Journal of the Peripheral Nervous System 17:331–340 (2012)

RESEARCH REPORT

A clinical pattern-based etiological diagnostic strategy for sensory neuronopathies: a French collaborative study

Jean-Philippe Camdessanché[1,2,3], Guillemette Jousserand[1], Jérôme Franques[4], Jean Pouget[4], Emilien Delmont[5], Alain Créange[6], Thierry Kuntzer[7], Thierry Maisonobe[8], Karima Abba[1,2], Jean-Christophe Antoine[1,2,3], and the French CIDP study group*

[1] *Département de Neurologie, Centre de Référence Maladies Neuromusculaires Rares Rhône-Alpes, CHU de Saint-Etienne, France;* [2] *Université de Lyon, Saint-Etienne, France;* [3] *INSERM U1028, Lyon Neuroscience Research Center, Lyon, France;* [4] *Département de Neurologie et des Maladies Neuromusculaires, CHU La Timone, Marseille, France;* [5] *Département de Neurologie, Centre de Référence des Maladies Neuromusculaires et SLA, CHU de Nice, France;* [6] *Département de Neurologie, Hôpital Henri Mondor, Créteil, France;* [7] *Unité Nerf-Muscle, Service de Neurologie, Département des Neurosciences Cliniques, Centre Hospitalier Universitaire Vaudois, Université de Lausanne, Lausanne, Switzerland; and* [8] *Département de neurologie, Centre de Référence Maladies Neuromusculaires Rares, Hôpital de la Salpêtrière, Paris, France*

* *See Appendix.*

Abstract Sensory neuronopathies (SNNs) encompass paraneoplastic, infectious, dysimmune, toxic, inherited, and idiopathic disorders. Recently described diagnostic criteria allow SNN to be differentiated from other forms of sensory neuropathy, but there is no validated strategy based on routine clinical investigations for the etiological diagnosis of SNN. In a multicenter study, the clinical, biological, and electrophysiological characteristics of 148 patients with SNN were analyzed. Multiple correspondence analysis and logistic regression were used to identify patterns differentiating between forms of SNNs with different etiologies. Models were constructed using a study population of 88 patients and checked using a test population of 60 cases. Four patterns were identified. Pattern A, with an acute or subacute onset in the four limbs or arms, early pain, and frequently affecting males over 60 years of age, identified mainly paraneoplastic, toxic, and infectious SNN. Pattern B identified patients with progressive SNN and was divided into patterns C and D, the former corresponding to patients with inherited or slowly progressive idiopathic SNN with severe ataxia and electrophysiological abnormalities and the latter to patients with idiopathic, dysimmune, and sometimes paraneoplastic SNN with a more rapid course than in pattern C. The diagnostic strategy based on these patterns correctly identified 84/88 and 58/60 patients in the study and test populations, respectively.

Key words: diagnostic strategy, paraneoplastic neurological syndrome, sensory ganglionopathy, sensory neuronopathy, sensory neuropathy

Introduction

Sensory neuronopathies (SNNs) are characterized by primary involvement of sensory neurons in the dorsal root ganglia *(Kuntzer et al., 2004; Sghirlanzoni et al., 2005)*, although, with particular etiologies, the pathological process may extend to roots and nerves.

Address correspondence to: Jean-Christophe Antoine, Service de Neurologie, Hôpital Nord, 42055 Saint-Etienne cedex 02, France. Tel: +(33)-477127805; Fax: +(33)-477120543; E-mail: j.christophe.antoine@chu-st-etienne.fr

SNNs encompass paraneoplastic disorders *(Graus et al., 1990; Dalmau et al., 1991; Wanschitz et al., 1997; Antoine and Camdessanché, 2007)*, infectious disorders *(Scaravilli et al., 1992; Esiri et al., 1993)*, dysimmune disorders *(Griffin et al., 1990; Mori et al., 2005)*, and toxic, inherited, and idiopathic disorders *(Okajima et al., 1983; Sobue et al., 1988; Hainfellner et al., 1996; Kurokawa et al., 1998; Colli et al., 2008)*. The elaboration of an etiological diagnostic strategy for these neuropathies, which is essential in terms of therapeutic possibilities and prognosis for the patient, involves two steps. The first is the differentiation of SNN from other sensory neuropathies. We have recently shown that a relatively simple set of criteria established on a population of patients with disorders known to depend on sensory neuron involvement allows SNN to be differentiated from other sensory neuropathies with good sensitivity and specificity *(Camdessanché et al., 2009)* (Table 1), but do not differentiate between different types of SNN with different etiologies. The second step therefore is to rapidly and accurately make a good final diagnosis of the underlying cause of the neuropathy, but this is frequently difficult, as it may only become apparent months or years after onset and the initial negative checkup. The aim of this study was to devise and validate a suitable strategy for the diagnosis of the underlying causes of SNN.

