficult to use. The symptoms are often worst in the thumb, index, middle and ring fingers.

The pain may extend upwards past the shoulders. The symptoms may start on one side but usually eventually occur on both sides. It is mainly a sensation disorder, but sometimes paralysis of the thumb and finger muscles may occur. Neurological investigation is indicated and there are various possible treatments, depending on the cause and severity.

Ultimately, surgery is often necessary to give the nerve more room. This is a relatively minor outpatient procedure. Nerve entrapment can also occur in other parts of the body, including the foot and diagonally below the knee.[5]

Involvement of multiple peripheral nerves
Peripheral polyneuropathy may results from many different disorders (see table 8.1) It occurs in about 25% of patients with Sjögren's syndrome.

Peripheral neuropathy is usually divided into sensory, motor and autonomic neuropathy, depending of the nerve fibre type that is most prominently involved but mixed types are common.

Sensory peripheral neuropathy
Sensory peripheral neuropathy is the most common form of neuropathy in Sjögren's syndrome. It is expressed in the form of a tingling, burning or numb sensation in the lower legs, feet or hands. It usually progresses no further than this and is a relatively mild disorder in many patients.[3-5]

It may be the presenting feature of Sjögren's syndrome and other features usually develop within a year. However, Stell *et al* described a 39-year old women with a 13-year history of a sensory neuropathy associated with anti-SSA/Ro antibodies, in whom there were no clinical or pathological features of Sjögren's syndrome. She also had an increased IgG and decreased C4 level.[38]

It should be realized that sensory neuropathies may also be caused by antineuronal antibodies, *e.g.* as part of limbic encephalitis (see table 8.3).

Small fibre neuropathy
Small fibre neuropathy occurs in about 3% of patients with Sjögren's syndrome.[24] It is a peripheral neuropathy characterized by the impairment of thinly myelinated Aδ and unmyelinated C-fibres. Both somatic and autonomic fibres may be involved, thus leading to sensory and autonomic neuropathies. Isolated autonomic neuropathies are rare. Symptoms of somatic nerve fibre dysfunction, such as burning, pain, and hyperaesthesia, frequently prevail over those related to autonomic nerve fibre impairment. This may explain why the term "painful neuropathy" is often used as a synonym but painful symptoms can also be a feature of large fibre neuropathies.[25]

Patients with Sjögren's syndrome-associated neuropathy often show severe neuropathic pain which is not relieved by conventional treatments.

Morozumi *et al* [28] described five patients who were treated with intravenous immunoglobulin (IVIg), 0.4 g/kg/day for 5 days. All five patients showed a remarkable improvement in neuropathic pain following IVIg therapy. Pain, assessed by the determination of mean VAS score, was reduced by 73.4% from days 2-14 following treatment. The observed clinical improvement persisted for 2 to 6 months. IVIg might be an effective treatment for pain in Sjögren's syndrome-associated neuropathy.
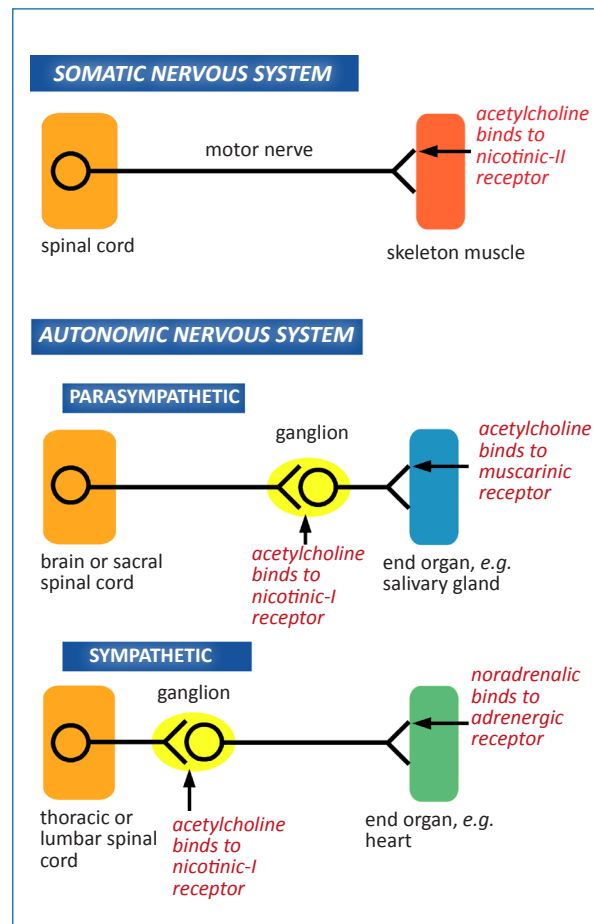
Figure 8.2 *Diagram of the nervous system with the different transmitters and receptors. Sacral spinal cord: spinal cord on a level with the sacrum, lumbar is on a level with the loins and thoracic with the chest. For further information, see text in the box above.*

