Sensory ganglionopathy

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Originally released May 22, 2001; last updated April 21, 2017; expires April 21, 2020

Introduction

This article includes discussion of sensory ganglionopathy, sensory ataxic polyneuropathy, sensory ataxic ganglionopathy, ataxic polyneuropathy, ataxic neuropathy, sensory ataxic neuronitis, sensory neuronopathy, sensory ganglionitis, acute sensory neuropathy, acute sensory neuronopathy syndrome, acute autonomic sensory neuropathy, sensory variant of Guillain-Barré syndrome, and non-length-dependent small fiber ganglionopathy. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Sensory ganglionitis, variably called ganglionopathy, is a disease of sensory neurons in dorsal root ganglia. Major forms of these diseases are associated with neoplasm, Sjögren syndrome, and paraproteinemia or polyclonal gammopathy with or without known autoantibodies. Most cases follow subacute courses, but there are forms that develop chronically and acutely as well. Clinical signs seen include sensory ataxia exhibited by gait unsteadiness, a positive Romberg sign, reduced deep tendon reflexes, poor coordination, and pseudo-athetoid movements in the hands. Axonal degeneration warrants the treatment as early as possible. Early cases of immunologic origin that are immune-mediated may respond to plasmapheresis and immunosuppression. Differential diagnoses include environmental and industrial intoxication and adverse effects of antineoplastic and antibiotic drugs. The term “sensory neuronopathy” or “ganglionitis” refers to disorders of small neurons, larger neurons, and/or neurons of both sizes in the sensory ganglia. This article will focus on the ganglionopathy involving larger neurons.

Key points

- Axonal degeneration in sensory ganglionitis warrants treatment as early as possible.

Historical note and terminology

In parenchymal peripheral nerve diseases, there are 2 major categories: (1) axonal and (2) neuronal neuropathy (Schroeder 1975). The former results from abnormalities in axons and is also called axonopathy; the latter, from abnormalities in neuronal cell bodies, and is also called neuronopathy (Spencer and Schaumburg 1976). As disease progresses, axonal neuropathy induces central chromatolysis of the neuronal cell body and neuronal neuropathy induces central-peripheral distal axonopathy of a dying back type (Spencer and Schaumburg 1976). In the peripheral nervous sensory system, sensory neurons are grouped in the dorsal root ganglia at the spinal level and gasserian (trigeminal) ganglia in the cranium. When inflammatory processes target the sensory ganglia, it is called sensory ganglionitis. Alternative descriptive terms are sensory (sensory ataxic or dorsal root) neuronitis or ganglioneuronitis. When it is uncertain if the disease is derived from inflammation, it is designated more vaguely as ganglionopathy or neuronopathy.

There are 4 major forms of sensory ganglionitis or ganglionopathy: (1) paraneoplastic sensory neuronopathy (Horwich et al 1977); (2) subacute sensory neuronopathy associated with Sjögren syndrome (Malinow et al 1986); (3) chronic ataxic neuropathy associated with paraproteinemia or polyclonal gammopathy with or without known autoantibodies (Dalakas 1986; Sobue et al 1988); and (4) acute sensory neuronopathy syndrome (Sterman et al 1980; Smith et al 1993), which is variably called acute sensory neuropathy (Windebank et al 1990) or acute autonomic sensory neuropathy (Colan et al 1980). Sensory ganglionitis occurs mostly in postinfectious conditions and resembles a sensory variant of Guillain-Barré syndrome (Asbury 1981; Dawson et al 1988).
A focal sensory ganglionitis may occur in viral or bacterial infections such as Herpes zoster (Gilden et al 2003), (possibly) HIV, and *Borrelia burgdorferi*. The inflammatory changes in vessels, Schwann cells, myelin, or the interstitium of the ganglia or nearby structures secondarily induce a sensory ganglionitis.

