INVITED REVIEW

SENSORY NEURONOPATHIES

KELLY GRAHAM GWATHMEY, MD

Department of Neurology, University of Virginia, P.O. Box 800394, Charlottesville, Virginia 22908, USA

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ABSTRACT: The sensory neuronopathies (or ganglionopathies) are a small subcategory of neuropathies characterized by primary degeneration of the dorsal root ganglia and trigeminal ganglion sensory neurons, resulting in a distinctive clinical presentation. Patients typically have subacute onset of asymmetric, non–length-dependent sensory impairment and early ataxia. The etiologies of acquired sensory neuronopathies are rather limited. Early identification is imperative, as they may herald an underlying malignancy or an autoimmune condition such as Sjögren syndrome. This review addresses the various causes of acquired sensory neuronopathies, the recommended diagnostic approach, and treatment options. Finally, I will briefly discuss a select few hereditary and degenerative sensory neuronopathies, which, in contrast to the acquired disorders, are slowly progressive and are usually associated with additional neurological symptoms.

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The sensory neuronopathies (SNs) are a rare, heterogeneous subgroup of neuropathies caused by primary degeneration of the dorsal root ganglion (DRG) and trigeminal ganglion sensory neurons and their central and peripheral sensory projections.[1,2] Identification of an SN (also termed sensory ganglionopathy) is of paramount importance, as there is a relatively short differential diagnosis, including toxic neuronopathies and immune-mediated and paraneoplastic disorders. The characteristic clinical presentation is early-onset ataxia (possibly due to proximal muscle spindle and joint denervation) and multifocal, asymmetric sensory deficits that differentiate SN from the more common length-dependent pattern of most axonal polyneuropathies.[1,3,4]

The first reported cases of SN were described by Denny-Brown in 1948.[5] Two patients with bronchial carcinoma developed sensory polyneuropathies. In addition to hand and foot numbness, 1 patient had facial numbness and loss of tongue proprioception and the other patient developed loss of sensation to the level of the umbilicus along with gastrointestinal symptoms. On autopsy, the DRG neurons were selectively affected with sparing of ventral roots, and in the patient with gastrointestinal symptoms, a dilated colon and stomach related to involvement of the myenteric plexus was found.[6,7] In 1968, Dyck *et al.* described histological damage to the DRG in patients followed for peripheral neuropathy of unknown etiology.[8] Since that time, our understanding of the spectrum of disorders affecting the DRG neurons has expanded to include immune-mediated diseases, paraneoplastic diseases, viral infections, vitamin B_6 intoxication, and neurotoxic drugs (Table 1). DRG involvement also occurs in a variety of hereditary and degenerative diseases, such as: hereditary sensory autonomic neuropathy (HSAN); Charcot–Marie–Tooth disease type 2B (CMT2B); sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO); facial-onset sensory motor neuronopathy (FOSMN); and cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS).[2,9–11] In approximately 50% of patients, an underlying cause is not identified, and SN is considered idiopathic.[12,13] This review focuses on the clinical presentation of SN, various etiologies of SN, diagnostic evaluation, and treatment approach.

ANATOMY

The sensory pseudo-unipolar neuron cell bodies are located in the DRG, and their afferent and efferent projections come off the dorsal roots housed in the intraforaminal space.[2] As the capillaries that supply the DRG are fenestrated, the blood–nerve barrier is loose, making the DRG susceptible to antibodies or toxins. Multipotential glial precursors, known as satellite cells, surround the ganglion cells.[14] There are 2 populations of neurons: the large-light cells, which give rise to the Aβ and Aδ fibers; and the small-dark cells, which make up the majority of the DRG neurons and

Abbreviations: ANA, antinuclear antibody; CANVAS, cerebellar ataxia, neuropathy, vestibular areflexia syndrome; CBC, complete blood count; CD, celiac disease; CMAP, compound muscle action potential; CMP, comprehensive metabolic panel; CMT, Charcot–Marie–Tooth; CNS, central nervous system; CSF, cerebral spinal fluid; CRMP-5, collapsing-response mediator protein-5; CRP, c-reactive protein; CT, computed tomography; DRG, dorsal root ganglion; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; FDG, fluorodeoxyglucose; FOSMN, facial-onset sensory motor neuronopathy; GAA, guanine–adenine–adenine; GCP, glutamate carboxypeptidase; HIV, human immunodeficiency virus; HSAN, hereditary sensory autonomic neuropathy; HTLV-1, human T-lymphotropic virus-1; IVIg, intravenous immunoglobulin; MEDIC, multiple-echo data image combination; MHC, major histocompatibility complex; PC, posterior column; PET, positron emission tomography; POLG, polymerase γ; SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; SCLC, small-cell lung cancer; SLE, systemic lupus erythematosus; SN, sensory neuronopathy (neuronopathies); SNAP, sensory nerve action potential; TDP, TAR DNA-binding protein; TIRM, turbo inversion recovery magnitude; TNF, tumor necrosis factor; VZV, varicella-zoster virus; VVOR, visually enhanced vestibulo-ocular reflex; 2-MPPA, 2-(3-mercaptopropyl) pentanedioic acid

Key words: dorsal root ganglion; paraneoplastic neuropathy; sensory ganglionopathy; sensory neuronopathy; Sjögren syndrome

Correspondence to: K.G. Gwathmey; e-mail: kgg2p@virginia.edu

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Table 1. Differential diagnosis of the acquired sensory neuronopathies

