

The pattern and diagnostic criteria of sensory neuronopathy: a case–control study

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Acquired sensory neuronopathies encompass a group of paraneoplastic, dysimmune, toxic or idiopathic disorders characterized by degeneration of peripheral sensory neurons in dorsal root ganglia. As dorsal root ganglia cannot easily be explored, the clinical diagnosis of these disorders may be difficult. The question as to whether there exists a common clinical pattern of sensory neuronopathies, allowing the establishment of validated and easy-to-use diagnostic criteria, has not yet been addressed. In this study, logistic regression was used to construct diagnostic criteria on a retrospective study population of 78 patients with sensory neuronopathies and 56 with other sensory neuropathies. For this, sensory neuronopathy was provisionally considered as unambiguous in 44 patients with paraneoplastic disorder or cisplatin treatment and likely in 34 with a dysimmune or idiopathic setting who may theoretically have another form of neuropathy. To test the homogeneity of the sensory neuronopathy population, likely candidates were compared with unambiguous cases and then the whole population was compared with the other sensory neuropathies population. Criteria accuracy was checked on 37 prospective patients referred for diagnosis of sensory neuropathy. In the study population, sensory neuronopathy showed a common clinical and electrophysiological pattern that was independent of the underlying cause, including unusual forms with only patchy sensory loss, mild electrical motor nerve abnormalities and predominant small fibre or isolated lower limb involvement. Logistic regression allowed the construction of a set of criteria that gave fair results with the following combination: ataxia in the lower or upper limbs + asymmetrical distribution + sensory loss not restricted to the lower limbs + at least one sensory action potential absent or three sensory action potentials <30% of the lower limit of normal in the upper limbs + less than two nerves with abnormal motor nerve conduction study in the lower limbs.

Keywords: sensory neuronopathy; sensory ganglionopathy; sensory neuropathy; paraneoplastic neurological syndrome; cisplatin

Abbreviations: CSF = cerebrospinal fluid; ENMG = electroneuromyographic study; ROC = receiver operator characteristic; SAP = sensory action potentials; SNN = sensory neuronopathies

Introduction

Acquired sensory neuronopathies (SNN) or ganglionopathies encompass different disorders characterized by a primary degeneration of sensory neurons in dorsal root ganglia (Kuntzer *et al.*, 2004; Sghirlanzoni *et al.*, 2005). This has been pathologically demonstrated with paraneoplastic SNN (Graus *et al.*, 1990; Dalmau *et al.*, 1991; Wanschitz *et al.*, 1997), HIV infection (Scaravilli *et al.*, 1992; Esiri *et al.*, 1993), Sjögren's syndrome, unclassified connective diseases and rare idiopathic cases (Okajima *et al.*, 1983; Sobue *et al.*, 1988; Griffin *et al.*, 1990; Hainfellner *et al.*, 1996; Kurokawa *et al.*, 1998; Colli *et al.*, 2008). Interestingly, in all of these circumstances, dorsal root ganglia degeneration was associated with an inflammatory T-cell reaction suggesting that the disorder is mainly driven by a cell-mediated immune response. That sensory neuron cell body is the target of cisplatin toxicity is also recognized (Gill and Windebank, 1998; Krarup-Hansen *et al.*, 2007). Conversely, with vitamin B6 toxicity (Windebank, 1985; Xu *et al.*, 1989) or anti-disialosyl antibodies (Kusunoki *et al.*, 1996), the demonstration of dorsal root ganglia involvement relies on animal models only. Finally, recent reports suggest that a variety of pure small fibre neuropathy may depend on a ganglionopathy, but this has not yet been demonstrated by dorsal root ganglia examination (Mori *et al.*, 2003; Brannagan *et al.*, 2005; Gibbons *et al.*, 2008).

Differentiating SNN from other sensory neuropathies is important owing to the possibility of detecting disorders that may benefit from specific investigations and treatments. However, this is difficult in the absence of methods that allow easy and non-traumatic exploration of dorsal root ganglia. In addition, several conditions associated with SNN such as Sjögren's syndrome are not specifically connected with a ganglionopathy, as they also occur with other forms of neuropathy. Lastly, there is evidence that both dorsal root ganglia and peripheral nerves can simultaneously be affected in the same patient. This explains why some authors maintain descriptive terminologies such as ataxic sensory neuropathy or even sensory neuropathy (Dalakas, 1986; Windebank *et al.*, 1990). Hence, there is a need for diagnostic criteria for SNN that can easily be used in general practice. Several years ago, Asbury (Asbury, 1987; Asbury and Brown, 1990) proposed that a non-length-dependent distribution of sensory loss and an almost pure and severe electrophysiological sensory involvement are distinctive of SNN. Specific criteria have also been proposed for paraneoplastic cases (Graus *et al.*, 2004). Recently, skin biopsy has been used to demonstrate non length-dependence of small fibre loss (Lauria *et al.*, 2001) and spinal cord MRI to show degeneration of the central process of large sensory neurons (Lauria *et al.*, 2000). Although universally used, Asbury's criteria have not been validated and do not take into account several questions: is there a uniform pattern of acquired SNN? What is the sensitivity and specificity of the proposed criteria? Can different easy-to-use criteria differentiate SNN from other sensory neuropathies? We addressed these questions in a case-control study.

Materials and Methods

Patient selection

Patients consisted of two populations, the study and the test population.

The study population was used for the construction of diagnostic criteria. For this, we retrospectively reviewed the files of 85 patients with paraneoplastic neurological disorders and 511 with sensory non-paraneoplastic neuropathy referred between January 1993 and January 2007 to the Rhône-Alpes Reference Centre for Rare Neuromuscular Diseases. To be selected for the study, patients had to present a clinically pure sensory neuropathy even though electrophysiological investigations may have shown motor nerve conduction study abnormalities, and a complete and detailed record of the clinical and electrophysiological investigations had to be available. All of the patients had to have been examined by one of us and to have received a biological check-up with a search for at least diabetes mellitus, renal failure, abnormal white blood cell count, plasma ion abnormalities, monoclonal (M) gammopathy, liver perturbations, B12 deficiency, thyroid hormone abnormalities, well-characterized onconeural antibodies and organ- and non-organ-specific antibodies. Patients with multiple causes of neuropathy, clinical radiculopathy, entrapment neuropathy or hereditary neuropathy were excluded.