**Table 1. Classification of Sensory (Autonomic) Neuronopathy or Ganglionopathy by Disease Onset and Etiology**

**Inflammatory or idiopathic (probably autoimmune)**
- **Acute**
  - Autoimmune sensory neuronopathy with or without ganglioside autoantibodies
  - Autoimmune autonomic ganglionopathy
  - Acute vestibular neuronitis or ganglionitis
- **Subacute**
  - Carcinomatous neuronopathy
  - Sensory neuronopathy associated with Sjögren syndrome
  - Idiopathic sensory neuronopathy
- **Chronic**
  - Paraproteinemic sensory neuronopathy
  - CANOMAD (chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and anti-GD1B (disialosyl) antibodies)
  - Idiopathic sensory neuronopathy
  - Autoimmune autonomic ganglionopathy

**Toxic, metabolic, hereditary (gene mutations)**
- **Acute**
  - Toxic sensory neuronopathy
- **Subacute**
  - Sensory neuronopathy associated with vitamin E deficiency
  - Sensory polyneuropathy after vitamin B6 overdose
- **Chronic**
  - Toxic sensory neuronopathy
  - Hereditary sensory neuronopathy associated with various ataxias
  - Sensory neuronopathy associated with vitamin E deficiency

Another classification has been proposed based on the differential diagnosis (Gwathmey 2016).

**Clinical manifestations**

**Presentation and course**

In general, the key symptoms of sensory ganglionopathy are a decrease or loss of kinesthetic and proprioceptive sensation. When large diameter ganglionic neurons are decreased or lost, the clinical signs seen include sensory ataxia exhibited by gait unsteadiness (“stamp and stick” type of walk), positive Romberg sign, reduced or absent deep tendon reflexes, poor coordination, and pseudo-athetoid movements in the hands with fingers assuming hyperextended positions (Smith et al 1993). When small-diameter neurons are affected as a non-length-dependent small fiber ganglionopathy, symmetric or asymmetric sensory symptoms such as paresthesias, numbness, shooting pains, or burning dysesthesias of the feet and hands occur, often in a segmental fashion (hyperalgesic type) (Gorson et al 2008). When ganglionic neurons with short segmental roots or nerves are affected, symptoms proceed from distal to proximal parts of the body and occasionally involve the face and trunk. Although an ataxic picture is most commonly seen, both manifestations of the syndrome can be variably mixed depending on the pathophysiology.

The symptoms of sensory ganglionitis are exclusively sensory by definition. However, in many instances of both carcinoma and paraproteinemia, motor weakness and muscle atrophy may appear during the course of disease. Less frequently, autonomic symptoms such as Adie pupils, loss of sinus arrhythmia, orthostatic hypotension, sudden hypertension, or segmental loss of sweating may appear. Demyelinating changes are not observed either in electrophysiological or pathological studies. Although the disease may remit when associated with Sjögren syndrome, it is almost always progressive; recovery is poor in cases related to paraproteinemia and toxic exposures.

Sensory ganglionopathy associated with carcinoma typically develops in middle-aged or older men and less frequently in women (Graus et al 2001). It has a subacute onset with hyperalgesic features and progresses in a few months. This type constitutes about 10% of paraneoplastic neuropathies, and most cases also have a sensory ataxia as well. It may rarely involve the trunk and face, possibly appearing in the face as the “numb-chin syndrome.” In some cases, nystagmus, diplopia, memory loss, and dementia may accompany the disease as a consequence of paraneoplastic encephalomyelitis. The onset of neuropathy may often precede symptoms and signs of the primary cancer. Small-cell lung cancer is associated with most cases (Horwich et al 1977; McLeod 1993) of paraneoplastic sensory
ganglionopathy.

Sensory ganglionitis associated with Sjögren syndrome (Mori et al 2005) mostly occurs in middle-aged women. It varies in onset from acute to indolent, progresses rapidly, and is usually a mixed type featuring numbness and sensory ataxia. It can be a polyneuropathy and/or mononeuropathy. The trigeminal nerve may be affected, manifesting as perioral numbness (Griffin et al 1990). In severe cases, the entire body may be numb.

Sensory ganglionitis associated with paraproteinemia is usually seen in older males. It has an indolent onset in months, progresses slowly, and is usually ataxic in type. Cases with IgM paraproteinemia can be hyperalgesic. Patients often become wheelchair-bound after several years. There are also similar cases with polyclonal gammopathy. A coarse action tremor of hands may be present (Sobue et al 1988).

Acute sensory ganglionitis or neuronopathy syndrome usually develops with rapidly progressing sensory ataxia and widespread sensory loss either as a postinfectious complication or following certain events such as child delivery. Both women and men aged between 30 to 70 years are typically affected. Symptoms stabilize in most cases but progress in some; however, improvement of symptoms is usually poor (Windebank et al 1990).