	Onset	Etiology
Paraneoplastic	Subacute–chronic	Small-cell lung cancer, bronchial carcinoma, breast cancer, ovarian cancer, Hodgkin lymphoma, transitional cell bladder cancer, prostate cancer, malignant mixed Müllerian tumor, neuroendocrine tumor, sarcoma
Immune-mediated	Subacute–chronic	Sjögren syndrome, systemic lupus erythematosus, autoimmune hepatitis, celiac disease
Infectious	Subacute	HIV, EBV, VZV, HTLV-1
Toxic	Subacute–chronic	Pyridoxine, cisplatin, carboplatin, oxaliplatin
Idiopathic	Chronic	Unknown

HIV, human immunodeficiency virus; EBV, Epstein–Barr virus; VZV, varicella-zoster virus; HTLV-1, human T-lymphotropic virus-1.

give rise to unmyelinated C fibers.[15] The afferent projections of the larger neurons travel through the posterior columns carrying proprioceptive and tactile sensation from the legs through the gracile tracts and from the arms in the cuneate tracts. The smaller neurons project thermal and nociceptive sensation through the spinothalamic tracts after synapsing in the spinal cord and decussating to the contralateral side.

PATHOPHYSIOLOGY

Our understanding of the pathophysiology of SN largely comes from anti-Hu–associated paraneoplastic SN. As the pathophysiology of chemotherapy-induced and vitamin B_6 intoxication SNs differ considerably, they will be discussed separately under their respective headings. The current hypothesis is that paraneoplastic disorders result from an immune reaction directed against the cancer when the cancer expresses neuronal proteins or cross-reacting antigens.[16] The onconeural antibodies induce cell-mediated damage to the neurons and axons, resulting in paraneoplastic neurological disorders.[17] The way in which anti-Hu antibodies react to intracellular antigens is still being investigated. They appear to be taken up by living neurons, and intracellular binding results in cell death[18] and satellite cell proliferation.[1] Intraneuronal IgG deposits and anti-Hu antibodies have been identified in the DRG on postmortem studies.[19–22] There is an absence of complement deposition, and natural killer cells are rarely detected.[20] SN does not appear to be a primarily humoral process, but is a cytotoxic T-cell–mediated disorder.[1,23] CD8 cytotoxic T-cells travel to the neurons by recognizing major histocompatibility complex (MHC) class I molecules.[19,21,22] Anti-Hu antibodies react with HuD (official name: ELAV-like neuron-specific RNA binding protein 4, ELAVL4), HuC (official name: ELAV-like neuron-specific RNA binding protein 3, ELAVL3), and HuB (official name: ELAV-like neuron-specific RNA binding protein 2, ELAVL2, also known as Hel-N1), proteins that bind mRNA and are expressed only in neurons.[17,23,24] Although HuB, HuC, and HuD are all expressed in the central nervous system (CNS), HuD is most frequently expressed by small-cell lung cancer (SCLC) cells and is therefore thought to be the initiator of the autoimmune response.[23,24] Only tumors associated with anti-Hu antibody production express MHC type I molecules, which indicates that the anti-Hu immune response is T-cell mediated and is triggered by the tumor.[1,25] SCLC patients with anti-Hu syndrome exhibit an accumulation of $CD45RO^+CD4^+$ helper T-cells and $HLA\text{-}DR^+CD4^+$ T-cells in peripheral blood.[26,27]

An autopsy of an 88-year-old woman with Sjögren-associated SN helps provides insight into the underlying pathophysiology of immune-mediated SN.[28] DRG neurons were severely diminished in the cervical, thoracic, and lumbar segments. Nageotte nodules and CD8 T-cell predominant infiltration were visualized. The large neurons were principally affected, and myelinated fiber density was reduced in the dorsal spinal roots. Sympathetic ganglion cells were also diminished across all spinal segments.

CLINICAL FEATURES COMMON TO ALL SENSORY NEURONOPATHIES

The clinical features of SN depend on the type of neuron involved. Large-fiber neurons mediate proprioception, and degeneration results in gait ataxia. Injury to small- and medium-size neurons results in positive sensory symptoms: burning pain; hyperesthesia; and allodynia.[2] Early ataxia likely results from involvement of afferent fibers carrying proprioceptive information from the proximal limbs and trunk and is not unique to SN; demyelinating neuropathies must be included in the differential diagnosis.[2] When loss of proprioception is severe, the patient may demonstrate pseudoathetosis of the fingers and toes.[2,29] Patients may also endorse generalized, multifocal, asymmetric impaired sensation and positive sensory symptoms. The multifocal, asymmetric presentation distinguishes it from most length-dependent polyneuropathies. Nystagmus has

also been reported, likely due to failure of proprioceptive input from the extraocular muscles or vestibular system.[12,13] Strength is usually spared, although this may not be immediately evident on examination, as patients have difficulty generating sustained strength due to inability to maintain constant motor output and muscle contraction.[30] Tendon reflexes are frequently unobtainable. Patients with paraneoplastic, immune-mediated, toxic, and postinfectious SN present subacutely.[2,31–36] Idiopathic SN is commonly indolent and slowly progressive, mimicking a sensory axonal polyneuropathy.[12,37,38]