The study population consisted of two groups:

- SNN patients were provisionally classified as having unambiguous or likely SNN. Unambiguous SNN included definite paraneoplastic SNN according to the PNS Euronetwork criteria (Graus *et al.*, 2004) and acute or subacute sensory neuropathy due to cisplatin toxicity. SNN was considered likely by the clinician of the reference centre in the absence of gold standard criteria in those patients presenting with a clinically pure sensory neuropathy with a non-length dependent distribution and pure or predominant sensory abnormalities on the nerve conduction study independently of the associated context according to Asbury's criteria. The rationale for this classification relies on the fact that in the unambiguous group there was no alternative diagnosis for the neuropathy, and a fair demonstration of dorsal root ganglia involvement exists in the literature while in the likely group several mechanisms of neuropathy were theoretically possible for a given aetiology as it is the case with Sjögren's syndrome, unspecific dysimmune or idiopathic disorders.
- Controls were used as a reference population for the elaboration of diagnostic criteria by comparison with patients with unambiguous or likely SNN. They consisted of patients with a clinically pure sensory neuropathy and either a length-dependent distribution, or an etiological context or electrophysiological pattern that clearly excluded SNN. They were *a priori* selected among our population of patients with sensory neuropathy to represent the largest possible panel of neuropathies of different origins and patterns, whatever the actual relative frequency of each of these neuropathies in the population.

The test population was an external group used for the validation of diagnostic criteria established on the study population. It consisted of 37 unselected consecutive patients prospectively investigated in our centre for the diagnosis of a pure sensory neuropathy between January 2007 and June 2008. In the test population, the selected models were compared with the final diagnosis of the clinician taken as an expert centre diagnosis.

Data recorded for the study

The following data were recorded and analysed for the study: sex and age; clinical information including: at disease onset, modalities of onset (acute ≤ 1 month; subacute >1 month and ≤ 6 months; progressive >6 months), presence of paresthesia/dysesthesia, ataxia, pain, first involvement in the lower, upper or four limbs; at maximum development of the neuropathy: topography of sensory loss in the four limbs (proximal or distal), face or trunk, presence of pain, dysesthesia/paresthesia, ataxia in the upper or lower limbs, small (thermal and pin-prick sensation) or large (vibration and joint position sense) fibre involvement, number of elicited tendon reflexes, symmetry or asymmetry of the sensory loss, modified Rankin score, autonomic system abnormalities including orthostatic hypotension, constipation or diarrhoea, sexual impotence, bladder disturbances, abnormal sweating and pupil abnormalities. In addition, the distribution of sensory involvement was classified as consistent or not with a length-dependent pattern. For this, limbs were segmented into six sections from distal to proximal and the trunk into two vertical anterior and posterior sections. Criteria for a length-dependent distribution were as reported (Thomas and Ochoa, 1993). Cerebrospinal fluid (CSF) analysis abnormalities included protein concentration >0.5 g/l, white cell count $>1/\text{mm}^3$ or oligoclonal pattern.

For the electrophysiological study, conduction velocities were recorded at full development of the neuropathy with classical procedure in median, ulnar and radial nerves in the forearm and peroneal, tibial, superficial peroneal and sural nerves in the leg. Sensory action potentials (SAP) were recorded with an orthodromic procedure for median, ulnar and radial nerves, antidromically in the superficial peroneal and sural nerves and expressed as a percentage of the lower limit of the laboratory normal value. Motor distal latencies, compound muscle action potential and minimal F-wave latencies were recorded for median, ulnar, tibial and peroneal nerves. The pattern of each motor nerve was classified as normal, axonal/neuronal, demyelinating or intermediate according to published criteria (Camdessanche *et al.*, 2002). To compare action potentials, conduction velocities and distal and F wave latencies, the worst value of the right or left recorded nerve was kept. Several dichotomized electrophysiological criteria were tested including the presence of at least one, two or three abolished SAP or SAP $<30\%$ of lower limit of normal of the laboratory and one, two or three motor nerve with abnormal nerve conduction study in the upper or lower limbs. MRIs were analysed for the presence of spinal cord T2 high signal and somatosensory evoked potentials (SEPs) were evaluated for the presence of an involvement of the peripheral and central pathway. Superficial peroneal or radial nerve biopsy were analysed on semithin sections for the estimation of myelinated fibre density, presence of demyelination, remyelination, wallerian degeneration or regenerating clusters and on paraffin embedded sections stained with H&S and by immunohistochemistry with an anti-T3 antibody (Dako, Glostrup, Denmark) for the detection of inflammatory T lymphocytes.

Statistical analysis

First, to test the homogeneity of SNN patients, we compared the unambiguous and likely SNN groups with respect to demographic, clinical, electrophysiological and biological data. Differences were determined using the Fisher exact test for qualitative data and Student's *t*-test or Wilcoxon Mann–Whitney test for quantitative data.

Second, SNN patients (unambiguous and likely) were compared with controls as previously. Areas under receiver operator characteristic (ROC) curves were used to determine thresholds of sensory nerve

conduction studies differentiating SNN from controls. Sensitivity and specificity were estimated for each of 85 items analysed using controls as the reference group. When related to a test procedure, sensitivity is defined as the probability of correctly detecting a condition which is present while specificity is the probability of failing to detect the condition when it is indeed absent. Likelihood ratios for positive (sensitivity divided by $1 - \text{specificity}$) and negative ($1 - \text{sensitivity}$ divided by specificity) test results were computed to evaluate the relative clinical utility of each item. Likelihood ratios above 10 and below 0.1 were considered to provide strong evidence to rule in or rule out diagnosis, respectively.

Third, logistic regression was used to construct multivariable models to identify the association of variables that may discriminate the SNN group from controls with the best accuracy in which each selected variable was weighted according to the logistic regression coefficient. Goodness-of-fit was evaluated using the Hosmer–Lemeshow test. Areas under ROC curves (AURC) + 95% confidence interval were computed as a measure of the overall discrimination and to determine the cut-off value separating patients as having or not having SNN. We first tested the Asbury's and PNSEuronet group criteria and then tried several *a priori* constructed models by introducing in block in the logistic regression either the items included in the aforesaid criteria or different combinations of items having the best likelihood ratios. Finally, to select the best discriminative model, we performed a stepwise logistic regression with all the clinical and electrophysiological items recorded at onset or maximum development of the neuropathy and having the best likelihood ratio+ or likelihood ratio-.