Inflammatory neuropathies of the enteric nervous system have been described. These are autonomic and, therefore, motor syndromes. This enteric ganglionitis is infectious, inflammatory (but not infectious), or paraneoplastic in origin and produces acutely or slowly progressive segmental symptoms such as achalasia, gastroparesis, and pseudo-obstruction (De Giorgio et al 2004). There is an autoimmune autonomic ganglionopathy in which IgG antibodies against the ganglionic acetylcholine receptors are found (Vernino et al 2008).

**Prognosis and complications**

Sensory ataxic patients have frequent falls and bone fractures; therefore, head injury can occur. Thus, patients may develop chronic subdural or epidural hemorrhage. Patients may have unnoticed burns, ulcers, and infections of the feet. If patients have autonomic involvement, they may develop syncopal attacks or sudden death.

About 70% of patients with paraneoplastic subacute sensory neuropathy develop a malignant tumor after 0.5 to 46 months, 60% of which are small cell lung cancer. Removal or destruction of tumors prolongs survival in one fourth of patients without an improvement of neurologic symptoms. In 1 study, median survival was 11.8 months, with a 3-year actuarial survival of 20% (Gray et al 2001). Although treatment for cancer improved or stabilized the symptoms in some cases, immunotherapy was effective only for a short time (Oki et al 2007).

In 46% of cases with Sjögren syndrome, neuronopathy improved or stabilized without relation to immunosuppression. Most patients improved by compensation and relearning of functions (Griffin et al 1990).

Patients with chronic idiopathic sensory ataxia usually do not improve, and continue to gradually worsen. In 1 report, 1 developed malignancy (Dalakas 1986). In another study, 66% of patients did not become seriously disabled and remained able to carry out most of their activities. Two died of a subdural hematoma (Windebank 1990).

**Clinical vignette**

A 47-year-old woman noted the insidious onset of numbness and tingling on the radial side of her left arm and right shoulder 7 years previously. Her symptoms gradually worsened to involve all of both arms and below her knees. She had difficulty writing, and her arms moved about uncontrollably, sometimes touching the face of a nearby person without notice. Her slippers often came off, and she had difficulty walking. Strength, vision, and bowel and bladder control remained normal. She did not have fever, arthralgia, skin changes, or dryness of her mouth or eyes.

On examination she walked slightly wide-based and landed her heel first, as if a doll were walking. She could not walk in tandem or on tip-toes. Romberg sign was strongly positive. Cranial nerves were normal without nystagmus. Pupils were reactive to light and accommodation. Deep tendon reflexes were absent in all extremities. Muscle strength was normal in the legs, but 4+/-4+/5 in arms and 3+/-4+ in fingers. The sensory examination revealed that temperature was slightly decreased, pain was hypalgesic, and touch was moderately decreased distally below the elbows and knees. Vibration and position sense were absent below the elbows and knees. Finger to nose test showed a coarse tremor in the hands. Heel-to-shin test was poorly performed.
She had normal blood counts and urinalysis. Serum IgG was 1760 mg/dL, IgM786 mg/dL, IgA478 mg/dL. Tests for cryoglobulin and M-proteins were negative. Anti-DNA antibody, rheumatoid factor, hepatitis B and C antibodies, C3, C4, immune complexes (C1Q), thyroid antibodies, T3 and T4 values, and SS-A and SS-B antibodies were normal. There was a slightly positive antinuclear antibody with a speckled pattern. Schirmer and saliva secretion tests were normal. No antibodies against gangliosides were found. Bone scan and x-rays were normal. Cerebrospinal fluid showed a slight increase in protein. Electrophysiological study showed normal motor nerve conduction velocity with normal amplitudes. Attempts to measure sensory conduction velocities evoked no response in any limb. Sural nerve biopsy showed a complete loss of large myelinated fibers and a severe loss of small myelinated fibers. A few lymphocytic cells were noted around a vein. Demyelination was not present. She was diagnosed with a chronic sensory ataxic neuropathy associated with a polyclonal IgM and IgG gammopathy and possible Sjogren syndrome. She was treated with plasmapheresis and prednisone 60 mg a day, with the dose reduced gradually to 20 mg. Her symptoms stabilized, and presently she walks with a cane. She now takes 15 mg of prednisone every other day. Her serum IgM and IgG remain slightly elevated.