Autonomic neuropathy
The autonomic nervous system (see figure 8.2 and text box) regulates many "automatic" functions of organs. Autonomic functions can be disturbed by drugs or structural changes in pre- or postganglionic neurons. Autonomic neuropathy is usually part of a generalized neuropathy.

Examples of symptoms of loss of autonomic function are postural hypotension with faintness or syncope, anhidrosis, hypothermia, bladder atony, obstipation, dry mouth and dry eys from failure of salivary and lacrimal glands to secrete, blurring of vision from lack of pupillary and ciliary regulation, and sexual impotence in males.

Hyperfunction of the autonomic nervous system may also occur. Examples of symptoms are episodic hypertension, diarrhea, hyperhidrosis, and tachycardia or brady cardia.

Motor peripheral neuropathy
Occasionally there is involvement of the motor nerves responsible for movement of muscles. This is much more serious since it can hamper movement such as walking up stairs.

C. Various Neurologic Disorders

Depression
Various studies have suggested that depression occurs more frequently than normal in Sjögren's syndrome. This is, however, by no means certain and the background to this theory is equally unclear. [5,12]
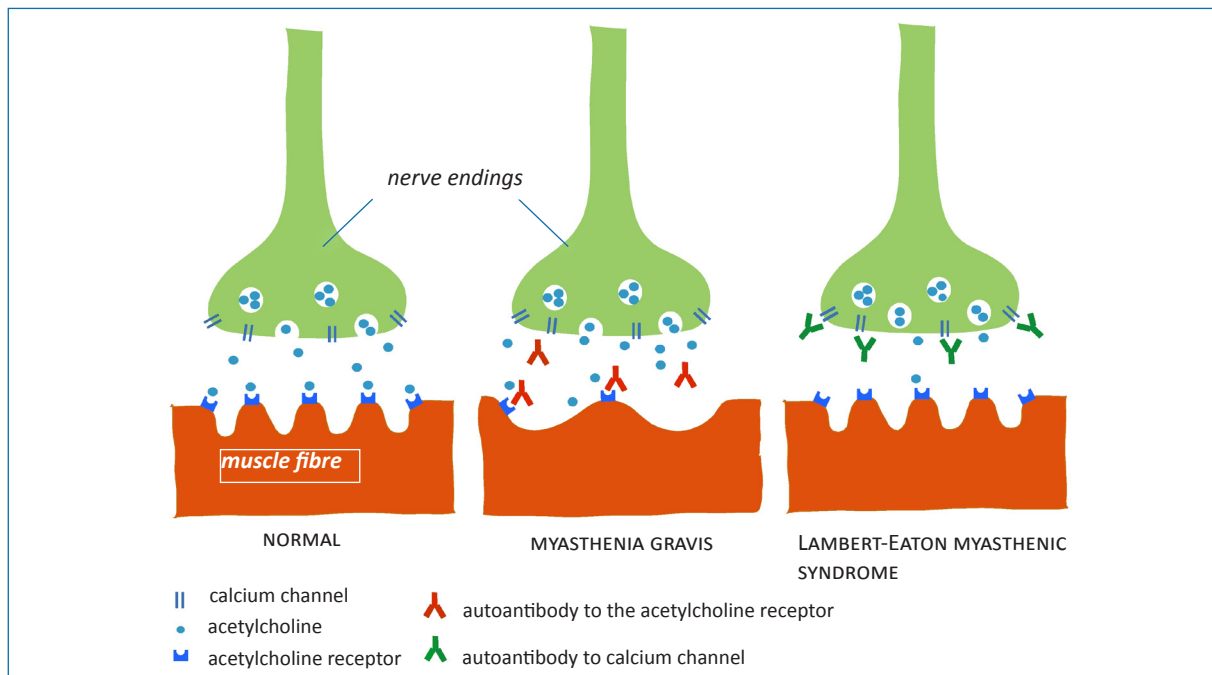
Migraine
Migraine is a unilateral (one-sided) headache often accompanied by nausea. It appears to occur more commonly than normal in people with Sjögren's syndrome.[1] There also seems to be a connection between migraine and a number of other disorders associated with Sjögren's syndrome. People with Raynaud phenomenon (bluish-white discoloration at low environment temperatures of hands and feet) and people with antiphospholipid antibodies in their blood possibly have migraine more frequently.[1] In addition to causing migraine, these antibodies may also be responsible for e.g. thrombosis in veins and arteries and low platelet levels.[2]