The validity of the models selected on the study population was then evaluated in two ways. First, the 'jackknife' method was performed on the study population and the results were presented as correct classification defined as the fraction of patients and controls, who were correctly classified. The jackknife method is a statistical cross-validation technique in which one patient is removed and the rule is rederived and used to classify the excluded patient (Efron, 1982; Wasson *et al.*, 1985). The patient's predicted state is then compared with the reference state. This process is repeated systematically for each patient to determine the frequency with which the excluded patient is correctly or incorrectly classified.

Second, models were tested on the external prospective test population. In this population, the clinician diagnosis was made blindly to this model approach. The number and percentage of patients well classified using the diagnostic final model compared with the clinician diagnosis were computed, and sensitivity, specificity and likelihood ratio+ were derived. Statistics were performed using SPSS TM 14.0 software.

Results

Patients and controls

In the retrospective study population, 78 patients were in the SNN group (mean age 58 years, male 59%). Forty-four had an unambiguous diagnosis of SNN with an acute or subacute sensory neuropathy due to cisplatin toxicity in 11 cases and a definite paraneoplastic SNN in 33 cases (30 anti-Hu and one anti-amphiphysin antibody) (Fig. 1). SNN was considered as likely in 34 patients. A dysimmune context occurred in 11 patients including detection of anti-nuclear, SSA or mitochondria antibodies, lupus anticoagulant, positive salivary gland biopsy or M

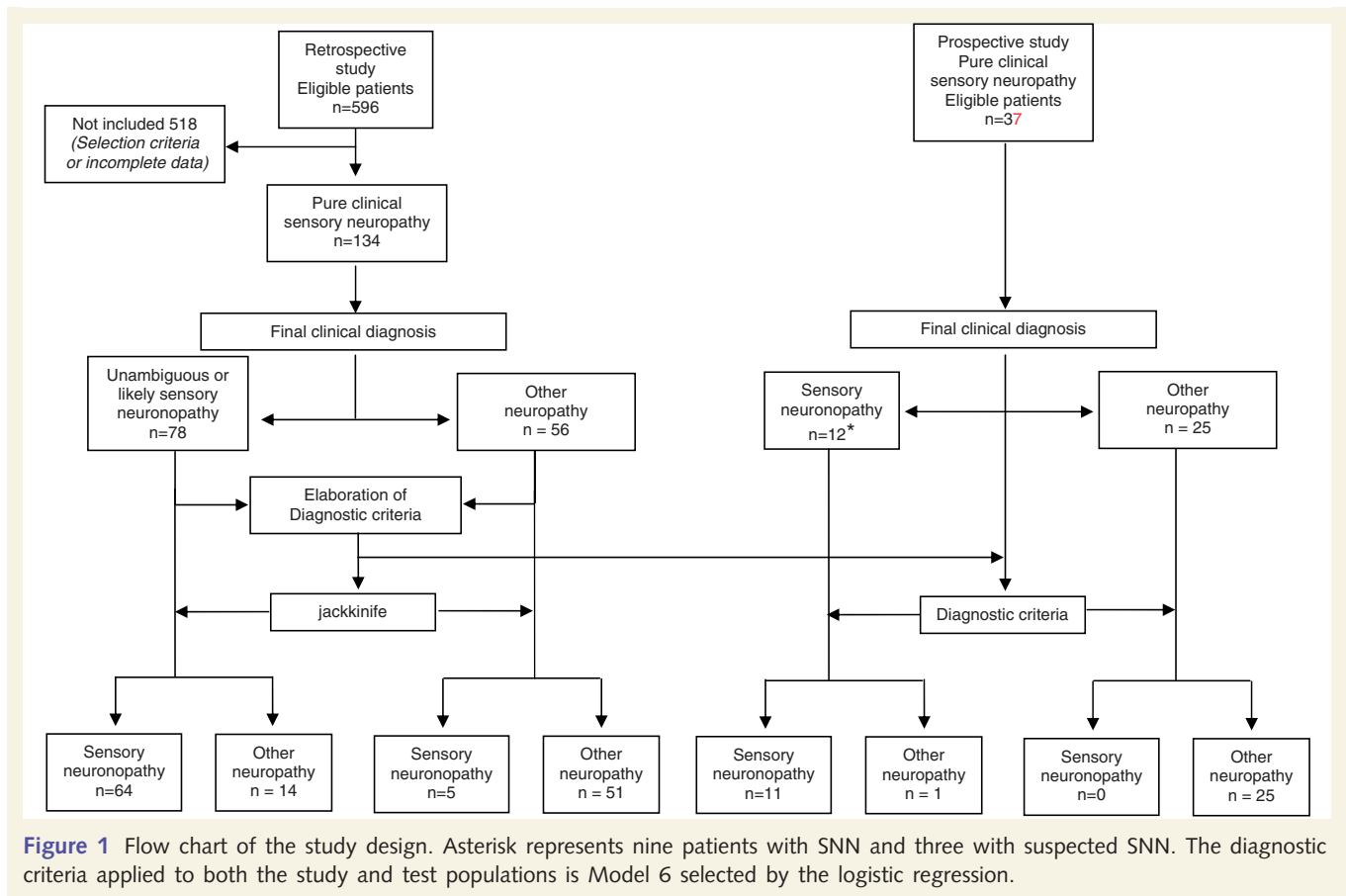


Figure 1 Flow chart of the study design. Asterisk represents nine patients with SNN and three with suspected SNN. The diagnostic criteria applied to both the study and test populations is Model 6 selected by the logistic regression.

component without known antibody activity. Sjögren's syndrome was diagnosed in three of them. One patient had HIV infection. In 22 patients with a negative diagnosis workup, SNN was considered as idiopathic.

The control group consisted of 56 patients with clinical sensory neuropathy (mean age 62 years, male gender 57%). The neuropathy was dysimmune in 16: three had a chronic inflammatory demyelinating polyneuropathy, one the Lewis and Sumner syndrome, one an acute inflammatory demyelinating polyneuropathy, seven a distal demyelinating sensory neuropathy with anti-MAG M IgM, one a chronic ataxic neuropathy with anti-disialosyl M IgM, two mononeuritis multiplex with vasculitis and one Sjögren's syndrome. A metabolic neuropathy occurred in 10 patients including diabetes mellitus (4), B12 deficiency (4), amyloidosis (1) and hypothyroidism (1). The neuropathy was toxic in six patients: two alcoholic and four treatment-induced toxicity other than cisplatin. Finally, 24 patients had an axonal neuropathy of unknown origin. The diagnosis of Lewis and Sumner syndrome was retained in patients with a clinically pure multifocal sensory presentation on the presence on the electroneuromyographic study (ENMG) of signs of multifocal motor nerve demyelination and that of mononeuritis multiplex on ENMG signs of motor axonal degeneration and nerve biopsy findings of vasculitis.