**Biological basis**

**Etiology and pathogenesis**

The etiology of sensory ganglionitis is not known. It is presumed to have an autoimmune origin (O'Leary and Willison 1997) except for cases that are clearly a direct result of an infection. A defect in the peripheral blood-nerve barrier may allow autoantibodies to reach the sensory ganglia. Retrograde axoplasmic transport of a pathogen or components of a pathogen from the periphery may also play a role (Olsson 1968). Genetics might also be involved in the development of ganglionopathy, as thought to be the case with CANVAS (cerebellar ataxia, neuropathy, vestibular areflexia syndrome) in which there appears to be a primary ganglionopathy involving autonomic, vestibular, facial, and trigeminal ganglia and sensory ganglia (Wu et al 2014). Cases with sensory ataxia with neuropathy, dysarthria, and ophthalmoparesis (SANDO), in which patients have multiple mitochondrial DNA deletions, have been reported (Hanisch et al 2015).

**Pathology, immunology, immunopathology.** In autopsies of carcinomatous sensory neuropathy cases, spinal and autonomic ganglia have shown subacute inflammation with diffuse endoneurial T-cell, B-cell, plasma cell, and macrophage infiltration. Large neurons are preferably lost. Adjoining myelinated fibers of dorsal roots and peripheral nerves as well as of the posterior column of spinal cord were decreased in number, with the distal part of the nerve and cervical cord affected more severely (Ogawa et al 1985). The cytoplasm and nuclei of some ganglion neurons displayed evidence of IgG by immunocytochemistry. Cytotoxic CD8+ T cells have been found to touch and indent the cell surface of neurons (Wanschitz et al 1997). In many cases, antineuronal nucleoprotein antibodies of the Hu type are present in high titers in sera and cerebrospinal fluid. It is of interest that Hu antigens are expressed throughout the central nervous system, in sensory and sympathetic ganglia, and in many cancer cells (Ichimura et al 1998).

In sensory ganglionitis associated with Sjögren syndrome, anticellular antibodies (anti-Ro:SS-A, anti-La:SS-B) are present in the sera in 12% to 55% of cases, and antibody to the 120 kD alpha-fodrin molecule, a salivary gland-specific protein, has been reported (Haneji et al 1997). Eighty-eight percent of Sjögren patients have evidence of this antibody (Mori et al 2005). Dorsal root ganglion biopsy shows a lymphocytic (T cell) infiltration without vasculitis, degeneration of ganglion cells, and loss of large-diameter myelinated nerve fibers (Malinow et al 1986; Griffin et al 1990). Two autopsy cases showed cytotoxic CD8+ cells infiltrating in large and/or small dorsal root ganglia, sympathetic ganglia, and peripheral nerve trunks (Kawagashira et al 2012). As detected by MRI, the posterior columns of the spinal cord may also be affected.

Tissues from cases of chronic sensory ataxic neuropathy associated with monoclonal or polyclonal gammopathy have demonstrated loss of large dorsal root ganglion neurons as well as marked axon depletion without demyelination in dorsal roots, peripheral nerve, and the posterior column of the spinal cord (Sobue et al 1988). Lymphocytic and plasmacytic infiltrations have been seen in nerves and some viscera without vasculitis. In one third of patients, an IgM, IgG, or IgA gammopathy has been found in sera (Dalakas 1986). In neuropathy with IgM M-proteins, only 3 of 65 patients had slowly progressive sensory axonal neuropathy with antisulfatide antibody, and 5 of 65 had antisulfoglucuronyl paragloboside antibody (Eurelings et al 2001). Neuropathy with antisulfatide antibody may be due to axonopathy, given that serum IgM from these patients stained axons in peripheral nerve but not dorsal root ganglion cells (Lopate et al 1997).
There are cases diagnosed as a sensory variant of Guillain-Barré syndrome that have proven to be acute sensory autonomic neuropathy. A case diagnosed as Guillain-Barré syndrome and myocarditis, which had all-modalit-sensory loss and autonomic symptoms, revealed severe destruction of sensory and autonomic ganglion neurons and Wallerian degeneration of dorsal root nerves without demyelination in the peripheral nervous system (Hodson et al 1984); another case had similar findings along with some lymphocytic infiltration in dorsal roots (Fagius et al 1983). Another autopsied case of an acute sensory neuropathy patient who died 5 weeks after its onset revealed widespread inflammation of sensory and autonomic ganglia with CD8+ T cell-mediated cytotoxic attack against ganglion neurons (Hainfellner et al 1996).