SPECIFIC SENSORY NEURONOPATHIES

Paraneoplastic Sensory Neuronopathies. Sensory neuronopathies are among the most common paraneoplastic neurological syndromes and are most often associated with anti-Hu antibodies.[39] Although anti-Hu–associated paraneoplastic SN is characterized by subacute sensory ataxia, there are reports of painful sensory symptoms[40] and, in a series of 20 patients, 80% reported pain.[41] Many patients have a concomitant motor neuropathy, cerebellar degeneration, brainstem involvement, limbic encephalitis, or Lambert–Eaton myasthenic syndrome.[7,42–44] Patients may have evidence of autonomic involvement with tonic pupils, orthostatic hypotension, gastroparesis, sicca symptoms, and sexual dysfunction.[6,7,45] The reported frequency of SN in anti-Hu paraneoplastic syndromes has varied. In a series of 27 patients with anti-Hu syndrome, 20 had a clinical neuropathy (74.1%), and 7 had CNS symptoms consistent with encephalomyelitis (25.9%).[41] The majority of the patients had a pure sensory neuropathy clinically, but, on electrodiagnostic testing, most had motor nerve abnormalities. In contrast, other patient series have highlighted the rarity of SN in the setting of anti-Hu paraneoplastic syndrome. In a series of 16 patients with anti-Hu antibody syndrome, only 5 had clinical SN, and only 3 patients had electrodiagnostic findings of SN.[46] Patients with anti-Hu antibodies and also anti-CV2/CRMP-5 antibodies may have a mixed axonal and demyelinating sensorimotor polyneuropathy as well as subacute SN.[47]

In 2004, Graus *et al.* proposed diagnostic criteria for paraneoplastic SN.[48] Classical SN is supported by: (1) subacute onset with a Rankin score of at least 3 before 12 weeks of evolution; (2) onset of numbness and often pain; (3) asymmetry of symptoms at onset; (4) arm involvement; (5) proprioceptive loss in areas affected; and (6) electrodiagnostic studies that demonstrate pronounced sensory fiber involvement and at least 1 absent sensory nerve action potential (SNAP).[49,50] Lesser involvement of motor nerves or other portions of the nervous system does not exclude a classical SN.

Identifying anti-Hu antibodies strongly predicts an underlying cancer; the estimated specificity is 99%, but sensitivity is 82%. The absence of anti-Hu antibodies does not preclude a cancer diagnosis.[51] SCLC is the most commonly associated cancer, but many other malignancies have been reported,[52] including breast cancer, ovarian cancer, Hodgkin lymphoma,[49] transitional cell bladder cancer,[53] prostate cancer,[54,55] neuroendocrine tumors,[56] malignant mixed Müllerian tumor,[57,58] and sarcoma.[59] SN precedes cancer diagnosis by a median interval of 3–8 months.[41,44,60,61]

Routine chest X-rays and computed tomography (CT) imaging fail to reveal an underlying malignancy in over half of cases.[62,63] Whole-body [^{18}F]-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) is necessary if conventional radiographic studies are negative.[64–68] If the screening radiographic studies (including ^{18}FDG-PET if necessary) are negative, repeat screening is recommended at 3 or 6 months and then every 6 months for 4 years.[68] Cerebrospinal fluid (CSF) analysis in patients with paraneoplastic SN reveals elevated protein, pleocytosis, and sometimes oligoclonal bands.[40,69] One large series of 170 anti-Hu patients (74 of whom had peripheral nerve involvement) showed that 93% of patients had abnormal CSF with a mean protein level of 78 mg/dl, and 43 of 73 had oligoclonal bands.[70]

Electrophysiologically, most patients with SN demonstrate reduced or absent SNAPs with normal or slightly reduced sensory conduction velocities and normal motor conduction velocities.[71] Not infrequently, however, in anti-Hu syndromes, motor nerve involvement and conduction abnormalities are seen, even without motor deficit.[41,46] One study suggested that reduced compound muscle action potentials (CMAPs) were more common in patients with pain symptoms than in those with ataxia.[40]

As paraneoplastic neuropathies are exceptionally rare, there is a paucity of randomized, controlled clinical trials to guide treatment.[72] Published reports of various treatments for all acquired SN cases consist of uncontrolled studies and expert opinion (American Academy of Neurology Class IV evidence).[73] The reader should be advised that any treatment recommendations that follow are made based on relatively limited clinical experience. It is unlikely, given the rarity of these disorders, that a large, randomized, controlled clinical trial will ever be feasible. Treatment can be divided into 3 categories: tumor treatment; immunomodulatory treatment; and symptomatic treatment. Immunomodulatory therapy includes corticosteroids,[74,75] intravenous immunoglobulin (IVIg),[76,77] plasma exchange,[78] cyclophosphamide,[77] rituximab,[79] and

sirolimus.[80] Efficacy of these treatments is not clear, although patients with mild disability and early disease demonstrate more improvement. Guidelines recommend that, with anti-Hu or anti–CV2/CRMP-5 antibodies, treatment should begin with high-dose steroids and/or IVIg followed by cyclophosphamide if a cancer is not found.[72] Amitriptyline, duloxetine, venlafaxine, gabapentin, or pregabalin can be used for treatment of associated neuropathic pain.[72,81] If the paraneoplastic syndrome is associated with intracellular antigen antibodies, such as anti-Hu antibodies, then tumor treatment stabilizes and occasionally improves the paraneoplastic disease, as indicated in a series of 200 patients with anti-Hu–related polyneuropathies.[61] The outcome in this large series was poor overall, with a median survival of <1 year and 36-month survival of only 20%. Patients > 60 years of age who had worse Rankin scores at time of diagnosis, had received no therapy, and had >1 area of the nervous system involved had a worse prognosis. Patients with paraneoplastic neurological disorders may have a less aggressive course compared with patients with identical tumors without a paraneoplastic disorder.[82,83]