Myasthenia gravis and Lambert-Eaton myasthenic syndrome
Myasthenia gravis and Lambert-Eaton myasthenic syndrome are diseases characterised by weakness of the voluntary muscles caused by a defect in the transmission of nerve impulses to muscle fibres.[16,17]

Acetylcholine (ACh) is normally present in the nerve ndings in vesicles (see figure 8.3). Release of the ACh is dependent on calcium which enters the nerve endings via calcium channels. The released ACh binds to ACh receptors (AChR) on the muscle fibre. This causes the muscle fibre to contract. The ACh is quickly broken down by the enzyme cholinesterase in order to prevent the effect continuing. Nerve gases used as chemical weapons generally work by blocking the effect of the cholinesterase.

NORMAL　　　　MYASTHENIA GRAVIS　　　　Lambert-Eaton myasthenic syndrome

‖ calcium channel
• acetylcholine
⊌ acetylcholine receptor
autoantibody to the acetylcholine receptor
autoantibody to calcium channel

Figure 8.3 *Normal situation: acetylcholine (ACh) is released from the nerve ending and binds to the ACh receptor on the muscle fibre. This leads to contraction of the muscle fibre. The ACh is quickly broken down by the enzyme cholinesterase.*
***Myasthenia gravis**: acetylcholine is released as normal from the nerve ending but there are fewer acetylcholine receptors (AChR) present on the muscle fibre because these have been damaged by antibodies against AChR. In addition, the antibodies against the AChR can also block the receptor.*
***Lambert-Eaton myasthenic syndrome**: insufficient acetylcholine is released from the nerve ending because this is inhibited by antibodies against calcium channels.*

Myasthenia gravis

Myasthenia gravis (MG) occurs in approximately 1 in 15,000 people and affects women twice as commonly as men. In women the disease often starts between the ages of 10-30 years, in men between 40 and 60 years. Approximately 15% of MG patients also have another autoimmune disease such as rheumatoid arthritis, SLE, Sjögren's syndrome or pernicious anaemia. A usually benign tumour of the thymus gland (thymoma) is present in 10-15% of MG patients. MG can occur or be exacerbated as a side effect of certain drugs such as d-penicillamine and interferon-α. A chronic rejection (chronic *graft-versus-host)* response following a bone marrow transplant can also cause MG. In 80% of MG patients, antibodies to the acetylcholine receptor can be seen. These antibodies cause a reduction in the number of ACh receptors (AChR) and their activity. 70% of the remaining 20% of MG patients have antibodies against a tyrosine kinase receptor that is specific to muscles (MuSK, musclespecific tyrosine kinase). MuSK plays an important role in the activity of the AChR.

