Sensory Neuronopathies

It is imperative to promptly recognize and treat sensory neuronopathies because arrest of disease progression and reversal of deficits may be possible.

By Kelly G. Gwathmey, MD

Sensory neuronopathies (ie, dorsal root ganglionopathies or sensory neuron disease) are rare sensory polyneuropathies resulting from damage to the sensory neurons of the dorsal root ganglia (DRG) and trigeminal ganglia. Early onset ataxia and asymmetric nonlength-dependent or generalized sensory deficits are clinical hallmarks. These unique features set these disorders apart from the more common length-dependent axonal sensory polyneuropathies. Prompt recognition of sensory neuronopathies is imperative because treatment may arrest disease progression and even reverse deficits.

Etiologies

Sensory neuronopathies occur in diverse contexts including autoimmune diseases, paraneoplastic syndromes, vitamin B_6 toxicity, neurotoxic drug exposures (eg, chemotherapeutic agents), and viral infections (Table). After the exclusion of these typical causes, almost half of all cases are ultimately classified as idiopathic, which is generally assumed to be autoimmune.[1] Apart from those associated with chemotherapeutic agents, sensory neuronopathies are quite rare and incidence and prevalence rates are unknown. The most common sensory neuronopathies are the paraneoplastic sensory neuronopathy associated with antiHu (antineuronal nuclear antibody [ANNA-1]) antibodies and Sjögren's syndrome-associated sensory neuronopathy. The involvement of the DRG is also seen in numerous hereditary and degenerative diseases; discussion of these is beyond the scope of this article, however.

Paraneoplastic

AntiHu-associated sensory neuronopathy is distinguished by sensory ataxia that is often painful. Concomitant neurologic manifestations (eg, limbic encephalitis, motor neuropathies, cerebellar dysfunction, and brainstem symptoms) are often present. Autonomic dysfunction is also common. Although small cell lung cancer is classically associated with antiHu paraneoplastic syndromes, many other malignancies have been reported including Hodgkin lymphoma, breast cancer, ovarian cancer, prostate cancer, sarcoma, and neuroendocrine tumors. The sensory neuronopathy is often the harbinger of the cancer, preceding the diagnosis of malignancy by up to 8 months. Amphiphysin antibodies are commonly linked to breast cancer and have recently been described in association with a diffuse sensory neuronopathy.[2] AntiCV2/collapsin response mediator protein 5 (CRMP-5) antibodies have also rarely been reported in association with sensory neuronopathies.[3]

Autoimmune

Sjögren's syndrome is an autoimmune disorder defined by the presence of sicca symptoms (ie, xerophthalmia and xerostomia) that can affect the peripheral nervous system in myriad ways. Sensory axonal polyneuropathies, sensorimo-

TABLE. DIFFERENTIAL DIAGNOSIS OF ACQUIRED SENSORY NEURONOPATHIES

Etiology	Onset	Causes
Paraneoplastic	Subacute-chronic	Small cell lung cancer, bronchial carcinoma, ovarian cancer, Hodgkin lymphoma, transitional cell bladder cancer, prostate cancer, mixed Mullerian tumor, neuroendocrine tumor, sarcoma, hepatocellular carcinoma, thymoma, breast cancer
Autoimmune	Subacute-chronic	Sjögren's syndrome, systemic lupus erythematosus, autoimmune hepatitis, antifibroblast growth factor receptor 3 (antiFGFR3)-associated, immune checkpoint inhibitor-associated
Toxic	Subacute-chronic	Pyridoxine, platinum-based chemotherapy
Infectious	Subacute	HIV, human T-lymphotropic virus-1 (HTLV-1), Epstein-Barr virus (EBV), varicella zoster virus (VZV), enterovirus, leprosy, Zika
Idiopathic	Chronic	Presumed to be autoimmune, diagnosis of exclusion

tor polyneuropathies, small fiber polyneuropathies, vasculitic neuropathies, polyradiculopathies, dysautonomic neuropathies, trigeminal neuropathies, and rarely, myopathies have been linked to Sjögren's syndrome. Nearly half of all Sjögren's syndrome-associated neuropathies are sensory. In addition to the expected clinical features of sensory neuronopathies, people with Sjögren's syndrome will often have trigeminal neuropathy and dysautonomia. Other autoimmune diseases, such as systemic lupus erythematosus and autoimmune hepatitis, have been associated with sensory neuronopathy.