Immune-Mediated Sensory Neuronopathies. Sjögren syndrome is an immune-mediated disease that is commonly associated with SN. It is characterized by clinical presentation of sicca symptoms (xerophthalmia and xerostomia) and affects 1%–2% of the population.[84,85] Other systems are frequently involved such as lung (bronchiolitis),[86] pancreas,[87] and kidneys (renal tubular acidosis.).[88] In a series of 82 Sjögren patients, over half developed their neurological symptoms before other symptoms, and over half had isolated neurological symptoms.[89] Various CNS presentations include acute myelitis, neuromyelitis, optic, and brainstem disease, and may mimic multiple sclerosis.[90–93] Sjögren syndrome is associated with a number of peripheral nervous system manifestations including: sensory polyneuropathy; sensory neuronopathy; sensorimotor polyneuropathy; small-fiber polyneuropathy; mononeuropathy multiplex; polyradiculopathy; dysautonomia; multiple cranial neuropathies (often trigeminal); and myopathy.[94] The prevalence of peripheral nervous system involvement is likely between 5% and 15%, but it has been reported to vary from 0% to 56%.[95,96] Nearly 40% of all Sjögren syndrome–related neuropathies may be SN (comprising about 5% of all Sjögren syndrome patients.).[1,96,97] SN is subacute and presents over weeks to months with a mean onset age of 65 years.[36] In addition to the features common to all SN, trigeminal involvement and autonomic dysfunction are common.[1,28,31]

Sjögren syndrome is classically associated with anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies, which are present in only 10%–55% of patients with Sjögren-associated SN.[28,98–100] Given that the sensitivity of autoantibody testing in Sjögren patients with neuropathy is low (just over 50%), it is recommended to proceed with further testing, including the Schirmer test, Rose Bengal test, and/or lip or salivary gland biopsy.[96,100] In 29 patients with Sjögren-associated SN, Schirmer testing was found to be abnormal in 93%, Rose Bengal testing in 69%, and salivary gland biopsy in 93%.[28]

MRI has been used in Sjögren-associated SN.[101] Twelve of 14 patients in 1 series demonstrated T2 hyperintensity in the dorsal columns. The 2 patients without change on MRI had sensory involvement restricted to the limbs. The authors deduced that abnormal signal in the posterior columns in Sjögren-associated SN may help predict the severity of the SN.

No randomized, controlled trials of treatments in Sjögren-associated SN exist. A variety of treatments have been reported, including plasma exchange,[102] IVIg,[103] rituximab,[104] corticosteroids, and cyclophosphamide.[105] Azathioprine as an oral agent has also had some success.[84] Some data indicate that patients with sensorimotor polyneuropathy without ataxia respond better to IVIg than Sjögren-associated SN.[28,106] One protocol recommends treating initial presentation of SN with IVIg (0.4 g/kg/day × 5 days for a total of 2 g/kg), followed by monthly infusions if there is minimal or no improvement or if symptoms recur.[95]

Autoimmune hepatitis is an inflammatory liver disease characterized by T-cell–mediated attack upon liver antigens, leading to progressive inflammation and fibrosis.[84] Autoimmune hepatitis is diagnosed based on specific clinical and laboratory criteria and the exclusion of other toxic, viral, and genetic conditions.[107,108] Three patients have been described with autoimmune hepatitis and SN, and all failed to respond to immunosuppressive therapy.[109–111] One patient has also been reported to have a combination of autoimmune hepatitis, sensory-predominant neuropathy, and Sjögren syndrome.[112]

Several patients have been reported to have both systemic lupus erythematosus (SLE) and SN.[113–115] Two of 3 patients developed SN well in advance of their SLE symptoms.[114,115] IVIg resulted in improvement in 1 patient.[113] Despite treatment with methylprednisolone and hydroxychloroquine, neurological symptoms remained static in 1 patient for > 1 year.[114] One patient failed multiple immunosuppressive therapies but responded to etanercept, a tumor necrosis factor-beta (TNF-α) inhibitor.[115]

Celiac disease (CD) is a chronic autoimmune condition characterized by diarrhea, flatulence, weight loss, and iron deficiency anemia.[84] The neurological manifestations of CD involve the central and peripheral nervous system and are found in 10%–28% of patients.[116] Peripheral nervous system involvement includes a symmetric sensorimotor polyneuropathy, small-fiber neuropathy, motor neuropathy, mononeuritis multiplex, and SN.[117,118] The association between CD and SN is controversial. Although many studies have reported a high incidence of CD and polyneuropathy,[119,120] a large meta-analysis identified an alternative explanation for large-fiber polyneuropathy in 95% of patients.[121] In a survey of 409 British patients, CD-related SN accounted for 8% of all CD-related neuropathies.[116] These results must be interpreted cautiously, as enteropathy on biopsy was seen in 7 of 17 patients, and all were biopsied. CD-related antibodies, specifically first-generation gliadin antibodies, in the absence of histologic evidence of CD, have a high association with alternative causes of neurological dysfunction and are known to have a high false positive rate.[122] A full discussion of the sensitivity and specificity of the various CD-related antibodies is beyond the scope of this article, although there is an excellent review of this topic available, which highlights the improved specificity and sensitivity of second-generation antibodies (in particular the IgA anti-tissue transglutaminase autoantibody) compared with the first-generation anti-gliadin antibodies.[123] Most patients in the series presented with mild sensory symptoms and mild ataxia, unlike other classic immune-mediated SN patients.[116] Four patients demonstrated electrodiagnostic evidence of length-dependent sensory fiber involvement and may have been better classified as a sensory polyneuropathy, not SN. Despite a gluten-free diet, SN continued to progress in some patients, whereas it stabilized or improved on the gluten-free diet in others. In refractory patients, immunosuppressive therapy has been used successfully.[116,118,122]

