INTRODUCTION
The different disorders characterized by a primary degeneration of sensory neurons in dorsal root ganglia (DRG) are referred to as polyganglionopathies, ganglionopathies, ganglioneuritis, or simpler sensory neuronopathies (SNNs) (1–3). They represent a rare specific subgroup of peripheral nervous system diseases that should be differentiated from polyneuropathies because they need specific investigations and treatments because of their frequent association with neoplastic or dysimmune disorders and with toxic agents and more rarely with genetic disorders (1,2).

In the late 1940s, Denny-Brown (1901–1981) recognized the 2 most severe forms, those resulting from a remote effect of cancer (the paraneoplastic subtype) (5) and a hereditary subtype (6). During the last 40 years (see Refs (3,7) for historical reviews), it has been demonstrated pathologically that DRG degeneration was associated with an inflammatory T-cell reaction in different disorders driven by a cell-mediated immune response such as in paraneoplastic SNN (8–10), HIV infection (11,12), Sjögren syndrome (SS), unclassified connective diseases, and rare idiopathic cases (13–19). That sensory neuron cell is the target of cisplatin toxicity has also been recognized (20,21). Conversely, with vitamin B₆ toxicity (22,23) or antidisialosyl antibodies (24), the demonstration of DRG involvement relies on animal models only.

Asbury (25) proposed that a non-length–dependent distribution of sensory loss and an almost pure electrophysiological (EDX) sensory involvement are distinctive of SNN, the involvement of DRG sensory neurons causing degeneration of both their central and peripheral sensory projections. Although universally accepted, the Asbury criteria have not been validated until recently (26) (see the Common Pattern of SNN section), and these have been used to understand why this distinct pathological process leads to the concomitant degeneration of short- and long-length axons, which is reflected in the proximodistal clinical presentation. However, as DRG cannot easily be explored, the clinical diagnosis of these disorders may be difficult due to the presence of combined neurological manifestations, such as autonomic neuropathy, motor neuron disorder, limbic dysfunction, or cerebellar signs, and in some conditions, the DRG involvement is not the rule but may be associated with other forms of neuropathy, as exemplified in SS.

This chapter will therefore focus on the clinical presentation and mechanisms involved in acute and chronic SNN and describe the treatment strategies before discussing the differential diagnosis that include the dysimmune, the hereditary, and the infectious ataxic neuropathies.

GENERAL CLINICAL PRESENTATION
Onset and Rate of Evolution
SNN, particularly when paraneoplastic, toxic, or associated with SS, can have a subacute onset within a few days to several weeks. However, the course of SNN may also be indolent, such as in hereditary, idiopathic, or associated with unclassified connective diseases. The extension of the sensory loss may be limited and an absence of progression may be observed over several months or years, or conversely, the predominantly loss of deep sensation may extend over all 4 limbs and may affect the face, tongue, chest, or abdomen, and patients may become bedridden and die from complications of bed rest.

Clinical Manifestations
Patients typically show early loss of kinetic (motion) sense due to denervation of muscle spindles and joints, loss of vibration, denervation of receptors situated in the skin and periosteuem, areflexia, together with various combinations of positive and negative sensory and
painful symptoms that involve, sometimes asymmetri-
ically, both proximal and distal sites of the body, includ-
ing the trunk and the face. The upper limbs may be
preferably involved, and the patient is unable to appreci-
te the slight movements at the interphalangeal joints
by passively moving 1 digit. As the pathological process
becomes more extensive, loss of such recognition for
the hand or entire extremity develops, with abnormal
finger-to-nose test. Some patients develop pseudoathet-
toid (waver) movements in the hands or fingers when
asked to hold hands outstretched while eyes are closed
(figure 20.1). In the foot, the perceptions of motion, po-
position, and vibration may be equally affected, with an
abnormal heel-to-knee-to-toe test and an early Romber-
g sign when the patient is able to stand with his feet to-
gether while his eyes are open but sways or falls when
they are closed. The gait may be unsteady, particularly
when asked to walk tandem by placing one heel directly
in front of the opposite toes. These manifestations have
led to the designation of “ataxic neuropathies,” a mis-
leading term because it could also include demyelinat-
ing neuropathies. In some patients, neuropathic pain and
predominantly small-fiber sensory loss involve prox-
imal regions of the limbs, face, and trunk, either sparing
the acral extremities or with simultaneous involvement
of distal and proximal areas in a non-length-dependent
pattern. This pattern suggests that the pathology may
be localized to small-fiber neurons in the DRG and is
similar to what had been described clinically and patho-
logically in patients with Fabry disease (27).

Common Pattern of SNN

A recent study has proposed diagnostic criteria for SNN
(26). Logistic regression was used to test sets of clinical,
EDX, cerebrospinal fluid (CSF) parameters, and para-
aneoplastic antibody results to retrospectively discriminate
patients with SNN and distal sensory neuropathies. The
optimum set of criteria for SNN was tested prospectively
in 37 patients with sensory neuropathies and accurately
identified 81.6% of them as SNN. This study proposes to
use a validated score to recognize SNN independently of
the underlying cause (Table 20.1).

GENERAL INVESTIGATIONS

Electrophysiological Testings

The most common abnormality of nerve conduction in
SNN is absent or low-amplitude sensory action poten-
tials (SAPs) with normal or relatively preserved conduc-
tion velocities in the clinically involved extremity. Most
published series report a widespread decrease in SAPs
amplitudes, which involved both upper and lower limb
nerves, even in patients with asymmetrical or patchy
clinical presentation (28–30), arguing for a need of sys-
tematic and bilateral recording of the median, ulnar,
radial, superficial peroneal, and sural sensory nerves.
In the recently published SNN score (26) (Table 20.1),
least 1 SAP should be absent or 3 SAPs should have an
amplitude <30% of the lower limit of normal in the upper
limbs, and fewer than 2 nerves may have abnormal motor
nerve conduction studies in the lower limbs motor (ab-
normalities significantly more frequent in patients with
paraneoplastic SNN). Nerve conduction studies should
not reveal the cardinal features of demyelination as ob-
erved in neuropathies associated with gammopathy (46)
or in chronic inflammatory demyelinating polyneuropa-
thy (47) (Table 20.2). Somatosensory-evoked potentials
(26,28) and the trigeminal blink reflex (31) can be useful
to demonstrate abnormal proximal sensory conduction.