Autoantibodies to the intracellular domain of fibroblast growth factor receptor 3 (FGFR3) have been identified in some people with sensory neuronopathy and can often be the only marker of autoimmunity.[4] These antibodies are unknown to be pathogenic or simply a biomarker of autoimmunity. The clinical characteristics of 65 Brazilians and Europeans with FGFR3 sensory neuronopathy have recently been described. Most of these individuals had a nonlength-dependent presentation, with asymmetry occurring in one-third of this cohort. The onset of the neuropathy tended to be either in the lower limbs or all limbs. The sensory neuronopathy was characterized as painful in approximately half the cohort with symptoms of dysautonomia occurring rarely. The neuronopathy tended to become prominent in the lower limbs and less severe in the upper limbs. In approximately half of these individuals, immunotherapy was attempted, but there was no evidence of improvement or even stabilization with treatment. Clinical worsening appeared to be associated with intravenous IgG immunoglobulin (IVIg) and corticosteroid treatments.

Immune-checkpoint inhibitors (ICIs) are efficacious for many solid tumors that trigger humoral and cell-mediated immune responses directed towards self-antigens. These ICIs have also been associated with autoimmune disorders of the central and peripheral nervous systems. Pembrolizumab was associated with antiHu- and antiCV2-mediated sensory neuronopathy in a person with Merkel cell carcinoma.[5] Sensory neuronopathy without specific antibodies similarly developed in a person with melanoma treated with ipilimumab.[6] A case of Sjögren's-associated sensory neuronopathy triggered by pembrolizumab in the setting of melanoma was also reported.[7]

After an extensive but fruitless search for an underlying etiology, nearly half of sensory neuronopathy cases will be considered as idiopathic. Compared with other forms of the disease, there may be an indolent gradually progressive course. These disorders are felt likely to represent an autoimmune process and a trial of immunotherapy is warranted.[1]

Toxic

The 3 natural forms of vitamin B_6 are pyridoxal, pyridoxamine, and pyridoxine, the latter of which is the form typically used in commercially available supplements. Sensory neuronopathy has been reported in people taking toxic doses of pyridoxine for several months. The dose generally needs to exceed 2 g/day, although a single person was reported to develop a sensory neuronopathy with a dose as low as 200 mg/day.[8,9] It is unclear how B_6 toxicity results in damage to the DRG, although it is known that microtubule-neurofilament dissociation in the DRG is ultimately what leads to neuronal death.[10] Discontinuing vitamin B_6 should result in some improvement of symptoms, although in many cases, residual deficits remain.

The platinum-based chemotherapeutic drugs, including cisplatin, oxaliplatin, and carboplatin, induce programmed cell death (ie, apoptosis) of DRG sensory neurons and diminish fast axonal transport. These drugs have dose-dependent neurotoxicity. Individuals may develop chronic painful nonlength-dependent sensory neuronopathy or a length-dependent axonal sensory polyneuropathy. These neuropathic symptoms may emerge months after completion of treatment, termed *the coasting effect*.

Infectious

There are rare reports of viruses triggering sensory neuronopathies, including HIV, human T-lymphotropic virus-1 (HTLV-1), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), leprosy, enterovirus, and most recently Zika virus. A length-dependent polyneuropathy is more commonly associated with HIV and myelopathy is more common with HTLV-1.

Pathophysiology

The DRG contain cell bodies of sensory pseudounipolar neurons and have a fenestrated blood supply, resulting in a relatively leakier blood-nerve barrier and making these cells more susceptible to antibodies and toxins. The pathophysiology of sensory neuronopathies varies depending on the underlying etiology, and much remains to be learned about the exact pathomechanisms of these diseases. In paraneoplastic neuronopathies, the expression of neuronal proteins on cancer cells likely triggers the immune reaction. Onconeural antibodies then induce cell-mediated damage to neurons and axons. The antiHu antibodies are thought to be taken up by living neurons with downstream intracellular binding resulting in cell death. Sjögren's-associated and paraneoplastic sensory neuronopathies appear to be CD8 cytotoxic T cell-mediated disorders.