Some patients with sensory or ataxic polyneuropathy have antibodies against various gangliosides, including GD1b. GD1b is at least 1 of the antigens targeted in ganglionic neurons. Immunohistochemical studies have shown that anti-GD1b antibody binds to human dorsal root ganglion neurons and perinodal myelin of the peripheral nerve (Kusunoki et al 1997). Two acute sensory ataxic neuropathy cases are reported to have had monospecific anti-GD1b IgG (Pan et al 2001). There also are cases of CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, M-protein, cold agglutination, and antidisialosyl antibodies) in which serum antibodies, and associated M-protein (IgM-lambda) against b-series gangliosides such as GQ1b, GT1a, GD1b, and GD3 are present (Willison et al 2001). Purified IgM-lambda containing antibodies to GD1b, GD3, GT1b, GQ1b, GM3, and GD1a from chronic ataxic neuropathy patients has been reported to immunostain human dorsal root ganglion neurons, but not perinodal myelin (Oka et al 1996; Jacobs et al 1997). An autopsy case of sensory ataxia-dominant polyradiculoneuropathy with anti-GD1b and other antibodies had evidence of dorsal root ganglion damage and demyelination of nerve roots (Obi et al 1999). An autopsy case of CANOMAD, which is characterized by anti-GD1b (disialosyl) antibodies, showed severe dorsal column atrophy and dorsal root ganglionopathy with B-lymphocyte infiltration into dorsal roots (Mckelvie et al 2013). It is not known whether ganglioside antibodies such as anti-GD1b induce axon neuronal membrane modifications, leading to immune-mediated membrane destruction and possibly secondary demyelination. A novel anti-M phase phosphoprotein-1 autoantibody was found in a patient with a longstanding ataxic demyelinating polyneuropathy with degeneration of sensory ganglia (Zochodne et al 2003). A retrospective study of gluten sensitivity and neuropathy showed that a third of gluten-sensitive patients had sensory ganglionopathy (Hadjivassiliou et al 2010).

**Epidemiology**

In anti-Hu associated paraneoplastic encephalomyelitis, 111 of 167 patients (85%) had lung cancer of which 77% had small cell lung cancer, and 108 of 200 (54%) had large fiber sensory neuropathy (Graus et al 2001). The incidence of primary Sjögren syndrome is approximately 0.5% to 1.0%. Peripheral neuropathies as an extraglandular manifestation are estimated as 2% (Moutsopoulos 2005). Monoclonal gammopathy of undetermined significance occurs in 1% of the population over 50 years and in 10% over 75 years. Polyneuropathy occurs in 1.4% of myelomas (Longo 2001). Forty-two cases with acute sensory neuropathy (ganglionopathy) were recognized during a period of more than 20 years at the Mayo clinic after the original report of such cases (Windebank et al 1990). Nine out of 445 patients with Guillain-Barré syndrome had monospecific anti-GD1b antibodies, all of which showed sensory disturbance with demyelinating features (Miyazaki et al 2001).

**Prevention**

Early diagnosis and treatment of associated conditions may possibly stabilize the disease.

**Differential diagnosis**

Sensory ganglionitis or gangliopathy is a consideration when a patient has pure sensory distal polyneuropathy with clinical findings involving predominantly large fibers and electrophysiologic evidence of axonal degeneration without demyelination. The diagnosis of sensory ganglionitis is considered when a known autoimmune condition exists. Autoimmune diseases like Sjögren syndrome and rheumatoid arthritis may be associated. Malignant tumors such as small cell lung cancer should be sought. Monoclonal gammopathy, cryoglobulinemia, multiple myeloma, plasmacytoma, and osteosclerotic-lytic bone lesions should be sought by appropriate diagnostic testing.