Imaging Techniques

Increased T2-weighted magnetic resonance imaging
(MRI) signal changes were detected in the posterior col-
umns of 15 patients with chronic SNN (28) and in 9 of
the 12 examined patients with SS SNN in T2*-weighted
MRI (19). The extent of dorsal-column high-intensity
T2* signal was correlated with the distribution and in-
tensity of sensory involvement and sensory ataxia, indi-
cating the presence of central rami involvement due
to sensory ganglion neuron damage (19,32). In a more
recently published study, the percentage of abnormalities
was lower: in the 22 patients who underwent spinal
cord MRI (4 cisplatin, 2 paraneoplastic, and 16 likely
SNN), an abnormal high signal of the posterior column
was observed in only 1 of them (26).
**CHAPTER 20: SENSORY NEUROPATHIES OR GANGLIONOPATHIES**

**Blood and Biological Parameters**

Erythrocyte sedimentation and other systemic markers are usually normal. Serological markers (rheumatoid factor, antinuclear antibodies) may suggest specific connective tissue disorders.

CSF examination is usually normal or demonstrates a slightly elevated protein value (18,19,29,33). In one study in which CSF was examined in 48 patients (3 cisplatin, 24 paraneoplastic, and 21 likely SNN), it was significantly abnormal in patients with paraneoplastic SNN with a

### TABLE 20.1 Diagnosis of SNN

Diagnosis of SNN is considered as “possible” based on examination and on results of the electrodiagnostic studies, “probable” as related to the biological workup and imaging data, and “definite” if DRG degeneration is pathologically proven, although DRG biopsy is not recommended (26).

A. In a patient with a clinically pure sensory neuropathy, a diagnosis of SNN is considered as possible if score >6.5

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Ataxia in the lower or upper limbs at onset or full development</td>
<td>□</td>
<td>+3.1</td>
</tr>
<tr>
<td>b. Asymmetrical distribution of sensory loss at onset or full development</td>
<td>□</td>
<td>+1.7</td>
</tr>
<tr>
<td>c. Sensory loss not restricted to the lower limbs at full development</td>
<td>□</td>
<td>+2.0</td>
</tr>
<tr>
<td>d. At least 1 SAP absent or 3 SAP &lt;30% of the lower limit of normal in the upper limbs, not explained by entrapment neuropathy</td>
<td>□</td>
<td>+2.8</td>
</tr>
<tr>
<td>e. Fewer than 2 nerves with abnormal motor nerve conduction studies in the lower limbs</td>
<td>□</td>
<td>+3.1</td>
</tr>
</tbody>
</table>

Total

B. A diagnosis of SNN is probable if the patient’s score is >6.5 and if

1. The initial workup does not show biological perturbations or ENMG (electroneuromyography) findings excluding SNN; or
2. The patient has 1 of the following disorders: onconeural antibodies or a cancer within 5 years (34), cisplatin treatment, SS (74); or
3. MRI shows high signal in the posterior column of the spinal cord.

C. A diagnosis of SNN is definite if DRG degeneration is pathologically demonstrated although DRG biopsy is not recommended.

### TABLE 20.2 Differential Diagnosis of Sensory Neuronopathy

<table>
<thead>
<tr>
<th>Neuropathy</th>
<th>Examples</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious ataxic neuropathies</td>
<td>Syphilis, diphtheria, human T-cell lymphotrophic virus, HIV</td>
<td>Appropriate laboratory testing needed</td>
</tr>
<tr>
<td>Tropical ataxic neuropathy</td>
<td>Strachan syndrome, Cuba epidemic neuropathy, Konzo epidemic paralytic disease</td>
<td>Appropriate laboratory testing needed</td>
</tr>
<tr>
<td>Neuropathy associated with gammopathy</td>
<td>Neuropathy associated with osteosclerotic myeloma, with monoclonal gammopathies of undetermined significance and with Waldenström macroglobulinemia, POEMS syndrome</td>
<td>Workup for underlying cancer and appropriate laboratory testing needed, see EFNS/PNS guidelines (118)</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polineuropathy</td>
<td>–</td>
<td>Progressive polyradiculoneuropathy with clinical course for &gt;2 mo, see EFNS/PNS guidelines (119)</td>
</tr>
<tr>
<td>Inherited neuropathy</td>
<td>Friedreich ataxia, ataxia with vitamin E deficiency, abetalipoproteinemia, SANDO with mutation of the POLG gene, combined SNN, and motor neuron disorders</td>
<td>Family history often negative, DNA analysis needed</td>
</tr>
</tbody>
</table>
more frequent raised protein level and oligoclonal pattern (26). Pleocytosis suggests infiltrative or infectious conditions, particularly HIV infection, but is reported in 80% of limbic encephalitis, potentially associated with paraneoplastic SNN (34).

A number of molecules that are principally localized to the neuronal compartment of the peripheral nerve have been identified as relevant to the pathogenesis of autoimmune neuropathy (7). These antigens include the paraneoplastic antigens Hu, CV2, and amphiphysin, which are associated with the development of paraneoplastic SNN and the antidisialosyl gangliosides antibodies.

In the paraneoplastic SNN, the origin of the immune response is presumed to be against the tumor cells in which the neural antigens are inappropriately expressed. When the antigens are expressed on the plasma membrane, the immunopathology is primarily dependent on antibody-mediated processes. However, in those paraneoplastic syndromes involving an intracellular antigen, the mechanism of pathogenesis is not clear, but there is evidence for the involvement of cytotoxic T cells.

In the mid-1980s, investigators described antibodies in the serum and CSF of patients with small-cell lung carcinoma (SCLC) and SNN that were subsequently shown to recognize specific antigens expressed on neural cells and the underlying tumor (35). A number of such nervous system-specific autoantibodies have now been described in a variety of paraneoplastic neurological diseases (36). Among the antibodies directed against neural antigens in serum and CSF, the most characteristic being antibodies directed against neuronal nuclear antigens, anti-Hu or ANNA-1 (both nomenclature remain in current use). Among 979 patients with paraneoplastic neurological syndrome recruited from 20 European centers (36), the onconeural antibody profile confirmed Hu as the most frequent antibody (38.8%), followed by Yo or anti-Purkinje cell antibodies (13.4%). All other antibodies had frequencies below 10.0%. The antibody types were within the spectrum for onconeural antibodies and in association with paraneoplastic neurological syndrome have significant diagnostic value for an underlying cancer, with an association between anti-Hu antibodies, the subacute SNN and SCLC, and between antiamphiphysin and anti-CV2 and paraneoplastic SNN and sensorimotor neuropathy and SCLC, breast, colon, prostate, thymoma, and other cancers for the peripheral neuropathies (7,36).

