

THE PERIPHERAL NERVOUS SYSTEM IN SJOGREN'S SYNDROME

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The nervous system is the “essence of human beings or being human.” Basically, the nervous system can be divided into the central (CNS) and peripheral (PNS) nervous systems. The CNS is composed of the brain and spinal cord. Although some patients with Sjogren’s syndrome can develop CNS or PNS disease (or both), this article will focus on defining and describing PNS disease in Sjogren’s syndrome.

Description of the Peripheral and Autonomic Systems

The PNS can be viewed as the “executor” of impulses or signals generated by the brain and spinal cord. The spinal cord connects the brain to the peripheral nerves. Anatomically, the PNS is composed of the cranial nerves, spinal nerves with their roots, rami and ganglia (relay stations that send impulses to and from the CNS), the peripheral nerves, and the peripheral components of the autonomic nervous system.

There are three basic major types of peripheral nerves: sensory, motor and autonomic. These nerves stimulate sensory organs, the musculoskeletal system and internal organs. Sensory nerves serve as “sensors” of the environment, picking up signals or input from such organs as the eyes, ears, organs of taste and smell, mucous membranes covering or lining many tissues, and skin. These sensory messages are relayed to the brain for interpretation, integration, planning, and execution of subsequent actions.

The motor system responds to these sensory stimuli and initiates voluntary/involuntary activity. Motor actions are mediated by motor nerves. Motor actions include such activities as blinking, swallowing, speaking, writing, standing, walking, running, etc.

The autonomic system is another very important “noncentral” part of the nervous system and can be classified into the sympathetic, parasympathetic and gastrointestinal systems. The autonomic nervous system is the key to regulation of internal organ function. It controls vital functions of the lungs, cardiovascular system, gastrointestinal organs, and bladder and sexual function. Malfunction of any one or more parts of this system potentially can result in significant clinical symptoms of dysfunction.

The types of abnormalities that can affect the peripheral or autonomic nervous systems in Sjogren’s syndrome patients are described below.

Clinical Spectrum of PNS Disease in Sjogren’s Syndrome

The sensory, motor and autonomic components of the peripheral nervous system alone or in combination may be affected in Sjogren’s. In many respects, the spectrum of PNS disease in Sjogren’s syndrome resembles the many types of neuropathy seen in diabetes.

Sensory Neuropathy

Among the most common PNS manifestations of primary Sjogren’s syndrome is a disease of the nerves (neuropathy) involving sensory nerves supplying the feet and hands. The neuropathy usually involves the lower extremities more than the upper extremities.

The symptoms are numbness, tingling, pins and needles sensations, burning, painful or uncomfortable sensations in a distribution corresponding to a stocking or glove. Usually symptoms are relatively mild and non-disabling.

Severe pain, however, may result from a neuropathy affecting the legs and feet and less prominently, the hands and arms. This type of neuropathy may make patients very uncomfortable. A less common condition, mixed polyneuropathy (i.e. both sensory and motor neuropathy), is also characterized by painful or uncomfortable sensations.

Pure Sensory Neuropathy (Neuronopathy)

Recently, a pure sensory neuropathy (i.e. neuronopathy) has been recognized as a PNS complication of Sjogren's syndrome. This type of neuropathy is characterized by loss of sensory fibers that recognize position and vibratory impulses that are essential for maintaining awareness of limb position, posture, balance and walking with a normal gait. There are also uncomfortable sensations characterized as pulling or crawling that affect the extremities, as well as, the trunk. The patient may make snake-like involuntary movements of the upper extremities.

There may be damage or destruction to joints because of the inability to perceive or detect sensation. Sensory neuronopathy involving the extremities may be accompanied by painful sensations of the trigeminal nerve that provides sensation to the face. Trigeminal neuropathy, occurring alone, is one of the most common and well recognized forms of peripheral neuropathy in Sjogren's.

Autonomic Neuropathy

There is growing recognition of autonomic neuropathy as a peripheral nervous system complication of Sjogren's syndrome. Autonomic neuropathy can occur alone or in association with a sensory neuropathy and is characterized by a mixture of sympathetic and parasympathetic dysfunction.

The most common problems include pupil and lid abnormalities, circulatory reflex abnormalities, motility (spontaneous movement) disorders of bowel and bladder, genital organ dysfunction and autonomic insufficiency. Esophageal and gastric dysmotility (impaired spontaneous movement) are observed commonly in Sjogren's syndrome; and also may be secondary to autonomic dysfunction.