Differential diagnoses include chronic or acute environmental and industrial intoxication and adverse effects of antineoplastic and antibiotic drugs. Pyridoxine abuse, doxorubicin, cisplatin (Krarup-Hansen et al 2007), thalidomide (Giannini 2003), and methyl mercury (Minamata disease) can cause sensory neuropathies of a neuronal type; isoniazid, vincristine, and arsenic may also cause neuropathy. These diseases usually begin with symmetric distal
sensory symptoms such as pain, paresthesia, and numbness. Sensory ataxia also becomes apparent in many cases. Careful environmental, blood, urine, hair, and nail examinations for toxic chemicals as well as a medication history are required (Le Quesne 1993).

Meningeal and interstitial involvement around dorsal roots with syphilis (tabes dorsalis), sarcoidosis (Reda et al 2011), and herniated discs can induce pain and sensory ataxic symptoms by compressing roots and posterior column of the spinal cord. MRI studies may show enhancement of dorsal root ganglia and roots on T1-weighted sequences with gadolinium as well as increased signals on T2-weighted sequences in the posterior columns (Birnbaum et al 2014). Infection of the peripheral nervous system by *Borrelia burgdorferi* (Lyme disease), HIV, and leprosy may induce sensory symptoms. Cerebrospinal fluid analysis may demonstrate antibodies against infectious agents or, by polymerase chain reaction, evidence of the genome of the pathogen.

Vitamin E deficiency in malabsorption, copper deficiency, gluten sensitivity, and abetalipoproteinemia can lead to sensory ganglionopathy (Zara et al 2009). Neuropathies associated with metabolic diseases such as diabetes mellitus, hypothyroidism, and uremia produce mainly axonal atrophy of sensory nerves and perinodal demyelination with modest conduction slowing. Direct involvement of dorsal roots with vasculitides, angiomas, or infiltrating tumor cells may initially mimic sensory ganglionitis. Hereditary ataxias such as ataxia telangiectasia, Friedreich ataxia, and Machado-Joseph disease can affect dorsal root ganglion neurons and induce sensory neuronopathy during their course. Hereditary sensory neuropathy, hereditary amyloid polyneuropathy, Charcot-Marie-Tooth diseases, and adrenomyeloneuropathy are also to be considered. Genetic analysis may be necessary. Human DNA polymerase gamma (POLG)-related mutations can cause sensory ataxia with neuropathy, dysarthria, and ophthalmoparesis (SANDO) (Hanisch et al 2015). A gene encoding a heme-transporter protein, *FLVCR1*, can also cause a sensory ataxia called posterior column ataxia with retinitis pigmentosa (Ishiura et al 2011).

Guillain-Barré syndrome with dominant sensory involvement and acute sensory autonomic neuropathy is to be differentiated from acute neuronopathy. In cases of acute motor sensory axonal neuropathy, the major abnormality is in axons (either the most distal axon twigs or proximal roots). Recovery is usually similar to that of Guillain-Barré syndrome in most cases. Chronic inflammatory demyelinating polyneuropathy is also a consideration, especially in cases associated with monoclonal gammapathy of undetermined significance. Chronic immune sensory polyradiculopathy is a condition with chronic progressive sensory ataxia of the limbs. There is usually normal sensory nerve conduction and normal action potentials in the distal axons, but the sensory-evoked potentials and nerve root biopsy reveal abnormalities around the nerve roots (Sinnreich et al 2004), mimicking ganglionopathy.

**Diagnostic workup**

Electrophysiological sensory nerve studies can rule out demyelination, by finding no evidence of conduction slowing or conduction block. Axonal degeneration can be diagnosed electrophysiologically by a decrease or loss of sensory action potentials with normal nerve conduction. A widespread non-length-dependent pattern of peripheral axon degeneration is considered the hallmark of ganglionopathies, whereas axonal neuropathy shows more of a distal decrease in a length-dependent pattern in sensory nerve action potentials (Lauria 2003). The H-reflex is lost. Somatosensory evoked potentials in the median nerve may show prolonged N13 latencies or N9-N13 interpeak latencies. It is helpful to study an early phase of neuronopathy, in which sensory conduction and action potentials may still be elicited.

CSF shows a normal to moderate increase in protein and normal or mild increase in cell count, mostly lymphocytes. A large increase in CSF protein and cell count suggests a CSF circulation block or inflammatory process in the meninges such as sarcoidosis or tumor cell infiltration. Albumin-cellular dissociation does not differentiate acute sensory neuronopathy from sensory Guillain-Barré syndrome.