The prospective test population consisted of 37 patients with clinically pure sensory neuropathy (mean age 60.7 years, male gender 70%). The final diagnosis before evaluation of the criteria was unambiguous SNN in one patient with onconeural antibody

and likely SNN in eight patients. Three additional patients were suspected to have SNN but this diagnosis could not be definitively retained because of borderline clinical or ENMG data. The other patients had chronic inflammatory demyelinating polyneuropathy (4), Lewis-Sumner syndrome (2), amyloidosis (1), diabetes mellitus (1), B12 deficiency (1), alcoholic neuropathy (2), neuropathy with M gammopathy (1), small fibre neuropathy (1), neuropathy associated with heart graft (1) or neuropathy of unknown origin (11).

Comparison of unambiguous versus likely SNN

Results are summarized in Table 1. At full development, there was no significant difference in term of distribution, topography and quality of sensory involvement between the two groups. Characteristics that were shared by >80% of patients were the topography of sensory abnormalities involving the distal part of the four limbs, a non-length-dependent distribution, and presence of paraesthesia. Ataxia in the upper or lower limbs occurred in 71% of cases, small fibre involvement in 62% and pain in 50%. Asymmetrical distribution was present in 42% of patients. Rare particular clinical patterns that were not specific of one subgroup of SNN included: pure upper limb or lower limb involvement, sensory loss restricted to small fibres and multifocal distribution of patchy sensory loss that may be suggestive of mononeuritis multiplex.

Significant clinical differences only occurred during the neuropathy onset. Usually, in possible SNN, onset was progressive and

Table 1 Items differentiating unambiguous and likely SNN in the study population

	Unambiguous SNN (%)	Likely SNN (%)	P-value
Sex (Male/total patients)	31/44 (70.5)	15/34 (44.1)	0.019
Acute–subacute–progressive onset	15–24–5/44 (34.1–54.5–11.4)	4–10–20/34 (11.7–29.4–58.8)	<0.0001
Lower limb involvement only at onset	8/44 (18.2)	17/34 (50.0)	0.0036
Four limb involvement at onset	17/44 (38.6)	4/34 (11.8)	0.01
Pain at full development	27/44 (61.4)	12/34 (35.3)	0.0224
Raised CSF protein	25/27 (92.6)	8/21 (38.1)	<0.0001
Oligoclonal CSF pattern	7/18 (38.9)	2/20 (10.0)	0.0365
Electroneuromyography with all motor nerves normal	13/42 (30.9)	20/34 (58.8)	0.0148

P-value was determined with the Fisher's exact test.

The total number of unambiguous and likely SNN on which the statistics was performed for each item corresponds to the denominator. The numerator indicates the number of cases fulfilling the item and the percentage is given into brackets.

lower limbs were affected at first while in definite SNN, onset was acute/subacute and more frequently affected the upper limbs or the four limbs.

The electrophysiological study also demonstrated a similar pattern in the two subgroups. There were no significant differences in term of sensory abnormalities. The number of abolished SAP and the mean SAP amplitudes were similar in the four limbs. Concerning motor nerve conduction studies, abnormalities were significantly more frequent in the lower limbs in patients with paraneoplastic SNN consisting mostly of an axonal or intermediate pattern.

CSF examination was performed in 48 patients (3 cisplatin, 24 paraneoplastic and 21 likely SNN). It was significantly abnormal in patients with paraneoplastic SNN with a more frequent raised protein level and oligoclonal pattern. Twenty-two patients underwent spinal cord MRI (4 cisplatin, 2 paraneoplastic and 16 likely SNN). It showed abnormal high signal of the posterior column in only one of them. SEPs were studied in 25 patients (5 paraneoplastic, 2 cisplatin and 18 likely). They were not recordable in five and showed a clear involvement of both the peripheral and central process in seven. The last 13 patients had a severe peripheral involvement preventing any valuable recording of the central pathway.

Nerve biopsy was obtained in 16 patients, eight paraneoplastic and eight non-paraneoplastic (dysimmune or idiopathic) SNN. There were no differences concerning myelinated fibre density and morphological fibre changes between paraneoplastic and non-paraneoplastic SNN. Fibre loss was universal with a proportion of fibre undergoing axonal degeneration varying from 0% to 4%. Occasional regenerating clusters were encountered in one case of each group. One patient with dysimmune SNN had T-cell inflammatory infiltrates around epineurial blood vessels.

Comparison of SNN versus control sensory neuropathies

As unambiguous and likely SNN showed only few differences concerning clinical and electrophysiological presentation, data of the whole SNN population and controls were compared. Results are summarized in Table 2. Comparatively to SNN, controls had a neuropathy significantly restricted to the lower limbs, especially the distal part, with a symmetrical distribution. If the trunk was equally involved in both groups, controls did not show

facial involvement. Ataxia and large sensory fibre involvement or autonomic perturbations were rarer. From the electrophysiological point of view, in the SNN group, motor nerve conduction was less severely altered in the four limbs. SAP amplitude was more severely reduced in the median, ulnar and radial nerves, and abolished SAP were more frequent in the upper limbs, but there was no difference in the lower limbs. ROC curves analysis of SAP amplitude expressed as a percentage of the lower limit of normal showed that it was not possible to determine a threshold value distinguishing SNN from controls in the lower limbs (superficial peroneal and sural nerves). In the upper limbs, the best compromise was a threshold of SAP amplitude <30% of the lower limit of normal that gave 70% sensitivity and specificity for the ulnar and median nerves, and 70% sensitivity and 85% specificity for the radial nerve in favour of SNN (Fig. 2).

Similar results were observed when comparing independently unambiguous SNN and likely SNN with controls.