Clinical Presentation

The early ataxia that is a hallmark of sensory neuronopathies likely results from damage to proprioceptive afferent fibers from the proximal limbs and trunk. In severe cases, pseudoathetosis of the fingers and toes may be present. Individuals also report generalized or multifocal asymmetric

sensory deficits and positive sensory symptoms (eg, burning, paresthesia, and electrical pain), suggesting involvement of small nerve fibers. In pure sensory neuronopathies, strength is spared, although individuals may have difficulty sustaining a constant muscle contraction. Deep tendon reflexes are often unobtainable. The Sensory Ataxia Rating Scale (SEARS), which uses examination findings, was recently developed to capture the severity of sensory neuronopathies.[11]

Diagnostic Studies

The diagnosis of sensory neuronopathy (Figure) relies on laboratory serum studies, electrodiagnostic studies,

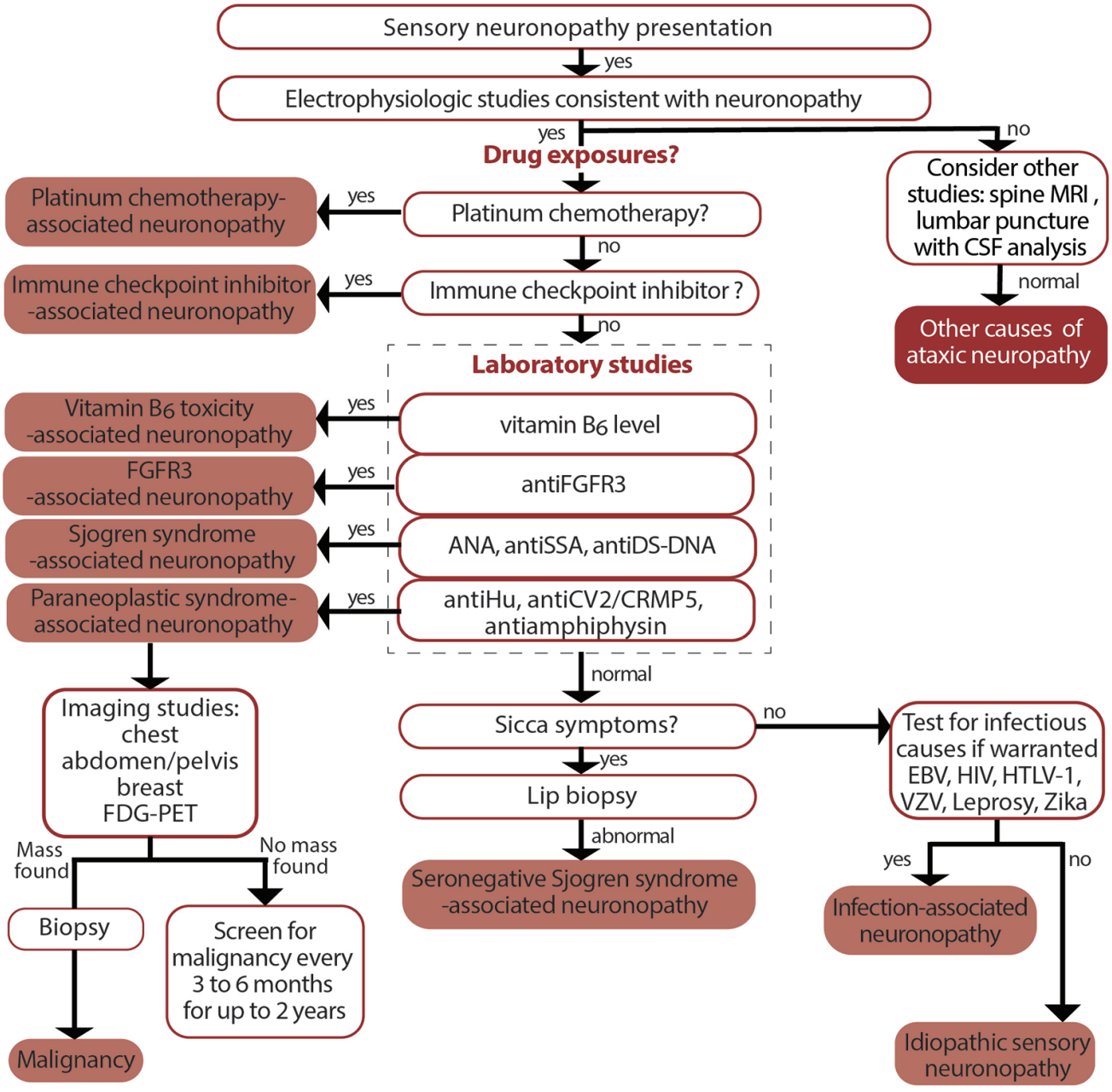

Figure. Diagnostic algorithm for sensory neuronopathies. Abbreviations: ANA, antinuclear antibody; antiSSA, antiSjögren's syndrome-related antigen A; antiSSB, antiSjögren's syndrome-related antigen B; antiDS-DNA, antidouble-stranded DNA; CRMP-5, collapsin receptor mediator 5; CSF, cerebrospinal fluid; EBV, Epstein-Barr syndrome; FDG-PET, fluorodeoxyglucose positron emission tomography; FGFR3, fibroblast growth factor receptor 3; HTLV-1, human T-lymphotropic virus 1; VZV, varicella-zoster virus.

and occasionally imaging and cerebrospinal fluid studies. If paraneoplastic sensory neuronopathy is a concern, tissue biopsy of any tumor is also mandatory. Electrodiagnostic studies are required and should demonstrate a severe generalized or nonlength-dependent sensory neuropathy with low amplitude or absent sensory responses. In contrast to axonal polyneuropathies, upper extremity sensory responses may be disproportionately affected compared with the lower extremity responses. In pure sensory neuronopathies, the motor nerves are spared, although, in practice, motor nerves are commonly involved in paraneoplastic and other autoimmune forms. Abnormal blink reflexes were previously thought to differentiate Sjögren's syndrome-associated and idiopathic sensory neuronopathies from paraneoplastic ganglionopathies, but more recent studies have discredited this.[12] Serum laboratory studies are obligatory and should be focused on the common underlying etiologies. Cerebrospinal fluid analysis is rarely necessary but has been reported to demonstrate pleocytosis, elevated protein, and oligoclonal bands in individuals with seronegative paraneoplastic sensory neuronopathy. Body imaging is required in suspected paraneoplastic sensory neuronopathy. Additionally, MRI may demonstrate increased T2-weighted signal in the posterior columns caused by degeneration of the large sensory neuronal central projections. In general, DRG biopsy is discouraged because of associated morbidity.