Typical characteristics of MG are weakness and fatigue of the skeletal (voluntary) muscles. This muscle weakness increases the longer the muscles are used. The first symptoms of MG are often double vision or drooping eyelids. The disease is treated with drugs that block the activity of the enzyme cholinesterase.

Lambert-Eaton myasthenic syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a rare disorder that occurs in 1 in 100,000 people and twice as commonly in men as in women. This disease can occur at any age but most patients are over the age of 40 years. In approximately half the patients, the disease is caused by small cell lung carcinoma. Conversely, around 3% of people with this form of lung cancer have LEMS. Other malignant diseases may also be accompanied by LEMS such as lymphosarcoma and malignant thymoma (malignant tumour of the thymus gland).

In many cases, the malignant tumour has not yet been found when the LEMS first starts and may only be discovered a couple of years later. The disease is characterised by muscular weak ness which makes it impossible to carry out normal everyday activities. The muscular weakness is often greatest in the thighs and hips. In contrast with MG, the muscular weakness improves the more the muscles are used. Many patients also have a certain degree of autonomic nervous system disorders expressed for example in the form of a dry mouth, dry eyes, reduced sweating or impotence. The possibility of LEMS should therefore be considered in men over the age of 40 years who have Sjögren's-like symptoms. This syndrome is caused by autoantibodies against the calcium channels in the nerve endings. The result is that insufficient acetylcholine is released from the nerve endings.

It can be difficult to distinguish this syndrome from myasthenia gravis. In MG the tendon reflexes are normal whereas in LEMS they are absent. There is also a difference in the effect of continuous exertion: an increase in muscular weakness in MG and a decrease in LEMS. Antibodies to calcium channels can be seen in 50-90% of patients with LEMS.

References

1. Pal B, Gibson C, Passmore J, Griffiths ID, Dick WC. A study of headaches and migraine in Sjogren's syndrome and other rheumatic disorders. Ann Rheum Dis 1989;48:312.
2. Lahita RG. Collagen disease: the enemy within. Int J Fertil Womens Med 1998;43:229.
3. Mellgren SI, Conn DL, Stevens JC, Dyck PJ. Peripheral neuropathy in primary Sjögren's syndrome. Neurology 1989;39:390.
4. Andonopoulos AP, Lagos G, Drosos AA, Moutsopoulos HM. The spectrum of neurological involvement in Sjögren's syndrome. Br J Rheumatol 1990;29:21.
5. Hietaharju A, Yli-Kerttula U, Hakkinen V, Frey H. Nervous system manifestations in Sjogren's syndrome. Acta Neurol Scand 1990; 81:144.
6. Alexander EL, Provost TT, Stevens MB, Alexander GE. Neurologic complications of primary Sjogren's syndrome. Medicine (Baltimore) 1982;61:247.
7. Alexander EL. Central nervous system (CNS) manifestations of primary Sjogren's syndrome: an overview. Scand J Rheumatol Suppl 1986; 61:161.
8. Alexander EL. Neurologic disease in Sjögren's syndrome: mononuclear inflammatory vasculopathy affecting central / peripheral nervous system and muscle. A clinical review and update of immunopathogenesis. Rheum Dis Clin North Am 1993;19:869.
9. Tajima Y, Mito Y, Owada Y, *et al.* Neurological manifestations of primary Sjogren's syndrome in Japanese patients. Intern Med 1997;36:690.
10. Belin C, Moroni C, Caillat-Vigneron N, *et al.* Central nervous system involvement in Sjogren's syndrome: evidence from neuropsychological testing and HMPAO-SPECT. Ann Med Interne (Paris) 1999;150:598.
11. Delalande S, de Seze J, Fauchais AL, *et al.* Neurologic manifestations in primary Sjogren syndrome: a study of 82 patients. Medicine (Baltimore) 2004;83:280.
12. Utset TO, Golden M, Siberry G, *et al.* Depressive symptoms in patients with systemic lupus erythematosus: association with central nervous system lupus and Sjogren's syndrome. J Rheumatol 1994;21:2039.
13. Vetrugno R, Liguori R, Cevoli S, Salvi F, Montagna P. Adie's tonic pupil as a manifestation of Sjogren's syndrome. Ital J Neurol Sci 1997;18:293.
14. Font J, Valls J, Cervera R, Pou A, Ingelmo M, Graus F. Pure sensory neuropathy in patients with primary Sjogren's syndrome: clinical, immunological, and electromyographic findings. Ann Rheum Dis 1990;49:775.
15. Font J, Ramos-Casals M, de la Red G, *et al.* Pure sensory neuropathy in primary Sjogren's syndrome. Longterm prospective followup and review of the literature. J Rheumatol 2003;30:1552.