In 1985, circulating IgM antibodies reacting with NeuAc (α2-8) NeuAc (α2-3) Gal-configured disialosyl gangliosides (including GD1b, GD3, GT1b, and GQ1b) were first described in a patient with chronic sensory neuropathy (37). Since then, neuropathies associated with IgM antibodies against disialosyl residues have been defined as either sensory ataxic neuropathy associated with anti-GD1b IgM antibody (38), or chronic sensory ataxic neuropathy associated with antidisialosyl IgM antibodies, a so-called chronic ataxic neuropathy involving ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies (CANOMAD) (39). The most prominent feature of these neuropathies is sensory ataxia with relatively well-preserved muscle strength and small-fiber sensation. An immunohistochemical study showed localization of GD1b in the neurons of human DRG (40,41). Moreover, experimental sensory neuropathy is induced by sensitization with monospecific GD1b (41). GD1b, therefore, is recognized as a putative target molecule for serum antibodies.

**Biopsies**

Morphological studies have focused on the sural nerve, with only a few reports of DRGs (8–10,13–21). In sural nerve biopsy and autopsy material, the characteristic features are a marked fiber loss, active axonal degeneration, and cellular infiltrates around epineurial blood vessels. There may be fascicle-to-fascicle variation in the degree of fiber loss or axonal degeneration, and necrotizing vasculitis may also be seen. We observed similar findings (Figure 20.2). The characteristic findings in the DRGs are inflammation and neuron loss with formation of residual nodules of Nageotte (clusters of supporting cells). The majority of inflammatory cells are T lymphocytes with scattered macrophages (Figure 20.3). Because of the risks involved, spinal ganglion biopsy is rarely performed and should be restricted to only a select group of patients (13).

**DISORDERS ASSOCIATED WITH SNN**

**Paraneoplastic Subacute SNN**

**Introduction and Epidemiological Data**

Paraneoplastic neuropathies may occur in isolation such as the disorder described in 1948 by Denny-Brown (5), but more commonly, there is a complex syndrome with a concomitant involvement of both the central and the peripheral nervous systems, called paraneoplastic encephalomyelitis (PEM) with subacute SNN or PEM/SNN (1,2,7). There is abundant evidence that the paraneoplastic SNNs represent disordered autoimmunity, the exact pathogenic mechanisms are yet to be elucidated (7).

In a clinicopathological review of 69 patients with paraneoplastic neurological disease, Henson and Urich (42) recognized that SNN and encephalomyelitis frequently developed together, particularly in association with SCLC. With the recognition and detection of anti-Hu antibodies (see the General Investigations section) in the serum of patients with PEM or SNN it was observed that these were different manifestations of the same underlying disease process. These anti-Hu antibodies react with a family of protein antigens of 35 to 40 kDa present in neurons and some tumors, especially SCLC. The binding of an antibody to a particular neural antigen on the exposed cellular structure of a fixed brain...
section does not indicate the mode of pathogenicity of the neurological syndrome; this varies. For example, anti-Hu is directed against nuclear antigens (a family of RNA binding proteins normally expressed in the nervous system); presumably, these ectopically expressed nuclear antigens become externalized during the antitumor immune response. Although high-titer IgG antibodies against Hu and related antigens occur in the circulation and CSF, it has not been possible to demonstrate any cytotoxic effect of this antibody on neurons, although the antibody can be detected in the nuclei of the exposed cells (43); for example, passive transfer of anti-Hu–containing IgG into animals does not induce disease (44). In anti-Hu syndromes the neuropathology is thought to be cell mediated (45) and the antibody is merely an immunological accompaniment.

SNN is a rare paraneoplastic complication. In a prospective study of 150 consecutive patients with SCLC, only 1 patient was found with SNN and 2 patients had the Lambert-Eaton myasthenic syndrome (LEMS) (46). In another study of 203 patients, 5 had peripheral neuropathy with no cause and 5 others manifested antibody-mediated paraneoplastic neurological syndromes (LEMS, limbic encephalitis, cerebellar degeneration) (47). There is less information regarding the incidence of neuropathy in breast and gynecological malignancies (48).

The prevalence of malignancy associated neuropathy in patients with peripheral neuropathy is not accurately known. From 422 consecutive patients with peripheral neuropathy, 26 were analyzed who concomitantly had carcinoma but no tumorous infiltration, drug toxicity, or cachexia (49). Twenty-one (5%) of these patients had either antineuronal antibodies or a short interval between onset of neuropathy and diagnosis of malignancy or a clinical course consistent with a paraneoplastic etiology. The remaining 5 patients had a long interval between onset of neuropathy and malignancy and a chronic progressive course suggesting a coincidental association.

**Clinical Manifestations**

They are well characterized (5,7,50–52). Symptoms include combination of paresthesias, sensory loss, and dysesthesia; pain is often severe. At onset, the distribution is frequently multifocal or asymmetrical and can be confused with mononeuropathy multiplex. The upper limbs are usually affected first. Sensory loss, with a predominantly loss of proprioception, extends over all 4 limbs and may affect the face, chest, or abdomen. This results in lower-limb ataxia and an unsteady gait, and in the upper limbs, some patients develop pseudoathetoid movements in the hands (see the previous General Clinical

**FIGURE 20.2** A, Sural nerve biopsy from a 61-year-old woman with SS and sensory neuronopathy with gait ataxia, demonstrating loss of nerve fibers. B, Age-matched control patient (Thionin blue, original magnification x600). The histogram shows the loss of large and small nerve fibers. C, Same case as in A, with lymphocytic epineural blood vessel wall infiltration without necrosis, showing the presence of vasculitis (hematoxylin and eosin, original magnification x400). With permission from John Wiley & Sons (1).
Loss of taste and hearing may be seen (53). Tendon reflexes are reduced or absent. Strength is usually preserved unless there is some degree of motor axon loss (54).