Management

Many sensory neuronopathies are autoimmune and thus, in theory, amenable to treatment with immunotherapy. Unfortunately, given the rarity of these polyneuropathies, there is a lack of high-quality evidence to guide treatment. Therapeutic recommendations are based on uncontrolled studies and expert opinion. AntiHu-associated paraneoplastic sensory neuronopathy should be treated with high-dose corticosteroids and/or IVIg followed by cyclophosphamide if the cancer is not found.[13] Other reported treatments include plasma exchange, rituximab, and sirolimus. Treatment of the underlying malignancy may stabilize or improve the associated paraneoplastic syndrome.[14] Similarly, in Sjögren's syndrome-associated sensory neuronopathy, no randomized-controlled trials exist. Various treatments including IVIg, plasma exchange, corticosteroids, azathioprine, rituximab and cyclophosphamide have been used. A treatment window has been suggested based on a study of serial nerve conduction studies in people with inflammatory sensory neuronopathy.[15]

Treatment should be initiated within 8 months of symptom onset for stabilization and within 2 months, if possible, potentially to reverse the deficits. In the few cases of ICI-associated sensory neuronopathy, corticosteroids have been used with some benefit. Treatment of toxic sensory neuronopathies consists of stopping the offending agent.

Regardless of the underlying etiology, symptomatic management of the associated neuropathic pain may be necessary. Typical medications used include gabapentin, pregabalin, amitriptyline, and duloxetine.

Summary

The sensory neuronopathies are unique heterogenous neuronopathies characterized by an early profound sensory ataxia and multifocal or generalized sensory deficits. The practicing neurologist should be aware of the acquired causes of these neuropathies to allow prompt diagnostic evaluation and initiation of treatment. It is hoped that future identification of associated autoantibodies will further understanding of the underlying pathophysiology and result in the development of more focused and successful therapies. ■

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Kelly G. Gwathmey, MD
Assistant Professor
Department of Neurology
Virginia Commonwealth University
Richmond, VA

Disclosure
KGG has disclosures at www.practicalneurology.com