Model testing for diagnostic criteria for SNN

Among the 85 items tested on the study population for the elaboration of diagnostic criteria, those with the best positive discriminative value (highest likelihood ratio+) were ataxia at onset or main development of the neuropathy, clinical asymmetry of sensory loss, at least one or two abolished SAP in the upper limb or the combination of at least one abolished SAP or at least three SAPs <30% of the lower limit of normal in the upper limbs, and no or less than one motor nerve with abnormal nerve conduction studies in the lower limbs. The best negative discriminative items (lowest likelihood ratio-) were the absence of clinical upper limb involvement or no large sensory fibre perturbation and a clinical involvement restricted to lower limbs (Table 2). However, as none of them reached a discriminative level (likelihood ratio+ > 10 or likelihood ratio- < 0.1), several models of combined criteria were constructed with the study population. Each model was elaborated by entering into a logistic regression the variables included in these models (Table 3). For scoring the different models, variables in the model were weighted by their respective logistic regression coefficient. Models 1 and 5 were obtained by entering in block the items of the Asbury's and PNSEuronet group criteria, respectively. Models 2–4 are examples of models built

Table 2 Items differentiating SNN and controls in the study population

Total cases = 134	P-value	SNN (%)	Controls (%)	Sensitivity	Specificity	LR+	LR–
Onconeural antibodies	<0.0001	31/78 (39.7)	0/56 (0)	0.4	1	∞	0.6
Onset ^a							
Acute	0.0236	19/78 (24.3)	5/56 (8.9)	0.24	0.91	2.73	0.83
Subacute	0.0148	34/78 (43.6)	13/56 (23.2)	0.44	0.77	1.88	0.73
Progressive	<0.0001	25/78 (32.0)	37/56 (66.0)	0.32	0.34	0.49	2
Ataxia	<0.0001	33/78 (42.3)	5/56 (8.9)	0.42	0.91	4.74	0.63
Asymmetry of sensory loss	0.0067	31/78 (39.7)	10/56 (17.8)	0.4	0.82	2.23	0.73
Including upper limb	<0.0001	54/78 (69.2)	15/56 (26.8)	0.69	0.73	2.58	0.42
Including LL	0.001	46/78 (58.9)	48/56 (85.7)	0.59	0.14	0.69	2.87
Clinical manifestations—at full development							
Distal upper limb	<0.0001	69/78 (88.5)	28/56 (50.0)	0.88	0.5	1.77	0.23
Proximal upper limb	0.0103	9/78 (11.5)	0/56 (0)	0.12	1	∞	0.88
Including upper limb	<0.0001	73/78 (93.6)	28/56 (50.0)	0.94	0.5	1.87	0.13
Lower limb only	<0.0001	5/78 (6.4)	27/56 (48.2)	0.06	0.52	0.13	1.81
Four limbs	<0.0001	70/78 (89.7)	28/56 (50.0)	0.9	0.5	1.79	0.21
Face involvement	0.0206	8/78 (10.2)	0/56 (0)	0.1	1	∞	0.9
Asymmetry of sensory loss	<0.0001	36/78 (46.1)	7/56 (12.5)	0.46	0.88	3.69	0.62
Non length dependent distribution	<0.0002	64/78 (82.0)	29/56 (51.8)	0.82	0.48	1.58	0.37
Superficial and deep sensation	0.0023	73/78 (93.6)	42/56 (75)	0.94	0.25	1.25	0.26
Ataxia (upper limb or lower limb)	<0.0001	55/78 (70.5)	14/56 (25)	0.71	0.75	2.82	0.39
Dysautonomia	0.0124	17/78 (21.8)	3/56 (5.4)	0.22	0.95	4.07	0.83
CSF^b							
Raised protein	0.0052	33/48 (68.8)	10/20 (50.0)	0.69	0.5	1.38	0.63
Raised cell number	0.0002	18/48 (37.5)	0/20 (0)	0.38	1	∞	0.63
Oligoclonal pattern	0.023	9/29 (31.0)	0/20 (0)	0.24	1	∞	0.76
Nerve conduction study: sensory nerves							
Sensory action potential median (μV)	<0.0001	2.53 ± 3.34	7.06 ± 5.91	–	–	–	–
Sensory action potential ulnar (μV)	0.0054	1.92 ± 4.78	4.44 ± 3.92	–	–	–	–
Sensory action potential radial (μV)	<0.0001	3.69 ± 4.72	12.21 ± 9.04	–	–	–	–
≥ 1 Sensory action potential abolished in upper limb	<0.0001	48/78 (61.5)	7/56 (12.5)	0.62	0.88	4.92	0.44
≥ 2 Sensory action potential abolished in upper limb	<0.0001	28/78 (35.9)	3/56 (5.4)	0.36	0.95	6.7	0.68
≥ 3 Sensory action potential abolished in upper limb	0.0078	15/78 (19.2)	2/56 (3.6)	0.19	0.96	5.38	0.84
≥ 2 Sensory action potential <30% lower limit of normal upper limb	<0.0001	49/78 (62.8)	12/56 (21.4)	0.63	0.79	2.93	0.47
≥ 3 sensory action potential <30% lower limit of normal upper limb	<0.0001	29/49 (37.2)	4/56 (7.1)	0.37	0.96	9.25	0.11
≥ 1 sensory action potential = 0 or 3 sensory action potential <30% lower limit of normal upper limb	<0.0001	53/78 (67.9)	8/56 (17.8)	0.68	0.86	4.76	0.20
Nerve conduction study: motor nerves							
Motor conduction velocities median (ms ⁻¹)	0.0046	50.19 ± 5.69	46.5 ± 8.23	–	–	–	–
Motor conduction velocities ulnar (ms ⁻¹)	0.0128	51.39 ± 6.19	47.43 ± 10.4	–	–	–	–
Compound muscle action potentials Peroneal (mV)	<0.0001	3.48 ± 1.9	1.84 ± 1.84	–	–	–	–
Motor conduction velocities Peroneal ms ⁻¹)	<0.0001	43.7 ± 4.97	33.44 ± 12.9	–	–	–	–
Compound muscle action potentials Tibial (mV)	<0.0001	6.19 ± 3.49	2.76 ± 2.99	–	–	–	–
Motor conduction velocities Tibial (ms ⁻¹)	<0.0001	40.64 ± 4.28	30.44 ± 14.2	–	–	–	–
All motor nerves normal lower limb	0.0001	34/55 (61.2)	8/55 (14.5)	0.62	0.85	4.25	0.45
All motor nerves normal	0.0005	33/76 (43.4)	8/56 (14.3)	0.43	0.86	3.04	0.66
≥ 2 abnormal motor nerve lower limb	<0.0001	29/76 (38.1)	42/54 (77.8)	0.38	0.22	0.49	2.78
No/minor motor abnormalities	<0.0001	49/76 (64.5)	12/56 (21.4)	0.64	0.79	3.01	0.45

Compares the clinical manifestations at onset and at the maximum development of the neuropathy, cerebrospinal fluid and nerve conduction study abnormalities. P-value was determined with the Fisher exact test for frequency comparison and with the Student *t*-test for numerical continuous variables. The number of SNN and controls on which the statistics was performed for each item corresponds to the denominator. The numerator indicates the number of case fulfilling the item and the percentage is given into brackets. For compound muscle action potentials, sensory action potential and motor conduction velocities the mean value_standard deviation is indicated.