The most frequent manifestation of PEM/SNN is SNN, occurring in 74% of cases. However, it is predominant in only 50% to 60% of patients and clinically pure in only 24% (34,54). About 50% to 75% of the patients develop more widespread neurological involvement, including limbic encephalitis, encephalomyelitis, medullary syndrome, with or without pontine or bulbar manifestations, dysautonomia, cerebellar degeneration, and LEMS (51,54–56). In one large series of 200 patients with anti-Hu antibodies, neurological dysfunction was confined to 1 area of the nervous system in 30% patients (SNN, 48; cerebellar ataxia, 4; limbic encephalitis, 4; brainstem encephalitis, 2; intestinal pseudo-obstruction, 1; parietal encephalitis, 1) (54). The other patients had evidence of multifocal involvement. A predominant neurological syndrome was identified in 118 of them, whereas in 22 more than 1 syndrome predominated during the clinical evolution.

The onset is usually subacute (a few days to several weeks) and rapidly progressive, although occasional patients have an indolent course with slow progression over months. Usually, paraneoplastic SNN is a severe disease. Many patients become bedridden and die from complications of bed rest or inactivity rather than from cancer progression. However, a subset undergoes an indolent course, with a very limited extension of the sensory loss and absence of progression after several months or years (57). The onset of neuropathy precedes diagnosis of cancer in the majority of cases (77%–88%), with a median interval from onset of symptom to tumor diagnosis 3.5 to 6 months (range, 1–47 months) depending on the series (51,54,55,57). Like other paraneoplastic syndromes, SNN usually presents in middle or older age. Age older than 60 years, neurological disability score at diagnosis, more than 1 area of the nervous system affected, and absence of treatment predict survival and neurological outcome (54).

**Diagnosis**

The classical paraneoplastic SNN should be considered if all the following criteria are present (34): subacute onset with a Rankin score of at least 3 before 12 weeks of evolution, onset of numbness, and often pain, marked asymmetry of symptoms at onset, involvement of the arms, proprioceptive loss in the areas affected, and EDX studies that show marked, but not restricted, involvement of the sensory fibers with absent SAPs in at least 1 of the nerves studied. A recent study has advanced diagnostic criteria for possible, probable, or definite SNN using a composite score (Table 20.1) (26).
Several large series have found that 85% of patients with PEM/SNN and high titers of anti-Hu antibodies have detectable underlying neoplasm, most commonly SCLC. However, a wide variety of cancers, including breast, prostate, ovarian, endometrial, and undefined adenocarcinomas, neuroblastomas, and germ cell tumors, have been reported (54,55,57,58). Tumor diagnosis may be challenging, when the tumor is restricted to the mediastinal lymph nodes (59). When conventional radiological methods are negative, whole-body $[^{18}]$F]fluorodeoxyglucose positron emission tomography (18FDG-PET) is recommended (59,60). This has a high sensitivity but is not specific, as inflammatory tissues can take up the tracer. In 15 patients with a paraneoplastic neurological syndrome and anti-Hu antibodies, radiological methods led to the diagnosis of cancer in 12 patients but not in the other 3, whereas 18FDG-PET showed abnormal uptake in the mediastinum in all 15 patients, in accordance with the expected location of the malignancy (59). Laboratory investigations and electrodiagnostic findings have already been described (see the Blood and Biological Parameters and Electrophysiological Testsings section). Detection of anti-Hu antibodies is of great value in the diagnosis of cancer. The estimated specificity is 99%, but the sensitivity is only 82%, so the absence of anti-Hu antibodies in patients suspected of having SNN does not exclude an underlying cancer (61). This finding highlights the importance of the Graus criterion (34) that paraneoplastic syndrome may be diagnosed in the absence of a malignant neoplasm or onconeural antibodies when the patient profile fulfills the other criteria for classic paraneoplastic syndrome. There is a lack of correlation between the Hu-Ab titers and the tumor evolution probably reflecting that Hu-Ab is a surrogate marker of the evolving immune response (62). Antibodies against the synaptic vesicle protein amphiphysin (described in paraneoplastic stiff-man syndrome and breast cancer) and against CV2 (associated with cerebellar degeneration, uveitis, and peripheral neuropathy with a variety of cancers) have subsequently been demonstrated to be rarely associated with SNN, with and without anti-Hu antibodies (36).

The pathological lesions in SNN have long been known in DRGs and in sural nerve (see the previous Biopsies section) (8–10). In DRGs, they consist of mononuclear cell infiltrates surrounding sensory neurons undergoing degeneration. Ultimately, the lost neurons are replaced by a proliferation of satellite cells, and presence of intraneuronal IgG deposits, anti-Hu antibodies cannot be demonstrated anymore from the lesions. Currently, T cells are thought to be mainly responsible for the disease. Although CD4 helper T cells are found around vessels and between sensory neurons, CD8 cytotoxic T cells are situated mainly around neurons and sometimes penetrate the capsule of satellite cells to come in close contact with sensory neurons. Some of these lymphocytes express the cytotoxicity-associated proteins, perforin, and TIA-1 (Figure 20.3). Although an autoimmune pathogenesis for PEM/SNN is indicated by the presence of specific anti-Hu antibodies in serum and CSF, lymphocytic pleocytosis and oligoclonal bands in CSF, and inflammatory infiltrates in affected areas of the nervous system, the exact pathogenic mechanisms remain uncertain. The central theory of pathogenesis is however based on the presence of specific anti-Hu antibodies that react with an underlying tumor and on the concept of molecular mimicry whereby expression of neuronal antigens by the tumor leads to a breakdown of immune tolerance and subsequent immune-mediated neuronal damage (7).