In sera and (sometimes) CSF, there may be IgM or IgG, IgA paraproteins, cryoglobulins, or increased polyclonal gammaglobulin. Bone x-rays of limbs, vertebrae, and skull can be checked for the possibility of a plasmacytoma and multiple myeloma; in addition, a bone marrow study may also be necessary. Autoantibodies against GD1b, sulfatide, sulfoglucuronyl paragloboside, and myelin-associated glycoprotein, if present, suggest an autoimmune mechanism of the disease. The presence of myelin-associated glycoprotein and sulfoglucuronyl paragloboside favors chronic demyelinating polyneuropathy. Antibodies such as SS-A, -B, anti-M3 muscarinic acetylcholine receptor (Tsuboi et al 2010), rheumatoid factors, antinuclear antigen, and the positive Schirmer test, and decrease in saliva indicate a diagnosis of Sjögren syndrome. Lip biopsy may be necessary for confirmation. Hu antibodies, tumor markers, and especially CT scan of the lung should be performed. An occurrence of cancer may be sought after 1 to 2 years when no
associated cause for subacute sensory ganglionitis has previously been identified.

MRI study often reveals a high-signal intensity in the posterior columns of cervical spine, in the T2 images showing degenerating central axons of ganglion cells (Lauria et al 2000; Birnbaum et al 2014).

Nerve biopsy is indicated in the case of unsuccessful or uncertain electrodiagnosis, of demyelination, or of suspected inflammation. However, biopsy is not recommended or should be undertaken with caution when disturbances of superficial senses (pain, temperature, touch) are severe and the patient’s general condition is poor, because of the danger of a resultant infection and necrosis of skin. For small fiber neuronopathy skin biopsy, laser-evoked potentials and electrochemical skin conductance using a Sudoscan device may be helpful (Lefaucheur et al 2015).

Management

In patients with paraneoplastic subacute sensory neuropathy, early and aggressive immunotherapy with pulsed intravenous glucocorticoids before the appearance of cancer was reported to lead to clinical improvement. In 1 case, 500 mg of methylprednisolone in 200 mL of low sodium isotonic solution was given 1 time daily for 5 days and was followed by glucocorticoids 60 mg a day, for which the dose was reduced gradually to 10 mg over 3 months. Another patient was given intravenous immunoglobulin (0.4 g/kg of body weight per day for 5 days) followed by 60 mg of prednisolone orally for 3 to 4 months (Oh et al 1997; Gray et al 2001). D-penicillamine and IVlg have some benefit in longstanding cases (Asahina et al 1998; Takahashi et al 2003). Early resection and chemotherapy of tumors as well as immunotherapy were also beneficial in improving or stabilizing the disease with or without reduction of Hu antibody titers, although most patients died of cancer (Oh et al 1997). Only 1 of 13 cases with Sjögren syndrome improved after immunosuppression (Griffin et al 1990), and 2 acute cases improved after plasmapheresis (Chen et al 2001). Two consecutive Sjögren patients improved with interferon alpha treatment (Yamada et al 2005). Four of 22 cases improved with prednisone and 3 of 13 with IVlg (Mori et al 2005). Rituximab, a monoclonal antibody against the B-cell surface marker CD20, was effective for sicca syndrome in a controlled study (Meijer et al 2010). No controlled treatment trials exist for sensory ganglionitis. In cases of neuropathy associated with a monoclonal gammopathy involving IgM, IgG, or IgA of undetermined significance, 16 patients (including 1 with evidence of demyelination) were reported to be improved or stabilized after a variety of immunosuppressive therapies with cyclophosphamide, plasmapheresis, and IVlg (Notermans et al 1996). Small fiber neuronopathy may also respond to immunotherapy (Oaklander 2016). Support for this approach comes from the fact that some small fiber neuropathies are caused by diseases with dysimmunity, such as Sjögren syndrome and celiac disease. Rituximab was studied in 54 patients with IgM anti-myelin-associated glycoprotein neuropathy in a placebo-controlled trial (Léger et al 2013). Primary outcome measures provided no evidence to support the use of rituximab, but there were improvements in several secondary outcomes. In other words, sensory ataxic patients with paraproteinemia without evidence of demyelination respond poorly to immunotherapy. However, continuous destruction of neuronal cells can be halted and possibly repaired by a form of immunosuppression. Rehabilitation, including balance exercise, may improve symptoms to some degree in chronic cases (Riva et al 2014). The author recommends performing aggressive plasmapheresis to start in early acute cases of immunological origin.