16. Meriggioli MN, Sanders DB. Myasthenia gravis: diagnosis. Semin Neurol 2004;24:31-9.

17. Takamori M. Lambert-Eaton myasthenic syndrome as an autoimmune calcium channelopathy. Biochem Biophys Res Commun 2004;322:1347.

18. Anaya JM, Villa LA, Restrepo L, et al. Central nervous system compromise in primary Sjögren's syndrome. J Clin Rheumatol 2002;8:189-96.

19. Ozgocmen S, Gur A. Treatment of central nervous system involvement associated with primary Sjögren's syndrome. Curr Pharm Des. 2008;14(13):1270-3.

20. Delalande S, de Seze J, Fauchais AL, et al. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore) 2004;83:280-91.

21. Warren SA, Svenson LW, Warren KG. Contribution of incidence to increasing prevalence of multiple sclerosis in Alberta, Canada.Mult Scler. 2008 Jun 23. [Epub ahead of print] PMID 18573834

22. Visser LH, Koudstaal PJ, van de Merwe JP. Hemiparkinsonism in a patient with primary Sjögren's syndrome. A case report and a review of the literature. Clin Neurol Neurosurg 1993;95:141-5.

23. Ferguson PL, Chiprich J, Smith G, et al. Prevalence of self-reported epilepsy, health care access, and health behaviors among adults in South Carolina. Epilepsy Behav 2008 Jun 26. [Epub ahead of print] PMID 18585962

24. Gøransson LG, Herigstad A, Tjensvoll AB, et al. Peripheral neuropathy in primary sjogren syndrome: a population-based study. Arch Neurol 2006;63:1612-5.

25. Lauria G. Small fibre neuropathies. Curr Opin Neurol 2005; 18:591-7.

26. Pournaras JA, Vaudaux JD, Borruat FX. Bilateral sequential optic neuropathy as the initial manifestation of Sjögren syndrome. Klin Monatsbl Augenheilkd 2007;224:337-9.

27. Hayashi Y, Kimura A, Kato S, et al. Progressive multifocal leukoencephalopathy and CD4+ T-lymphocytopenia in a patient with Sjögren syndrome. J Neurol Sci 2008;268:195-8.

28. Morozumi S, Kawagashira Y, Iijima M, et al. Intravenous immunoglobulin treatment for painful sensory neuropathy associated with Sjögren's syndrome. J Neurol Sci. 2009 Jan 23. [Epub ahead of print] PMID: 19168191

29. de Seze J, Devos D, Castelnovo G, et al. The prevalence of Sjögren syndrome in patients with primary progressive multiple sclerosis. Neurology 2001;57:1359-63.

30. Créange A, Laplane D, Habib K, et al. Démence révélatrice du syndrome de Gougerot-Sjögren primitif. Rev Neurol (Paris) 1992;148:376-80.

31. Venegas Fanchke P, Sinning M, Miranda M. Primary Sjögren's syndrome presenting as a generalized chorea. Parkinsonism Relat Disord 2005;11:193-4.