### Treatment

This is largely disappointing, and antitumor therapy seems to be more effective than immunomodulatory therapy. Large series failed to demonstrate a clear benefit of intravenous immunoglobulin (IVIg), steroids, plasma exchange, or cyclophosphamide, either alone or in combination (55,57,58,63). There are uncontrolled studies that report stabilization of treated patients with IVIg (64,65), combined immunosuppressive treatment (66,67), rituximab treatment (68), but its significance is difficult to assess given the tendency of the SNN to plateau in untreated cases and the occurrence of occasional spontaneous remission (57). A large series of PEM/SNN concluded that a trial with immunotherapy should be considered in PEM patients when antineoplastic treatment is not possible because a tumor is not found or when PEM/SNN appears during or after tumor treatment (54). Based on this and on clinical observations that T-cell autoimmune diseases regress during pregnancy, 15 patients with anti-Hu antibodies were treated in a prospective, uncontrolled, and blinded trial with 10 000 IU daily of human chorionic gonadotropin administered by intramuscular injection during 12 weeks. Seven (47%) patients improved or stabilized (69). The authors conclude that human chorionic gonadotropin may have immunomodulatory activity and may modify the course of Hu-paraneoplastic syndromes. The results of antitumor therapy are more promising. In a large series, treatment of the tumor was a predictor of improvement or stabilization of the neurological disorder (51,54,57,63), suggesting that early diagnosis of the cancer gives the best chance of helping the neurological disorder before it becomes too devastating.

## Dysimmune SNN

### Introduction

The dysimmune SNNs are uncommon but represent the most frequently encountered cause of SNN. They include disorders of the DRG thought to be immune mediated, excluding cases associated with malignancy and toxins affecting primary sensory neurons. In 1968, 2 patients were reported with acute pure sensory neuropathy not associated with malignancy with multifocal radicular sensory loss with selective loss of large-diameter sural
nerve fibers suggested DRG as locus of disease (70). Additional case reports confirmed this distinct clinical entity (33,71,72). In the 1990s, other findings such as the acute or subacute, often focal, onset in the absence of inflammation in distal peripheral nerve suggested an immune mediated or vascular process at the level of DRG (18,29,30). Since then, several authors have reported detailed clinical, electrodiagnostic, biological, and pathological data for cases with acute, subacute, or chronic SNN most often associated with SS (see reviews by Kuntzer et al (1), Sghirlanzoni et al (2), and Smith (3)).

**Clinical Manifestations**

In dysimmune SNNs, there is a large variation in clinical presentation, with a mixture of ataxia and pain syndrome (see the General Clinical Presentation section), with sensory disturbances often unilateral, strikingly asymmetric, at times predominantly in the upper limbs but may also initially involve the trunk, face, or lower limbs. These signs may be associated with autonomic signs, such as Adie pupil, anhidrosis, postural hypotension, areflexia with normal strength. The course ranges from an abrupt to an indolent progression over several years. Although symptoms and signs are asymmetric at onset, they become symmetric as the disease becomes generalized (29,30). The clinical manifestations of neuropathy preceded the development of an isolated sicca complex (keratoconjunctivitis sicca and xerostomia) or laboratory findings consistent with SS in most patients. Thus, in most patients, neuropathy developed first and then the diagnosis of SS may be made years later (18,19,73). This chronological sequence is true for all forms of neuropathy but is more characteristic in the SNN forms. Extraneural symptoms, such as pancreatitis and interstitial pneumonia, also can precede the clinical manifestations of SS. Peripheral neuropathy is the presenting problem in most patients, and SS-associated neuropathy has been shown to manifest as a variety of forms: in a study with 92 patients (19), 36 had SNN, 18 painful sensory neuropathy without sensory ataxia, 11 multiple mononeuropathy, 5 multiple cranial neuropathy, 15 trigeminal neuropathy, 3 autonomic neuropathy, and 4 radiculoneuropathy based on the predominant neuropathic symptoms. Acute or subacute onset was seen more frequently in multiple mononeuropathy and multiple cranial neuropathy, whereas chronic progression was predominant in other forms of neuropathy.

Abnormal pupils and orthostatic hypotension were particularly frequent in sensory ataxic, painful, trigeminal, and autonomic neuropathy. SNN frequently had painful features, autonomic symptoms and trigeminal nerve involvement. Painful sensory neuropathy also had autonomic and trigeminal nerve involvement, as well as sensory ataxic features.

**Diagnosis With Special Interest on SS**

These observations strongly suggest that neural tissues, particularly DRG cells and probably autonomic gan-
Some patients improve after plasma exchange. Chen et al. (78) reported dramatic and sustained improvement in 2 of 4 patients with SNN secondary to SS after 5 to 9 sessions of plasma exchange, with no detectable benefit in the other 2 patients, and suggested early treatment with plasma exchange. Also IVIg has been reported to be beneficial in longstanding SNN (79–81). In one study, IVIg was given to 5 patients with severe disabilities for an average of 12 years. Four patients showed remarkable improvement, 2 of whom responded after the first course (79), but controlled trials are lacking. Intramuscular interferon α recently demonstrated benefit in cases of sensory ataxic and sensorimotor neuropathy, with additional improvement in sicca symptoms, antibody titers, and salivary gland histology (82). Infliximab, although ineffective for uncomplicated SS, was of benefit in a case of severe sensory neuropathy (83), indicating that anti–TNF-α therapy may have a role in subgroups of patients with severe disease. In a case of SS-associated IVIg-dependent ataxic neuropathy, rituximab administration demonstrated a marked IVIg-sparing effect not observed in patients with other assumed antibody-mediated neuropathies (84). Based on the limited number of patients treated, there may be marked differences in the rates of favorable therapeutic response among the neuropathic forms, reflecting major differences in the causes of neuropathy. Prednisone is likely a good candidate for multiple mononeuropathy and multiple cranial neuropathy, and favorable improvement may be seen in the painful dysesthesias of the painful sensory neuropathy and radiculoneuropathy forms with IVIg therapy. Although these symptomatic therapeutic responses were seen in certain patients, overall progression of the neuropathic symptoms as well as of SS syndrome itself occurred (19).

**Autoimmune Ataxic Syndromes**

**Acute Sensory Ataxic Neuropathy**

There is a clinical spectrum of autoimmune acute ataxic syndromes, ranging from sensory ataxic Guillain-Barré syndrome (GBS) to ataxic syndromes in which limb weakness is absent, such as Fisher syndrome (FS) and Bickerstaff brainstem encephalitis (BBE) (85). Based on Fisher and Bickerstaff’s findings, “progressive, relatively symmetric external ophthalmoplegia, and ataxia by 4 weeks” are the clinical features necessary for the diagnoses of both BBE and FS (86). Although “hyporeflexia or areflexia” and clear consciousness are required for the diagnosis of FS, “impaired consciousness” is required for that of BBE. Hyporeflexia or areflexia is not an exclusion criterion for the diagnosis of BBE because half of the original patients had hyporeflexia or areflexia.