Idiopathic Sensory Neuronopathies. Despite extensive evaluation, an underlying etiology for SN is not found in approximately 50% of patients, and the disease is considered idiopathic.[2,12] These patients have an indolent, slowly progressive course, in contrast to the subacute presentation encountered in many of the acquired forms. Idiopathic SN is a diagnosis of exclusion and presumably has an autoimmune pathophysiology.[124] In a recent series of 6 patients with asymmetric, acute, or subacute progressive SN, 5 did not have inflammatory infiltrates on nerve biopsy. Despite this, the authors concluded that, given the asymmetric, multifocal, and progressive nature of the disorder, it likely represents an autoimmune process, as the 1 patient with a DRG biopsy demonstrated inflammation. The patients in this series were treated with various immunotherapies including corticosteroids, IVIg, and cyclosporine with generally poor response, although all were treated late in their disease course. Another series of 15 patients with chronic idiopathic ataxic neuropathy underwent similar treatment with immunosuppressive medications or plasma exchange without substantial improvement.[12]

Toxic Sensory Neuronopathies. Vitamin B_6 is an essential vitamin that plays a role in amino acid metabolism.[125] There are 3 natural forms of vitamin B_6: pyridoxine, which is the form used most commonly in pharmaceutical preparations and dietary supplements; pyridoxal; and pyridoxamine. The original case reports of pyridoxine-induced neuropathy/neuronopathy first emerged in the 1980s. Schaumburg *et al.* reported 7 patients who had taken high-dose pyridoxine (over 2 g/day) for several months.[126] Many other cases have since been published, and patients have been reported to have taken as little as 200 mg/day of pyridoxine.[127] Patients with sensory neuropathy/neuronopathy due to pyridoxine toxicity have severe sensory ataxia as a result of large-fiber involvement.[1] Weakness is minimal, and there is no evidence of CNS involvement apart from a transient Lhermitte phenomenon. One patient was reported to have had muscle weakness and motor involvement on electrodiagnostic studies after taking extremely high daily doses of pyridoxine (9.6 g/day).[128] The mechanism of vitamin B_6 toxicity is unknown.[129] One hypothesis is that the toxic levels of B_6 may affect other B vitamin levels has been suggested.[130] It is known that there is cytoskeletal derangement, likely caused by increased neurofilament protein synthesis leading to microtubule–neurofilament dissociation in the DRG, which precedes cytoplasmic change and neuronal death.[131,132] Animal models demonstrate that pyridoxine intoxication results in degeneration of both large sensory fibers and large-fiber neurons in the DRG.[133] The neuropathy in animals can be reversed by administration of trophic factors such as neurotrophin-2 and other compounds with nerve growth factor–like properties.[134,135] Recent data from a single study using a rat model suggest that glutamate carboxypeptidase II (GCP II) inhibition with orally bioavailable 2-(3-mercaptopropyl) pentanedioic acid (2-MPPA) results in improvement of neuropathy (motor coordination, heat sensitivity), electrodiagnostic parameters, and morphological features of DRG sensory fibers and

spinal cord.[136] The dose-dependent toxicity occurring after chronic exposure may explain the time lag to symptom onset. In Schaumburg's original series, discontinuation of pyridoxine resulted in improvement in most, but some patients had residual symptoms.[126]

Certain chemotherapeutic agents are particularly toxic to the DRG, including platinum-based drugs (cisplatin, carboplatin, and oxaliplatin).[137–139] The platinum drugs induce DRG sensory neuron apoptosis[140,141] and reduce fast axonal transport.[142] The limiting factor of cisplatin is its cumulative dose-dependent neurotoxicity. After a cumulative dose of 300 mg/m^2, patients may develop tingling, and almost all patients who receive >400–500 mg/m^2 experience peripheral neurotoxicity 3–6 months into treatment.[29] Although neuropathy may start during the treatment, it can also present up to several months after treatment completion ("coasting effect").[138] Large-fiber sensory impairment is pronounced and can progress to severe sensory ataxia. Oxaliplatin also has dose-limiting neurotoxicity, and 30% of patients will develop a fixed sensory deficit.[138] Although carboplatin is less neurotoxic than cisplatin and oxaliplatin, it causes severe SN when given in combination with paclitaxel.[138] Treatment of chemotherapy-associated SN includes discontinuation of the drug and symptom management.

Infectious Sensory Neuronopathies. Human immunodeficiency virus (HIV) has been reported to cause SN,[2,142] although it more frequently causes a length-dependent polyneuropathy. Lymphocytes infiltrate the DRG, and posterior column fibrosis (especially the gracile tract) is evident on MRI.[2,143] SN has also been described in the setting of infections such as human T-lymphotropic virus-1 (HTLV-1). Shimazaki *et al.* described 2 patients with chronic SN who had evidence of anti–HTLV-1 antibodies in serum and CSF without evidence of myelopathy.[34] Importantly, 1 of 2 patients had subclinical Sjögren syndrome. SN has also been reported in Epstein–Barr and varicella-zoster infections.[32,33]

Inherited and Degenerative Neuronopathies. Numerous hereditary and degenerative neurological disorders result from destruction of the DRG, but a comprehensive description is beyond the scope of this review. Friedreich ataxia, disorders due to polymerase-γ (*POLG*) mutations, CANVAS, and FOSMN, are highlighted below, as they have been pathologically demonstrated to have DRG degeneration. In addition to these, however, DRG destruction is a primary feature of the HSANs,[1,144] CMT2B,[145] Fabry disease,[146] Tangier disease,[147] certain spinocerebellar ataxias, and vitamin E deficiency–associated ataxia, among others.[1] It is emphasized, however, that these patients have a distinct presentation and would not be confused with paraneoplastic, immune-mediated, toxic, or idiopathic SN. Contrary to the clinical presentations discussed above, patients with inherited and degenerative dorsal root ganglionopathies will have additional neurological features.