LR = likelihood ratio.

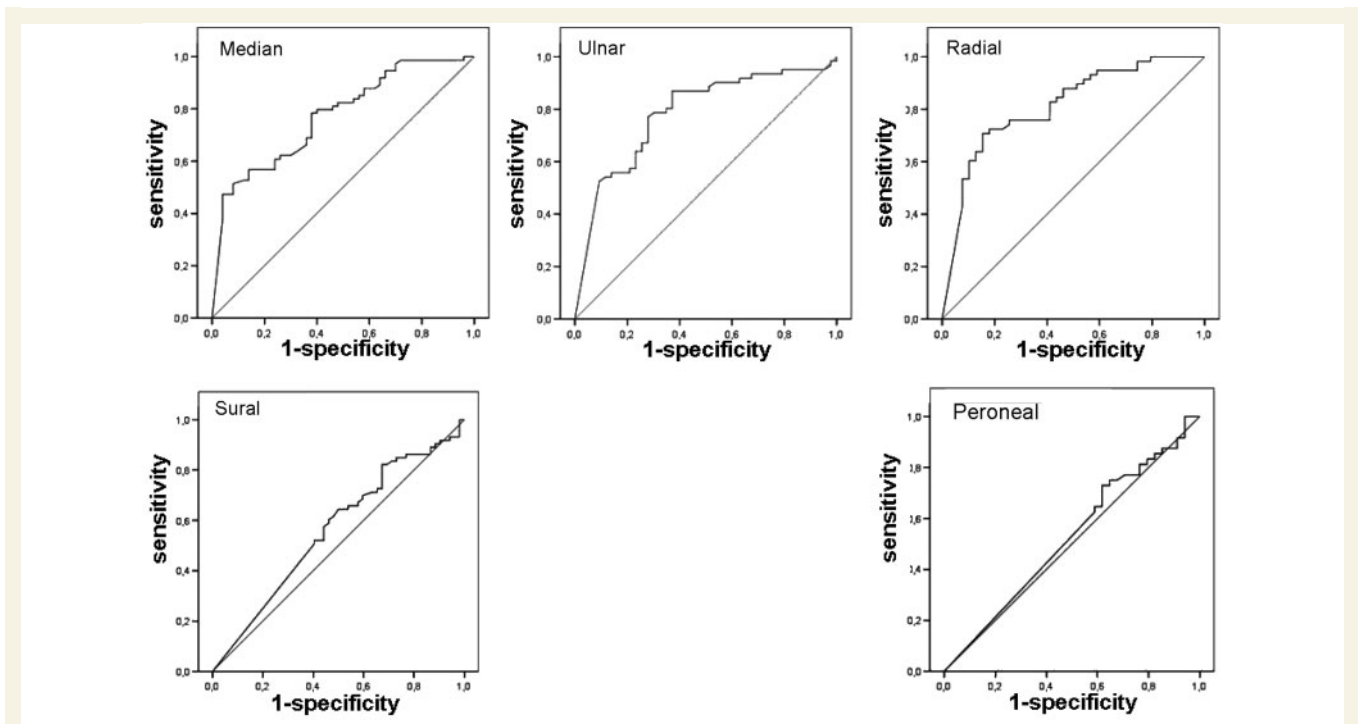


Figure 2 ROC curves for the determination of threshold differentiating SNN from other neuropathies for sensory action potentials expressed as a percentage of the lower limit of normal for the median, ulnar, radial, sural and superficial peroneal nerves.

Table 3 Models of diagnostic criteria

Model	Study population	Study population Percentage of correct diagnosis with the jackknife method				Test population		
		Area under ROC curve (95% CI)	All SNN	Unambiguous SNN	Likely SNN	Control	Sensitivity	Specificity
1	0.78 (0.70–0.86)	51.3	42.8	61.8	85.7	0.92	0.96	23.00
2	0.87 (0.80–0.93)	39.5	33.3	47.0	91.1	0.75	0.84	4.69
3	0.92 (0.85–0.95)	63.8	67.5	59.4	94.5	0.75	0.88	6.25
4	0.89 (0.83–0.94)	86.8	83.3	91.2	79.6	0.92	0.84	5.75
5	0.88 (0.83–0.94)	66.7	77.3	52.9	78.6	0.92	0.84	5.75
6	0.94 (0.90–0.98)	81.6	76.2	88.2	90.7	0.92	1.00	∞
7	0.99 (0.98–1.00)	94.7	100.0	88.2	94.4	0.92	1.00	∞

Model	Model formulation	Threshold
1	$1.35 \times \text{NLD distribution} + 1.95 \times \text{no or minor motor NCS abnormalities (Asbury's criteria)}$	2.6
2	$1.23 \times \text{NLD distribution} + 2.5 \times \text{ataxia} + 2.35 \times \text{no or minor motor NCS abnormalities}$	4
3	$2.12 \times \text{upper limb involvement} + 2.34 \times \text{ataxia} + 3.06 \times \text{normal motor NCS in LL} + 2.12 \times > 1 \text{ SAP} = 0 \text{ in UL}$	6
4	$2.35 \times \text{UL involvement} + 2.62 \times > 1 \text{ SAP} = 0 \text{ in UL} + 2.22 \times < 2 \text{ motor nerves with abnormal NCS in LL}$	4.5
5	$1.09 \times \text{subacute onset} - 0.41 \times \text{paresthesia} + 0.14 \times \text{pain} + 1.16 \times \text{asymmetry} + 2.51 \times \text{Rankin} > 3 + 1.64 \times \text{UL involvement} + 1.44 \times \text{deep sensation involvement} - 1.37 > 1 \text{ SAP} = 0 \text{ (PNSEuronet group criteria)}$	3
6	$3.1 \times \text{ataxia} + 2.04 \times \text{sensory loss not limited to LL} + 1.74 \times \text{asymmetrical distribution of sensory loss} + 2.82 \times > 1 \text{ SAP} = 0 \text{ or } 3 \text{ SAP} < 30\% \text{ lower limit of normal in UL} + 3.08 \times < 2 \text{ motor nerves with abnormal NCS in LL}$	6.5
7	Model 6 + $22.26 \times \text{onconeural antibody/cisp} - 22.13 \times \text{biology or electroneuromyography excluding SNN}$	6.5

Different tested models are shown with their area under the ROC curve + 95% CI and the percentage of correct diagnosis after jackknife on the study population and their sensitivity, specificity and likelihood ratio on the test population.