Studies published in the 1990s showed that serum anti-GQ1b IgG antibody levels are frequently elevated in patients with FS or BBE. In a large published series of 581 patients (86), anti-GQ1b IgG antibodies were positive in 68% of BBE patients and in 83% of FS. The presence of common antecedent infectious agents such as *Campylobacter jejuni* and *Haemophilus influenzae* in both conditions supports the hypothesis that BBE and FS have similar etiologies, as is the case for GBS and FS. Muscle spindles, proprioceptive transducers within the muscles, are an integral part of the γ-reflex loop. They contain specialized muscle fibers that have motor innervation and are enriched by a sensory ending. The neural components and intrafusal muscle fibers of these spindles may be important targets in FS patients because they are labeled by a monoclonal antibody against b-series gangliosides, including GQ1b, in mice and rats (87) and a monoclonal anti-GQ1b/GT1a antibody in humans (88). The latter staining pattern suggests that the group 1a afferents in muscle spindles contain GQ1b. Human immunohistochemical studies using a monoclonal anti-GQ1b/GT1a antibody have shown the existence of some large neurons in DRG, which could be group 1a neurons (89). GQ1b at the NMJs of oculomotor muscles and on muscle spindles may be targets and produce the characteristic combination of FS clinical symptoms. The probable sequence of events in the pathogenesis of BBE and FS therefore is as follows: Infection by a microorganism bearing the GQ1b epitope induces production of anti-GQ1b IgG antibodies in certain patients. The anti-GQ1b antibodies bind to GQ1b expressed on the oculomotor nerves and muscle spindles, inducing FS. In some cases, anti-GQ1b antibodies also enter the brainstem in areas where the BBB is deficient (eg, the area postrema) and binds to GQ1b, which may be expressed on the brainstem reticular formation, inducing BBE. The finding that both conditions have autoantibodies in common suggested that the autoimmune mechanisms are the same in both and are not distinct conditions. Common autoantibodies, antecedent infections, and neuroimaging and neurophysiological results from a large study offer conclusive evidence that these conditions form a continuous spectrum with variable central and peripheral nervous system involvement. A new eponymic terminology “Fisher-Bickerstaff syndrome” may be helpful for nosology (85). Because randomized controlled trials have established the efficacy of plasma exchange and IVIg for GBS, either treatment should be given to patients with FS/GBS or BBE/GBS overlap. Their efficacy for treating Fisher-Bickerstaff syndrome, however, has yet to be shown as there have been no randomized controlled trials (90).

**Chronic Sensory Ataxic Neuropathy Associated With Antidiasialosyl Ganglioside Antibodies**

In contrast to the acute FS associated with IgG autoantibodies against disialosyl epitopes, including GD1b and GQ1b, monoclonal IgM antidisialosyl ganglioside antibodies are typically associated with chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and anti-GD1b disialosyl antibodies (CANOMAD) (39). In this syndrome, the IgMs react with the disialosyl epitope shared by gangliosides GD1b,
Toxic or Chemotherapy-Induced SNN

Chemotherapy-induced peripheral neurotoxicity is a common and potentially disabling side effect of some widely used anticancer agents and can be a pure sensory or painful neuropathy (with thalidomide, cisplatin, oxaliplatin, or carboplatin) or a mixed sensorimotor neuropathy with or without involvement of the autonomic nervous system (with vincristine, paclitaxel, bortezomib, or suramin) (20,21,92,93). With vinca alkaloids and platinum analogues, a so-called coasting phenomenon due to a delayed release of the toxic drugs accumulated in tissues and is responsible for the development or worsening of the neuropathy up to several weeks after treatment interruption (93). In all cases, the neurotoxicity significantly interferes with function and compromises the quality of life. In general, the peripheral nervous system has a great capacity for regeneration in response to injury, but for regeneration to occur, the cell body must be spared, and this is not the case in SNN associated with thalidomide, cisplatin, oxaliplatin, or carboplatin.

Depending on the dosage and agent used, symptoms sometimes resolve completely, but in most instances, chemotherapy-induced peripheral neurotoxicity is only partly reversible even when the tumor has been successfully treated by the drugs. In individual cases, neuropathy can evolve even after a single application of the drug. A general predisposition for developing chemotherapy-induced neuropathy has been observed in neroves previously damaged by diabetes mellitus, alcohol, or inherited neuropathy (94). The incidence varies depending on the conditions. Severe neuropathy can occur in 2% to 7% of patients treated with single but in up to 38% of those receiving polychemotherapy regimens. The neurotoxicity of cisplatin and carboplatin is well documented. The first signs of the predominantly SNN appear about 1 month after initiation of therapy. The extent of the neuropathy correlates with the cumulative dose of the platinum compound but also depends on the dose received at each administration. Neuropathy can follow exposure to amounts as low as 200 mg/m², but doses above 400 mg/m² always lead to neuronal damage (21). The clinical picture of the neuropathy is a predominantly SNN with diminished vibration perception, loss of tendon reflexes, and discomforting paresthesias, starting in the lower extremities. The intensity of paresthesias ranges from light tingling to extensive pain. In advanced stages, the patient is ataxic, with a pronounced gait disturbance due to impaired proprioception; other symptoms include muscle cramps and Lhermitte phenomenon or a similar perception consisting of an electrical sensation in the shoulder girdle. This is due to demyelination of the dorsal roots and columns. Electrodiagnostic studies detect low SAP amplitude and secondary demyelinating neuropathy (reduced nerve conduction velocity) relatively late after the clinical manifestation of symptoms. The sural nerve is the most sensitive indicator for the neuropathy. Motor nerves are normally spared. Oxaliplatin is a platinum analog similar to the approved drugs, cisplatin and carboplatin. The most common toxicity resulting from oxaliplatin therapy is neurotoxicity, with early neuromyotonic discharges and then cold-sensitive paresthesias, which are unique among the manifestations of platinum complexes studied to date. They occur at low total cumulative doses, are always reversible, and do not require discontinuation of therapy. However, a peripheral sensory neuropathy also occurs, with symptoms similar to those of cisplatin. The risk of developing a severe neurological disturbance is related to the cumulative dose, generally becoming a clinical problem when the cumulative dose approximates 800 mg/m². It is reversible but may last for several months and may even require discontinuation of treatment. The mechanism of neurotoxicity induced by platinum drugs may involve the accumulation of platinum within DRG cells. However, in contrast to cisplatin, oxaliplatin leads to retention of platinum due to slower clearance rather than greater accumulation.