Friedreich ataxia is an autosomal recessive disorder due to a mutation of a homozygous guanine–adenine–adenine (GAA) trinucleotide repeat expansion on chromosome 9q13 that results in a deficiency of frataxin.[148] Deficiency of frataxin, a small mitochondrial protein, results in a progressive disease that affects the central and peripheral nervous systems, heart (cardiomyopathy), skeleton, and endocrine pancreas (diabetes). Long GAA expansions result in more severe disease and death in early life, whereas short expansions lead to a more benign course. Patients with Friedreich ataxia have neuronal atrophy, satellite cell hyperplasia, and absorption of dying nerve cells into residual nodules of the DRG.[148,149] The damage to the DRG results in thin dorsal roots, dorsal column degeneration, atrophy of the nerve cells in the Clarke column and dorsal spinocerebellar fibers, gracile and cuneate nuclei atrophy, and axonal sensory neuropathy. This, in combination with destruction of the corticospinal tracts and dentate nucleus, results in the characteristic neurological presentation of ataxia, dysmetria, titubation, distal extremity weakness and atrophy, Babinski signs in the presence of absent deep tendon reflexes, impaired proprioception and vibratory sensation, length-dependent loss of sensation, and spasticity.[148]

The mitochondrial DNA *POLG* maintains and replicates the mitochondrial genome.[150] Mutations in *PPOLG* result in a wide spectrum of neurological diseases of which SN is a common and often a predominant feature.[151,152] In most patients, the sensory symptoms prevail, although they may have mild motor symptoms.[153,154] SN in SANDO is progressive and disabling.[9,152,155,156] A larger series of 11 patients with autosomal recessive *POLG* mutations were recently studied, with neurophysiological testing and neuropathological assessment in 2.[157] Five of the 11 had clinical evidence of SN at time of presentation, and 6 developed SN between 1 and 14 years later. All patients had evidence of SN, 3 of whom had pure SN, and the remaining patients had motor involvement. Two patients had histopathological studies of the DRG demonstrating neuron loss and a reduction in cell body size. The spinal cords demonstrated loss of myelin in the posterior funiculus, most profound in the gracile tract as opposed to the cuneate tract. The remaining DRG neurons demonstrated