The different models are described as a mathematical formula where each clinical or electrophysiological item must be coded as 1 or 0 according as to whether the condition is fulfilled or not and multiplied by the logistic regression coefficient. The threshold differentiating patients as having or not having SNN is determined by the ROC curve.

NLD = non-length-dependent distribution, UL = upper limb, LL = lower limb, NCS = nerve conduction study, Cisp = cisplatin treatment. NLD or asymmetrical distribution and UL or LL involvement correspond to the clinical distribution of sensory loss.

arbitrarily by testing in block several combinations of variables with the best likelihood ratio+ or likelihood ratio-. Finally, Model 6 was provided by the stepwise logistic regression after entering all the items having the best likelihood ratio+ or likelihood ratio-. Model 7 corresponded to Model 6 with the adjunction of two further variables corresponding to items obtained after the initial workup and (i) making the diagnosis of SNN unambiguous (detection of onconeural antibodies or presence of a context of cisplatin treatment) or (ii) excluding SNN (presence of anti-MAG or anti-disialosyl antibodies, nerve conduction studies indicating demyelination, a context of diabetes mellitus, treatment-induced toxicity other than cisplatin or B12 deficiency).

In the study population, the jackknifed Asbury's criteria gave wholly poor results while the PNSEuronet group criteria correctly identified 77.3% of unambiguous SNN (84.8% in the paraneoplastic group), but only 52.9% of patients in the likely group. The best results were obtained with Model 6 which correctly identified 81.6% of the SNN patients and 90.7% of controls. Adjunction of contextual items improved the correctness of the diagnosis in the unambiguous and control groups.

In the small external prospective test population, Model 1 had good accuracy when compared with the clinician diagnosis (likelihood ratio+ = 23), but Model 6 was superior as the Asbury's criteria detected as a positive case a patient initially diagnosed as having SNN, a diagnosis ruled out later by a complementary ENMG and biological investigations and excluded by Model 6.

Finally, considering Model 6 as the best one in both the jackknifed study and test population, and taking into account the interest of the initial biological and electrophysiological workup, we propose the following easy-to-use score form for the diagnosis of SNN in which the coefficient of each variable is the logistic regression coefficient:

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

	Yes	Points
a—Ataxia in the lower or upper limbs at onset or full development	<input type="checkbox"/>	+3.1
b—Asymmetrical distribution of sensory loss at onset or full development	<input type="checkbox"/>	+1.7
c—Sensory loss not restricted to the lower limbs at full development	<input type="checkbox"/>	+2.0
d—At least 1 SAP absent or 3 SAP <30% of the lower limit of normal in the upper limbs, not explained by entrapment neuropathy	<input type="checkbox"/>	+2.8
e—Less than two nerves with abnormal motor nerve conduction studies in the lower limbs	<input type="checkbox"/>	+3.1
If >6.5, a diagnosis of SNN is possible	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 findings excluding SNN and
2. The patient has one of the following disorders: onconeural antibodies or a cancer within 5 years (Graus *et al.*, 2004), cisplatin treatment, Sjögren's syndrome (Vitali *et al.*, 2002).
3. Or MRI shows high signal in the posterior column of the spinal cord

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

Discussion

Because of the frequent absence of reference standard, diagnostic criteria of peripheral neuropathies have often been established on expert consensus raising the question of whether methodologies independent of subjective appreciations would be more pertinent. However, this remains a difficult challenge because none of these methods is free of potential bias especially in the selection of the reference and control populations. Here, to limit bias due to selection of diagnostic criteria on a preconceived representation of what a SNN should be, we used logistic regression to identify clinical and electrophysiological items that may accurately identify SNN from other sensory neuropathies. In the absence of definite proof of dorsal root ganglia involvement or other gold standard, we provisionally classified the SNN patients in the study population according to two levels of certitude for the diagnosis of SNN. The first was based on the fair demonstration in the scientific literature that the underlying disorder results from a primary degeneration of sensory neurons in dorsal root ganglia (e.g. paraneoplastic cases) and the second, on the absence of ambiguity concerning the main lesion site when several forms of neuropathy may be associated with the said disorder (Sjögren's syndrome or HIV infection for example). Despite this distinction, the general clinical and electrophysiological pattern was similar in unambiguous and likely SNN. This is an important point since it first shows that a general pattern of SNN can be established independently of the underlying disorder and second that patients here provisionally classified as likely SNN and who mostly conformed to the Asbury's criteria have a great chance to actually have developed a lesion in the dorsal root ganglia and hence that the whole study population could be used to establish diagnostic criteria.

Selection of the control population is another important methodological issue since it determines the negative reference against which the SNN population was compared. Here, we selected patients with neuropathies that can be without doubt (e.g. demyelinating neuropathy or mononeuritis multiplex) or likely (e.g. distal axonal sensory neuropathy) classified as non-SNN. These cases were selected not for the relative frequency of their neuropathy in our general population of neuropathy but to represent an as large as possible panel of the different patterns of sensory neuropathies.

By comparing SNN to other sensory neuropathies several statistically significant distinctive features appeared. Although we cannot rule out that some of them may have been selected by chance, the whole pattern of a predominantly distal sensory neuropathy with almost universal upper limb involvement extending sometimes to the face or trunk and frequent alteration of deep sensation conforms to what has been previously reported (Dalakas, 1986; Griffin *et al.*, 1990; Windebank *et al.*, 1990; Sobue *et al.*, 1993; Mori *et al.*, 2005). However, behind this general presentation we observed variants that were not specific

of a given aetiology, but need to be identified as SNN by any proposed set of diagnostic criteria. These include forms with only patchy sensory loss, mild electrical motor nerve abnormalities and predominant small fibre or isolated lower limb involvement. The existence of SNN restricted to small sensory neurons is still debated. It has been reported with Sjögren's syndrome (Mori *et al.*, 2003; Chai *et al.*, 2005), coeliac disease (Brannagan *et al.*, 2005) or idiopathic cases (Gorson *et al.*, 2008), but has not been demonstrated yet by an examination of dorsal root ganglia. In this study, all the patients with a clinical small fibre neuropathy had abnormal SAP indicating an associated involvement of large neurons.