Currently, there is no treatment that can significantly improve the clinical signs and symptoms of chemotherapy-induced peripheral neurotoxicity or SNN. Symptomatic treatment of paresthesias and pain with ion-channel blockers, such as carbamazepine or gabapentin, has proved effective. Carbamazepine (600–1200 mg daily) is particularly effective in the treatment of early hyperpathic symptoms under oxaliplatin therapy. Tricyclic antidepressants are also used as first-line therapy. Different strategies to prevent neuropathy have been developed in experimental models, and some have reached clinical application; these include adrenocorticotropic hormone analogues, amifostine (an organic thiophosphate), reduced glutathione, insulin-like growth factor 1, nerve growth factor, and neurotrophin 3. This is a heterogeneous group of compounds, most of which have failed to show any benefit in preclinical trials. Prophylactic measures for chemotherapy-induced neuropathies are a real challenge. In animal models with neuropathies induced by cisplatin, vincristine, or taxol growth factors, neuroprotective compounds or gene therapy resulted...
in neuroprotection (95). A recently published double-blind vs placebo clinical trial showed that vitamin E (α-tocopherol 400 mg/d) may have a neuroprotective effect (96).

**SNN and Pyridoxine Toxicity**

Although pyridoxine (vitamin B6) deficiency causes distal, predominantly sensory neuropathy pyridoxine has also been identified as a neurotoxicant. During the 1980s, the medical community was alerted to a neurological disease occurring in individuals consuming large quantities of vitamin B6 for prolonged periods of time (97,98). Since then, many more cases of pyridoxine neuropathy, some patients taking as little as 200 mg/d, have been described (22,99). It can occur with chronic use of pyridoxine supplementation over several years and also with acute overdosage with parenteral pyridoxine (100). A normal adult will require 1 to 2 mg of pyridoxine per day. This is adequately supplied by a normal diet. Requirements are increased in pregnancy, in malnourished patients, and in patients who are taking drugs that cause a depletion of pyridoxine, for example, isoniazid, theophyllines, and penicillamine.

Patients with pyridoxine neuropathy present a pure sensory neuropathy with signs of large-fiber sensory involvement, resulting in a pronounced sensory ataxia. Except for minimal weakness, there is no evidence of motor involvement. No sign of central nervous system dysfunction, except a transient Lhermitte phenomenon, has been described. Neurological disability gradually improves with discontinuation of pyridoxine. Although there are no recent data on the prevalence of pyridoxine-induced SNN, this condition should be considered in a patient presenting with a sensory neuropathy. In animal models, pyridoxine intoxication causes a predominant, but not exclusive, degeneration of large-diameter neurons in the DRG and the large sensory fibers derived from those neurons (99,101). This pattern is supported by electrodiagnostic data showing a decrement in the H-wave amplitude but no change in the direct motor response.

**Non-Length-Dependent Small-Fiber Ganglionopathy**

The syndrome of small-fiber ganglionopathy with early involvement of the face, trunk, or proximal limbs is not well recognized and contrasts with the burning feet syndrome of small-fiber neuropathy and classical large fiber features of sensory ganglionopathy. Twelve men and 11 women, with an average age of 50 years, were reported from 4 centers (27). Neuropathic pain developed over days or over months. The pain was characterized as burning, pricking, shooting, or allodynic. There was loss of pinprick sensation in affected regions in 19, with minimal or no loss of large fiber sensibility. Laboratory findings included abnormal glucose metabolism in 6 patients, Sjögren syndrome in 3, and monoclonal gamopathy, sprue, and hepatitis C infection in 1 each, with the remainder idiopathic. SAPs were normal in 12 and were reduced in the hands but normal in the legs in 6. Skin biopsies in 14 of 17 showed reduced nerve fiber density in the thigh equal to or more prominent than in the calf. Two of 7 patients improved with immune thera-pies, 13 symptomatically with analgesic medications. Ten considered the pain disabling at the last follow-up.

**Inherited Disorders With Degeneration of DRG Cells**

**Friedreich Ataxia**

Friedreich ataxia, an autosomal recessive neurodegenerative disease, is the most common of the inherited ataxias (102) and the most frequently encountered inherited ataxia with electrodiagnostic features of SNN (103). The cardinal clinical features are progressive gait and limb ataxia, absent lower limb reflexes, extensor plantar responses, dysarthria, and reduction in or loss of vibration sense and proprioception. Cardiomyopathy, scoliosis, and foot deformity are common but nonessential features. The phenotype spectrum is broader than previously considered, suggesting the usefulness of genetic testing of the FRDA gene in all patients with idiopathic ataxia (104).

**Ataxia With Vitamin E Deficiency**

Ataxia with vitamin E deficiency is a rare autosomal recessive neurodegenerative disease, due to mutations in TTPA gene (105), which encodes for α-TTP, a cytosolic liver protein that is presumed to function in the intracellular transport of α-tocopherol. This disease is char-acterized clinically by symptoms with often striking resemblance to those of Friedreich ataxia. The neurological symptoms include ataxia, dysarthria, hyporeflexia, and decreased vibration sense, sometimes associated with cardiomyopathy and retinitis pigmentosa (106). Vitamin E supplementation improves symptoms and prevents disease progress (107).

**Abetalipoproteinemia**

A SNN can be observed in familial hypocholester-olemia, namely abetalipoproteinemia, hypobetalipo-proteinemia, and chylomicron retention disease, a rare genetic disease that causes malnutrition and growth failure. The diagnosis is based on a history of chronic diarrhea with fat malabsorption and abnormal lipid profile. Upper endoscopy and histology reveal fat-laden enterocytes, whereas vitamin E deficiency is invariably present. Creatine kinase (CK) is usually elevated and hepatic steatosis is common. Genotyping identifies the Sar1b gene mutation. Treatment and follow-up remain poorly defined (108).