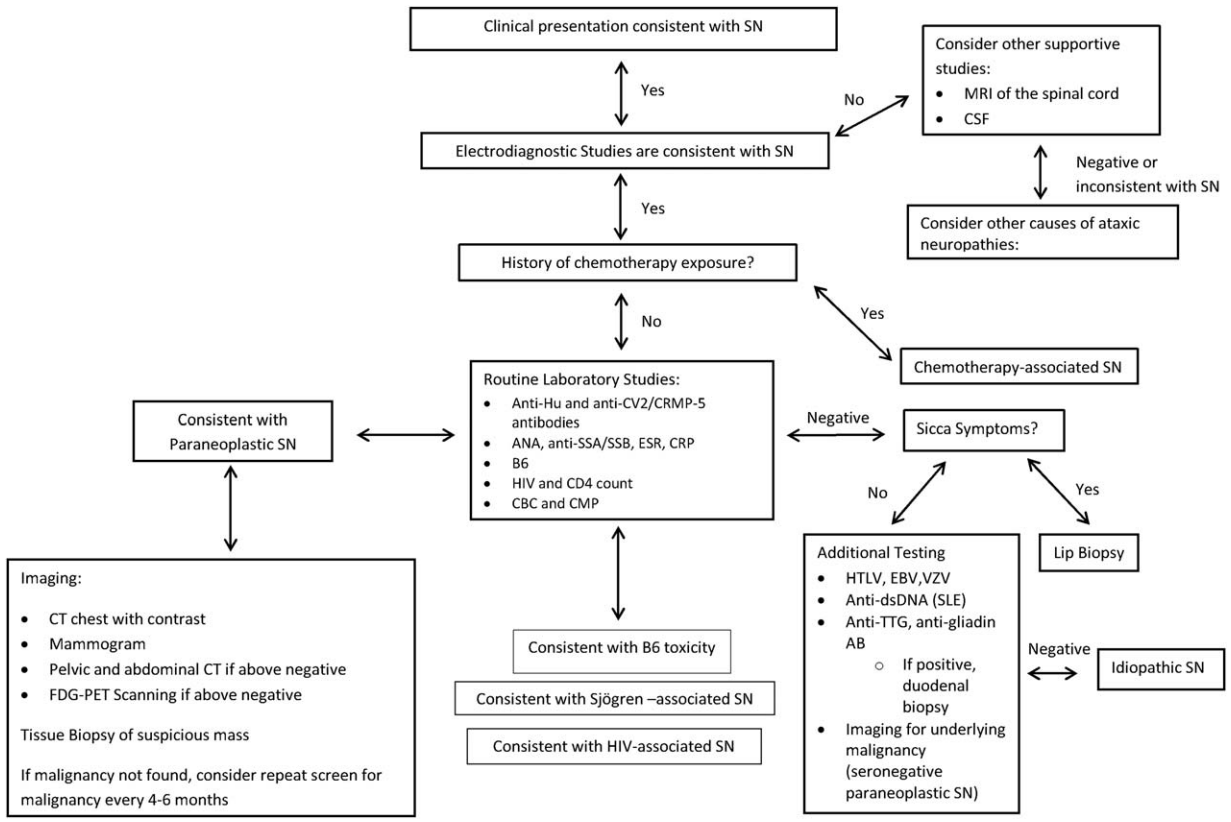

FIGURE 1. Proposed strategy for evaluation of patients with acquired sensory neuronopathies. ANA, antinuclear antibody; anti-dsDNA, anti–double-stranded DNA; CRMP, collapsin-response mediator protein; ESR, erythrocyte sedimentation rate; CBC, complete blood count; CMP, comprehensive metabolic panel; CRP, c-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography EBV, Epstein–Barr virus; FDG, fluorodeoxyglucose; HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus-1; VZV, varicella-zoster virus; PET, positron emission tomography; SLE, systemic lupus erythematosus; SN, sensory neuronopathy; TTG, tissue transglutaminase.

mitochondrial dysfunction in the form of respiratory deficiency of complexes I and IV.

CANVAS is a disease defined by a triad of cerebellar impairment, bilateral vestibular impairment, and somatic sensory deficit.[158] The clinical hallmark of the disease is abnormal visually enhanced vestibulo-ocular reflex (VVOR).[158] Patients have ataxia (which could be attributed to dysfunction of the sensory, vestibular, and cerebellar systems), ataxic dysarthria, central oculomotor abnormalities, impaired vestibulo–ocular reflex, dysesthesias, and allodynia. The sensory deficits have recently been demonstrated histopathologically to be due to dorsal root ganglionopathy.[159] The etiology of this condition is unknown, but 6 separate kindreds have been described, which suggests autosomal recessive inheritance.[10,159] In a recent series of 14 patients with CANVAS, including 13 of 14 who had sensory complaints, extensive nerve conduction studies were performed.[10] All 14 patients had absent upper and lower extremity SNAPs bilaterally, and 12 of 14 had a markedly abnormal blink reflex. Autopsy specimens demonstrated pathological change in the cranial nerves with DRG neuronal loss and loss of myelinated axons in the posterior columns.[158,159] The anterior horns and lateral columns were normal.

FOSMN is a rare, neurodegenerative, and possibly autoimmune neurological syndrome, first described in 2006 by Vucic *et al.*[11] The characteristic clinical presentation is slowly progressive lower facial numbness that spreads to the scalp, neck, shoulders, and arms over 2–6 years, followed by bulbar symptoms 4–9 years later with diffuse arm weakness.[11,160] Autopsy has demonstrated neuronal loss of cervical spinal cord anterior horn cells, and DRG, facial, trigeminal, and hypoglossal nuclei.[11] TAR DNA-binding protein-43 (TDP-43) pathology has been described, which suggests changes similar to ALS pathology.[161,162] A case of FOSMN has also been reported with a heterozygous D9A-SOD1 mutation, thus indicating that it could be a primary degenerative disorder in the spectrum of motor neuron disease.[163] Trials of several immunosuppressive agents have been mostly disappointing,[11,164] although a temporary response to plasma exchange and IVIg has been reported.[165,166]

Table 2. Sensory Neuronopathy Score form.[167]

A. In a patient with clinically pure sensory neuropathy a diagnosis of sensory neuronopathy is considered as possible if score is >6.5		
	Yes	Points
a. Ataxia in the lower or upper limbs at onset or full development		+3.1
b. Asymmetrical distribution of sensory loss at onset or full development		+1.7
c. Sensory loss not restricted to the lower limbs at full development		+2.0
d. At least 1 SNAP absent or 3 SNAP < 30% of the lower limit of normal in the upper limbs, not explained by an entrapment neuropathy		+2.8
e. Less than 2 nerves with abnormal motor nerve conduction studies in the lower limbs		+3.1
If > 6.5, a diagnosis of sensory neuronopathy is possible	Total score:	
B. A diagnosis of sensory neuronopathy is probable if the patient's score is > 6.5 and if:		
1. The initial work-up does not show biological perturbations or electroneuromyography findings excluding sensory neuronopathy *and*:		
2. The patient has one of the following disorders: onconeural antibodies or a cancer within 5 years, cisplatin treatment, Sjögren's syndrome		
3. Or MRI shows high signal in the posterior column of the spinal cord		
C. A diagnosis of sensory neuronopathy is definite if dorsal root ganglia degeneration is pathologically demonstrated although dorsal root ganglia biopsy is not recommended		

Reprinted from Camdessanché et al.,[167] *with permission from Oxford University Press and the authors. SNAP, sensory nerve action potential.*