Autonomic insufficiency could contribute to decreased tearing, salivation and sweating abnormalities—the clinical features of the sicca (dryness) syndrome. What relative role autonomic neuropathy plays in the development of the sicca complex in Sjogren's syndrome or modulation of an existing destructive inflammatory response in exocrine glands is unknown.

Motor Neuropathy

Motor involvement of the PNS in Sjogren's syndrome is less common than sensory involvement. The most common types of motor neuropathy are mononeuropathy or mononeuritis multiples, and an ascending polyneuropathy.

Cranial Nerves

There are twelve cranial nerves defined as sensory or motor (or both) nerves that stimulate structures within the cranium (above the neck). These nerves carry out important functions such as vision, taste and smell, coordination of movement of eye muscles, hearing and speech, chewing, swallowing, etc. Sjogren's syndrome patients may develop abnormalities of one or more of these cranial nerves.

Entrapment Neuropathy

Another common type of peripheral nervous system involvement in Sjogren's syndrome includes the "entrapment syndromes"—carpal, ulnar and tarsal syndromes. In these syndromes, the neurologic symptoms correspond to the abnormalities caused by compression of the nerves in the arm, wrist and ankle. Entrapment of the network of nerves stimulating the upper extremities and lower extremities has also been observed in Sjogren's syndrome.

Diagnosis

The main approach to the objective confirmation of suspected clinical PNS disease in Sjogren's syndrome is electro-physiologic. Electrophysiologic changes occur only after significant damage has been done to the PNS. Electrophysiologic studies include nerve conduction studies, electromyography, and quantitative sensory testing. Spinal cord (MRI) studies may be useful. Finally, nerve biopsies are used in certain cases to establish diagnosis and exclude other causes. Cerebrospinal fluid analysis should be performed in all cases. Central nervous system disease should be sought and evaluated in Sjogren's syndrome patients with PNS disease, because CNS and PNS disease co-exist in some patients.

Therapy

The current treatment of peripheral neuropathies can be divided into two fundamental approaches: symptomatic management and immunosuppressive therapy. Symptomatic treatment including salicylates (aspirin), acetaminophen, nonsteroidal anti-inflammatories, anti-depressants, and anti-epileptics. Supervised exercise, physical therapy, and rehabilitation are essential and important adjuncts to therapy.

The main reason(s) the peripheral and autonomic nervous systems may be impaired in Sjogren's syndrome relate to an inflammatory or autoimmune attack on the nerves or ganglia or both. Thus, immunosuppressive therapy may be indicated in progressive cases of peripheral neuropathy resistant to symptomatic measures. Immunosuppressive therapy includes corticosteroids (prednisone), hydroxychloroquine (plaquenil), azathioprine, methotrexate, and cyclophosphamide. Plasmapheresis and intravenous gammaglobulin has been used in some cases.

New Directions for More Effective Therapy

None of the current therapies for the treatment of peripheral neuropathy specifically addresses either the initiation of the vascular inflammatory process or the reversal of existing pathology. In addition, all of the immunosuppressive agents have

significant side effects. Axonal degeneration (destruction of the fibers that go from the neuron cell body to the target organ—muscle, sweat gland, etc.) and, to a lesser extent, demyelination (damage or destruction of the nerve-covering that conducts impulses), occur in peripheral neuropathy. In addition ganglia neurons are attacked by lymphocytes and die.

Recombinant human neurotrophic or growth factors (factors that protect neurons, ganglia cells and nerves from death and damage, as well as, facilitate repair of damaged nerves and muscles) and small molecules that either upregulate the expression of neurotrophic factors or molecules that mimic them, hold tremendous future promise for more effective and targeted therapy in Sjogren's syndrome associated peripheral and central nervous system disease.

Neurotrophic factors that might be beneficial in the treatment of neuropathy in Sjogren's syndrome include insulin-like growth factor (IGF-I), nerve growth factor (NGF), neurotrophin 3 (NT3) and new molecules currently under development. IGF-I has the potential for preventing or reducing the vascular-inflammatory response, protecting ganglia neurons, and enhancing nerve regeneration, collateral sprouting and remyelination of damaged axons. Such agents currently are being used in clinical trials of other neuropathies associated with diabetes and chemotherapy.