Special considerations

Pregnancy

Immunosuppressive therapy, in general, can induce early delivery, small size, malformations, and other adverse effects. Indications for treatment should be unusually strong, and the risk carefully considered and explained to the affected mother.

Anesthesia

In cases of concomitant involvements with autonomic and small sensory fibers, hemodynamic and delayed abnormal respiratory, bowel, as well as bladder responses may occur during anesthetic and recovery periods.

References cited


Pan CL, Yuki N, Koga M, Chiang MC, Hsieh ST. Acute sensory ataxic neuropathy associated with monospecific anti-GD1b IgG. Neurology 2001;57(7):1316-8. PMID 11591857


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

**ICD and OMIM codes**

**ICD codes**

**ICD-9:**
- disorders of the peripheral nervous system: 350-359
- Idiopathic progressive polyneuropathy: 356.4
- Polyneuropathy in collagen vascular disease: 357.1
- Polyneuropathy due to other toxic agents: 357.7
- Polyneuropathy, unspecified: 357.9

**ICD-10:**
- polyneuropathy and other PNS disorders: G60-G64
- inflammatory polyneuropathy, unknown: G61.9
- polyneuropathy associated with neoplasm: C00-D48+ C34.9,C70.1
- polyneuropathy associated with systemic collagen vascular disorder: G63.5 M30-M35+
- polyneuropathy associated with endocrine and metabolic diseases: G63.3 E03.9, E14
- polyneuropathy with other infections and parasites: G63.0, A30.8, A52.1, B23.8
- polyneuropathy associated with nutritional deficiencies: G63.4 E67.2, E56.0
- polyneuropathy related to hereditary ataxias: G60.2

**Profile**

**Age range of presentation**

19-44 years
Sex preponderance
female>male, >2:1
female>male, >1:1

Family history
none

Heredity
none

Population groups selectively affected
older men and middle-aged women

Occupation groups selectively affected
none

Differential diagnosis list
chronic environmental and industrial intoxication
acute environmental and industrial intoxication
adverse effects of antineoplastic drugs
adverse effects of antibiotic drugs
meningeal and interstitial involvement around dorsal roots with syphilis (tabes dorsalis), meningeal and interstitial involvement around dorsal roots with sarcoidosis
meningeal and interstitial involvement around dorsal roots with herniated discs
infection of the peripheral nervous system by Borrelia burgdorferi (Lyme disease)
infection of the peripheral nervous system by HIV
infection of the peripheral nervous system by leprosy
vitamin E deficiency
diabetes mellitus
hypothyroidism
uremia
vasculitis
angiomas
infiltrating tumor cells
ataxia telangiectasia
Friedreich ataxia
Machado-Joseph disease
hereditary sensory neuropathy
hereditary amyloid polyneuropathy
Charcot-Marie-Tooth diseases
POLG-related syndrome (SANDO)
adrenomyeloneuropathy
posterior column ataxia with retinitis pigmentosa
Guillain-Barré syndrome
chronic inflammatory demyelinating polyneuropathy
chronic immune sensory polyradiculopathy

Associated disorders
Acute autonomic sensory neuronopathy
Acute sensory neuropathy
Autoimmune disorders
Autonomic ganglionopathy
Cancer
Carcinoma
Chronic ataxic neuropathy
Chronic ataxic sensory neuropathy
Chronic immune sensory polyradiculopathy
Chronic sensory ataxic neuronopathy
Focal sensory neuropathy
Malignant tumors
Multiple myeloma
Paraneoplastic sensory neuropathy
Plasmacytoma
Rheumatoid arthritis
Sjögren syndrome
Subacute sensory neuronopathy
Subacute sensory neuropathy
Uremia

**Other topics to consider**

Guillain-Barre syndrome
Paraneoplastic sensory neuronopathy
Rehabilitation of peripheral nerve diseases
Sensory neuropathies associated with anti-GD1b ganglioside antibodies
Sjögren syndrome: neurologic complications
Small fiber neuropathies

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