DIAGNOSTIC EVALUATION OF THE PATIENT WITH SUSPECTED ACQUIRED SENSORY NEURONOPATHY

The diagnostic approach in SN requires a combination of laboratory studies, occasionally CSF analysis, electrodiagnostic studies, imaging, and sometimes tissue biopsy (Fig. 1). In 2009, new diagnostic criteria for SN were published to help differentiate between sensory neuropathies and SN (Table 2).[167] I recommend starting with electrodiagnostic testing to further support the clinical suspicion of SN. Although few studies have looked specifically at the electrodiagnostic findings in SN,[41,46,50,168] the hallmark of the disease is a severe, generalized, non–length-dependent sensory neuropathy resulting in SNAPs that are either absent or have severely reduced amplitude. In some patients, upper extremity sensory nerves are affected to a greater extent than lower extremity nerves, which suggests a diagnosis of SN. This is in contrast to axonal neuropathies that almost always affect lower extremity sensory nerves first. In most patients, CMAPs are normal,[35,109] although motor nerve conduction velocity slowing,[37,49] decreased CMAP amplitude,[101] or both may be encountered.[12,31,32,36] Needle electromyography may show abnormal spontaneous activity and mild chronic reinnervation changes in some patients.[31,36,168] As patients may not be able to activate muscles fully due to loss of sensory inputs from denervated spindles and Golgi tendon organs, a full interference pattern may not be achieved.[2,30]

The prevalence of blink reflex abnormalities was reported in a relatively large retrospective series of paraneoplastic, Sjögren-associated, and idiopathic SN patients.[169] Abnormalities were encountered in Sjögren-associated SN (43%, 6 of 14) and idiopathic SN (48%, 14 of 29), but in none of the paraneoplastic SN patients (0 of 17). These findings were consistent with the authors' observation that paraneoplastic SN patients have minimal facial numbness, as opposed to Sjögren-associated and idiopathic SN patients. Therefore, blink reflex testing could be used to help

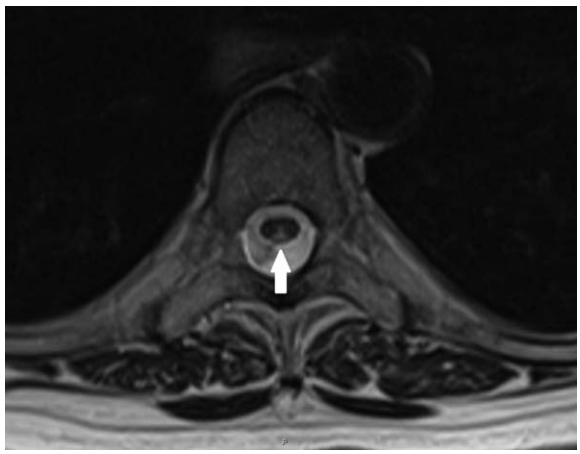

FIGURE 2. Axial T2-weighted turbo spin-echo MRI scan of the thoracic spinal cord. There is diffuse T2 hyperintensity (arrow) in the posterior columns in a 58-year-old woman with small-cell lung cancer and anti-Hu–associated sensory neuronopathy.

differentiate between these entities, although, in practice, laboratory studies and occasionally salivary gland biopsy are utilized more commonly.

In the absence of a history of chemotherapy exposure, a number of initial laboratory studies should be performed to look for the more common causes of SN (Fig. 1). Should these be negative in a patient with sicca symptoms, then a lip or salivary gland biopsy may further support the diagnosis of Sjögren syndrome–associated SN. Absence of sicca symptoms prompts additional laboratory testing for less common causes of SN (Fig. 1).

Approximately 18% of paraneoplastic SN patients are seronegative[51] and, in them, CSF examination may support the diagnosis by demonstrating elevated protein, pleocytosis, and oligoclonal bands, which are less likely in idiopathic or Sjögren syndrome–associated SN.[12,50,61,167,170] CSF can also be studied for paraneoplastic antibodies. This may be important if the patient has received IVIg or plasma exchange or has circulating systemic antibodies [antinuclear antibodies (ANA)] that can confound serum testing results.[171]

Imaging, apart from studies for malignancy in suspected paraneoplastic SN, is occasionally helpful. MRI is the most useful imaging tool in SN, as the large sensory neuron central projections degenerate and produce increased T2-weighted signal in the posterior columns (Fig. 2).[13,172–174] Recently, multiple-echo data image combination (MEDIC) and turbo inversion recovery magnitude (TIRM) imaging techniques were demonstrated to reveal characteristic findings in SN.[174] Nine SN patients were compared with 16 disease controls and 20 healthy volunteers. In all patients, the DRG, posterior column (PC), lateral column, and spinal cord areas at C7 were measured. Using MEDIC, the signal intensities of DRG and PC were higher in the SN patients. Compared with T2-weighted images that demonstrated increased signal intensity in 5 of 9 (56%) patients, MEDIC demonstrated increased PC signal intensity in 8 of 9 (89%). Spinal cord area was smaller in the SN group, and C7 nerve root diameters assessed with TRIM were decreased in the SN patients.

In patients with small-fiber–predominant SN (such as from CD), a skin biopsy may demonstrate a non–length-dependent pattern of diminished nerve fiber density.[117,175] The only definitive way to demonstrate DRG pathology is with a DRG biopsy, but this procedure is invasive and rarely recommended.[176]

CONCLUSIONS

Acquired SNs are a rare group of heterogeneous disorders that distinguish themselves from more typical length-dependent, sensory-predominant axonal polyneuropathies by their subacute presentation characterized by early ataxia and asymmetric, non–length-dependent sensory loss. Identification of SN is of utmost importance, as the differential is relatively short and may prompt expeditious discovery of an underlying malignancy or immune-mediated disease. The list of hereditary and degenerative neurological disorders that affect the DRG is lengthy and diverse. In the future, more extensive understanding of the pathogenic mechanisms in hereditary and degenerative SN may lead to discovery of more effective therapies.

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