**Mitochondrial Disorders**

Several phenotypes previously referred to as mitochon-drial recessive ataxia syndrome (MIRAS) and sensory
ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) harbor proprioceptive ataxia, with ophthalmoplegia, and have been reported in relation with nuclear mutation of the mitochondrial DNA with mutation of the polymerase γ (POLG) gene (109). The enlarging spectrum of sensory ataxic neuropathies associated with mitochondrial DNA (mtDNA) instability and POLG mutations should be recognized and considered in the differential diagnosis of this unusual presentation. Despite a growing appreciation of mitochondrial SNN phenotypes, there are a number of potential pitfalls in relation to confirming a diagnosis. First, the POLG-associated diseases are widely heterogeneous, and within the sensory ataxic phenotypes, there may be much overlap between syndromes as well as absence or delayed emergence of certain features such as ophthalmoplegia (108). Second, muscle biopsy may be normal, and multiple mtDNA deletions may be difficult to demonstrate (110).

Combined SNN and Motor Neuron Disorders
The combination of severe sensory and motor neuropathy is rarely encountered in clinical practice. It has been reported in patients with paraneoplastic Hu antibodies (see above), in facial onset sensory and motor neuronopathy (111), and in rare genetic diseases such as Tangier disease and the A382P TDP-43 mutation in the TARDBP gene (112).

DIFFERENTIAL DIAGNOSIS
The differential diagnosis involves distinguishing SNN from other sensory polyneuropathies, diseases primarily affecting posterior column fibers being beyond the scope of this discussion (Table 20.2).

Infectious Ataxic Neuropathies
In the preantibiotic era, syphilis was the most frequent cause of myelopathy (113). Patients presented with sensory levels, lower extremity weakness, pyramidal signs, and variable degrees of bladder and bowel dysfunction but also with polyradiculopathy. Pathologies have been related to meningomyelitis, meningovascular disease, and cord atrophy (tabes dorsalis) and also to cord compression from gummae or syphilitic osteitis. Tabes dorsalis is caused by the degeneration of the postganglionic sensory nerve roots and dorsal columns of the spinal cord due to syphilitic pachymeningitis, especially at the lower thoracic and lumbar levels. This results in abolished or reduced tendon reflexes, ataxia, loss of pain sensation, foot ulcers, arthropathy, and lancinating pain. In contrast to peripheral neuropathy or ganglionopathy, SAPs are normal. Guidelines recommend treatment of neurosyphilis with 18 to 24 million units of intravenous aqueous penicillin per day for 10 to 14 days.

Diphtheric Polyneuropathy
Diphtheric polyneuropathy occurs in 15% of patients after severe pharyngeal infection. The most frequent manifestations include bulbar paralysis or a demyelinating disorder resembling GBS (114). Impairment of deep sensation is frequent and, in some cases, can result in an ataxic pseudobulbar neuropathy.

Human T-Cell Lymphotropic Virus
Human T-cell lymphotropic virus I or II has been associated with some cases of tropical ataxic neuropathy (see below) (115,116).

HIV
Peripheral neuropathy is a common complication of HIV infection and has a broad spectrum of manifestations. The most frequent is a predominantly sensory and painful distal neuropathy, which is almost universal in the late stages of HIV infection. However, a few patients have been reported with a subacute ataxic sensory ganglionopathy (11,12).

Tropical Ataxic Neuropathies
Tropical ataxic neuropathies encompass a heterogeneous group of disorders characterized by an ataxic syndrome associated with other manifestations, including paraparesis, optic nerve involvement, and mental disorders (117). Most of these are caused by nutritional factors and attributed to toxic/nutritional causes. The disorder has been reported in prisoners of war (Strachan syndrome) and as epidemic neuropathy in Cuba, epidemic paralytic disease (Konzo) in Congo, and in Nigeria.

Demyelinating Neuropathies
The EFNS/PNS guidelines on the definition, investigation, and treatment of chronic inflammatory demyelinating polyradiculoneuropathy and of patients with paraproteinemic demyelinating neuropathy have been recently revised (118,119). These 2 neuropathies are the most common differential diagnosis of SNN.

CONCLUSIONS
SNN is a clinically, histologically, and pathogenetically distinct category of sensory neuropathy. Although it may not be easy to separate ganglionopathies from other sensory ataxic neuropathies, electrodiagnostic studies are useful in demonstrating an asymmetrical or multifocal reduction in amplitude of the proximal and distal SAPs. One important factor in the pathogenesis is the access of the autoantibodies to the target antigen in the central and peripheral nervous system in dysimmune and paraneoplastic neuropathies. Dysimmune sensory ganglionitis may be responsive to immunosuppressive therapy, whereas the paraneoplastic, toxic neuropathies, and associated SNN with genetic diseases are generally refractory. There is a great need to expand the number of confirmed therapies and explore treatments that could potentially stop or reverse damage to the DRG.
CLINICAL PEARLS AND KEY POINTS IN SENSORY NEURONOPATHIES (SNN)

- Those disorders are characterized by primary degeneration of sensory neurons in DRG. They encompass neoplastic or dysimmune causes and toxic agents and are more rarely encountered with genetic disorders.
- Non-length-dependent distribution of sensory loss and almost pure EDX sensory involvement are the distinctive signs, but in neoplastic SNN, combined neurological manifestations, such as autonomic neuropathy, motor neuron disorder, limbic dysfunction, or cerebellar signs usually occur.
- Investigations include EDX studies (all cases), imaging techniques (neoplastic cases), CSF examination (all cases except toxic), sural nerve biopsy (dysimmune cases), as well as genetic testing (selective cases).
- Diagnosis of SNN is possible based on examination and on results of the EDX studies, probable as related to the biological workup and imaging data, and definite if DRG degeneration is pathologically proven (DRG biopsy not recommended). A validated score to recognize SNN independently of the underlying cause is available.
- Treatments are tailored to the underlying cause.

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Q1: Please confirm if text corrections (changes to “and” and “or”) are as intended.
Q2: Please clarify the groups being compared. Is “between antiampiphysin, anti-CV2, paraneoplastic SNN, and sensorimotor neuropathy ans SCLC, breast, colon, prostate, thymoma, and other cancers for the peripheral neuropathies”?
Q3: Please check this fragment, this is not a sentence.