An electrophysiological pattern common to acquired SNN could also be established. Diffuse abnormal SAP recording was a universal feature but with important individual variations. Abolition of SAP in the upper limbs was frequent but not universal and a reduction of SAP <30% of the lower limit of normal in at least three nerves in the upper limbs, especially in the radial nerve was more discriminative. Mild motor nerve abnormalities were not uncommon particularly with paraneoplastic disorders (Camdessanche *et al.*, 2002). These results contrast with studies that stressed the severity of sensory nerve abnormalities and the almost absence of motor nerve perturbations in SNN possibly because patients have been selected with too restrictive criteria (Dalakas, 1986; Windebank *et al.*, 1990; Chalk *et al.*, 1992; Lauria *et al.*, 2003). Extension of electrophysiological abnormalities to motor fibres without any clinical counterpart probably results from a diffusion of the pathological process beyond sensory ganglia into the peripheral nerves. This is in keeping with the finding of inflammatory changes in peripheral nerves of patients with demonstrated SNN (Antoine *et al.*, 1998; Mori *et al.*, 2005). Finally, the only distinctive features between unambiguous and likely SNN concerned onset and CSF. Both were linked to the nature of the process underlying the neuropathy and could not be used for the elaboration of diagnostic criteria.

As peripheral neuropathy is a frequent cause of referral, there is a need for easy-to-use criteria that can differentiate SNN from other neuropathies and be sensitive enough to pick up the unusual variants. To be utilized in non-specialized centres, these criteria must also draw on materials available on first-hand investigation such as clinical examination and electrophysiological study, and so the Asbury's criteria was built (Asbury, 1987; Asbury and Brown, 1990). However, we found that although patients with likely SNN mostly conform to the Asbury's criteria, these criteria had low accuracy because first, a non-length-dependent distribution is not specific enough as it also occurs with other neuropathies such as B12 deficiency, sensory variants of, or neuropathies due to vasculitis or leprosy; and second, a significant but limited electrophysiological motor nerve involvement does not rule out a diagnosis of SNN. The PNSEuronet group criteria were accurate in patients with paraneoplastic SNN but were not reliable with other forms of SNN. Among the different models tested in this study, we selected the one built by the stepwise logistic regression that only used first-hand clinical data and ENMG recording of motor and sensory nerve conduction in the four limbs with at least a study of three sensory nerves in the upper limbs. This model was sensitive with both definite and possible SNN in the jackknifed

study population where it identified the unusual forms of SNN and gave fairly good results in the external test population. In particular, it excluded cases for which the clinician diagnosis was initially hesitant. In addition it was effective in excluding non SNN sensory neuropathies. However, the perfect specificity of this model in the test population probably results from the relative small size of the sample that likely did not include all the possible presentations. Validation on a larger population of patients originating from different centres will be needed.

The patients detected by these criteria should be investigated for the usual aetiologies of SNN. This set of criteria does not take into account items that can guide to specific underlying causes. However, an acute or subacute onset and an inflammatory CSF strongly argues for a paraneoplastic origin while chronic evolution or normal CSF favours the hypothesis of a dysimmune or idiopathic SNN (Chalk *et al.*, 1992; Dalakas, 1986; Graus *et al.*, 2001). The diagnostic criteria specifically built for paraneoplastic disorders (Graus *et al.*, 2004) or Sjögren's syndrome (Vitali *et al.*, 2002) can be used for the aetiological diagnosis of SNN. Thus, in a patient with possible SNN according to clinical and electrophysiological data, a context of cisplatin treatment, detection of onconeural AB, occurrence of cancer in a short delay within the evolution of the neuropathy, diagnosis of an HIV infection or Sjögren's syndrome can be considered as evidences of probable SNN. The absence of diagnosis items that rule out SNN such as demyelinating features on the ENMG, or biological perturbations may also contribute to a probable diagnosis of SNN. However, this may be modulated since it cannot be excluded that some conditions to date considered as not associated with SNN may in the future prove to be a cause of ganglionopathy as it has been for example suggested with diabetes mellitus (Kishi *et al.*, 2002). Here, we restricted the definite level of diagnosis to cases for which there is a pathological examination of dorsal root ganglia which is at present the only way to demonstrate neuron degeneration (Griffin *et al.*, 1990; Colli *et al.*, 2008). However, in want of a still unavailable method of non-traumatic exploration of dorsal root ganglia in living people, this level will seldom be reached as biopsy of these cells cannot be recommended as a routine examination.

Other markers have been proposed for the diagnosis of SNN. Spinal cord MRI may be used as a proxy of large sensory neuron degeneration. In our series, it was disappointing, possibly for technical reasons. Although it should be underlined that T2-high signal in the dorsal column is not specific of SNN as it occurs in B12 deficiency (Lauria *et al.*, 2000), its presence may be a supportive argument and was considered as such in the proposed criteria. SEPs may also help to demonstrate an involvement of both the central and peripheral sensory pathway but the rapid degeneration of the peripheral process is a strong limitation to their interest.

Finally, skin biopsy has been used to demonstrate a non-length-dependant distribution of small fibre loss for the diagnosis of SNN (Lauria *et al.*, 2001) and has recently been proposed for the investigation of patients with pure small fibre neuropathy (Sommer and Lauria, 2007). However, skin biopsy cannot presently be considered as a routine exam for the investigation of patients with sensory neuropathy, since it needs to be performed in

specialized centres. This is the reason why we did not introduce this method in our criteria. When applied to the patients reported by Gorson *et al.* (2008) as having a painful neuropathy possibly due to a SNN restricted to small sensory neurons and diagnosed on skin biopsy the selected model gave positive results in only 3/23 of these patients. Skin biopsy can be helpful in difficult cases. Whether it may be used as an equivalent of the ENMG when the latter is normal needs specific investigations.

In conclusion, the method used here was for the first time applied to the elaboration of diagnostic criteria in a group of peripheral neuropathy for which there is yet no validated gold standard. Our study confirms that despite their different origins, acquired SNN have a common clinical and electrophysiological pattern distinctively different from other sensory neuropathies despite the existence of variants. With statistical methods powered for determination of diagnostic accuracy, we evaluated several sets of diagnostic criteria applicable in routine clinical care by any clinician as they rely only on clinical examination and ENMG. We found that one set had a good discriminative value and may be useful for the diagnosis of patients with sensory neuropathy.

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