32. Nishimura H, Tachibana H, Makiura N, et al. Corticosteroid-responsive Parkinsonism associated with primary Sjögren's syndrome. Clinical Neurol Neurosurg 1994;96:327-331.

33. Hoshina T, Yamaguchi Y, Ohga S, et al. Sjögren's syndrome-associated meningoencephalomyelitis: cerebrospinal fluid cytokine levels and therapeutic utility of tacrolimus. J Neurol Sci 2008;267:182-6.

34. Owada K, Uchihara T, Ishida K, et al. Motor weakness and cerebellar ataxia in Sjögren syndrome - Identification of antineuronal antibody: A case report. J Neurol Sci 2002; 197:79-84.

35. Manabe Y, Sasaki C, Warita H, et al. Sjögren's syndrome with acute transverse myelopathy as the initial manifestation. J Neurol Sci 2000;176:158-161.

36. Coates T, Slavotinek JP, Rischmueller M, et al. Cerebral white matter lesions in primary Sjogren's syndrome: A controlled study. J Rheumatol 1999;26:1301-5.

37. Attout H, Rahmeh F, Ziegler F. Syndrome de Gougerot-Sjögren simulant une sclérose latérale amyotrophique. Rev Med Interne 2000;21:708-10.

38. Stell R, Zilko PJ, Carroll WM. Chronic sensory neuropathy with anti-Ro antibodies without clinical features of Sjögren's syndrome. Clin Neurosci 1998;5:110-2.

39. Rudnickia SA, Dalmau J. Paraneoplastic syndromes of the peripheral nerves. Curr Opin Neurol 2005;18:598–603.

40. Min JH, Youn YC. Bilateral basal ganglia lesions of primary Sjogren syndrome presenting with generalized chorea. Parkinsonism Relat Disord 2008 Aug 14. [Epub ahead of print] PMID: 18707916 (Letter)

41. Sanahuja J, Ordoñez-Palau S, Begué R, et al. Primary Sjögren syndrome with tumefactive central nervous system involvement. AJNR Am J Neuroradiol 2008 Sep 10 [Epub ahead of print] PMID: 18784216.

42. Yamout B, El-Hajj T, Barada W, et al. Successful treatment of refractory neuroSjogren with Rituximab. Lupus 2007;16:521-3.

43. Le Guern V, Belin C, Henegar C, et al. Cognitive function and ^{99m}Tc-ECD brain SPECT are significantly correlated in patients with primary Sjogren's syndrome: a case-control study. Ann Rheum Dis 2009 Jan 21. [Epub ahead of print] PMID: 19158115

44. Harboe E, Beyer MK, Greve OJ, et al. Cerebral white matter hyperintensities are not increased in patients with primary Sjögren's syndrome. Eur J Neurol 2009;16:576-81.

45. Rigamonti A, Lauria G, Balgera R, et al. Subacute inflammatory polyradiculopathy associated with Sjögren's syndrome. Muscle Nerve 2009. [Epub ahead of print] PMID: 19367638.

46. Javed A, Balabanov R, Arnason BGW, et al. Minor salivary gland inflammation in Devic's disease and longitudinally extensive myelitis. Multiple Sclerosis 2008;14:809-14.

47. Collison K, Rees J. Asymmetric cerebellar ataxia and limbic encephalitis as a presenting feature of primary Sjögren's syndrome. J Neurol 2007;254:1609-11.

48. http://www.encephalitis.info/Info/TheIllness/TypesEncephalitis/Limbic.aspx (accessed 13 April 2010).

49. Anderson NE, Barber PA. Limbic encephalitis - a review. J Clin Neuroscience 2008;15:961-71.

50. Malter MP, Helmstaedter C, PhD1, Urbach H, et al. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol (accepted for publication).

51. Giometto B, Grisold W, Vitaliani R, et al. Paraneoplastic neurologic syndrome in the PNS Euronetwork database. Arch Neurol 2010;67:330-5.