Materials and Methods

Patient selection

The study was approved by the Ethics Committee of the University Hospital of Saint-Etienne, France. Two populations of patients were included in the study. The first, the ''study'' population, consisted of 88 consecutive patients with a final diagnosis of SNN referred to the Rhône-Alpes Reference Centre for Rare Neuromuscular Diseases before January 2009 (monocenter study). The second, the ''test'' population, consisted of 60 patients with a final diagnosis of SNN consecutively investigated in 15 Francophone reference centers for neuromuscular diseases, who were entered in a French database of patients with SNN after January 2009 (multicenter study). The monocenter study population was used in the elaboration of the diagnosis strategy, which was then checked against the multicenter test population.

To be recruited in the study, all patients had (1) to fulfill the diagnosis criteria of possible or probable SNN (see Table 1 for detailed criteria) *(Camdessanché et al., 2009)*, (2) to have been investigated until a final etiological diagnosis of the SNN was made by the methods routinely used in this center, which were not based on the strategy proposed here, and (3) to have been followed up for a sufficient period for any underlying cause to become apparent before the final diagnosis of idiopathic SNN was made.

For each patient, a complete and detailed record of the clinical and electrophysiological investigations had to be available; these included laboratory investigations including screening for diabetes mellitus, renal failure, abnormal white blood cell count, plasma ion abnormalities, monoclonal gammopathy, liver perturbations, B12 deficiency, thyroid hormone abnormalities, and well-characterized onconeural antibodies and organ- or non-organ-specific antibodies, including antinuclear, mitochondrial, SSA, and SSB antibodies, and serology for human deficiency virus (HIV) and hepatitis B and C. In addition, a chest and abdominal computerized tomography (CT) scan were performed in some cases to search for a tumor. The patients were then classified into six etiological categories: (1) paraneoplastic SNN, defined by the presence of onconeural antibodies or a cancer within 2 years before or after onset, (2) toxic neuropathies, including patients treated with platin salts or with chronic B6 consumption or high

Table 1. The diagnostic criteria for SNN used in the study.

Step A: In a patient with a clinically pure sensory neuropathy, a diagnosis of SNN is considered possible if the total score is >6.5	Points
Ataxia in the lower or upper limbs at onset or full development	+3.1
Asymmetrical distribution of sensory loss at onset or full development	+1.7
Sensory loss not restricted to the lower limbs at full development	+2.0
At least one SAP absent or three SAPs <30% of the lower limit of normal in the upper limbs, not explained by entrapment neuropathy	+2.8
Fewer than two nerves with abnormal motor NCS results in the lower limbs	+3.1
Step B: A diagnosis of SNN is probable if the patient's score is >6.5 and if the initial workup does not show biological perturbations or ENMG findings excluding SNN and the patient has one of the following disorders: onconeural AB or a cancer 5 years before or after onset, cisplatin treatment, or Sjögren's syndrome or if the MRI shows a high signal in the posterior column of the spinal cord	
Step C: A diagnosis of SNN is definite if DRG degeneration is pathologically demonstrated, although DRG biopsy is not recommended	

AB, antibody; DRG, dorsal root ganglia; ENMG, electroneuromyogram; MRI, magnetic resonance imaging; NCS, nerve conduction study; SAP, sensory action potential; SNN, sensory neuronopathy.

alcohol consumption, (3) neuropathies associated with a dysimmune context, (4) infectious SNN, (5) inherited neuropathies with either an identified mutation or a well-established family history, and (6) idiopathic neuropathies.

Clinical data recorded for the study

Clinical characteristics

The following data were recorded: (1) sex and age, (2) family history, (3) at disease onset, the modality of onset (acute $\leq$1 month, subacute $>$1 month and $\leq$6 months, or progressive $>$6 months), presence of paresthesia/dysesthesia, ataxia, or pain and initial involvement of only the lower or upper limbs or all four limbs, and (4) at maximum development of the neuropathy, a topography of sensory loss in the four limbs (proximal or distal), face, or trunk and the presence of pain, dysesthesia/paresthesia, ataxia in the upper or lower limbs, and small (thermal and pin-prink sensation) or large (vibration and joint position sense) fiber involvement, the number of elicited tendon reflexes, symmetry or asymmetry of the sensory loss, the modified Rankin score, and autonomic system abnormalities, including orthostatic hypotension, constipation, diarrhea, sexual impotence, bladder disturbances, abnormal sweating, and pupil abnormalities. Cerebrospinal fluid (CSF) abnormalities included a protein concentration $>$0.5 g/l, a white cell count $>$5/mm^3, or an oligoclonal pattern.

Electroneuromyography

For the electrophysiological study at full development of the neuropathy, conduction velocities were recorded using a classical procedure in the median, ulnar, and radial nerves in the forearm and peroneal, tibial, superficial peroneal, and sural nerves in the leg. Sensory action potentials (SAPs) were recorded in the median, ulnar, radial, superficial, peroneal, and sural nerves and expressed as a percentage of the lower limit of the laboratory normal values. Motor distal latencies, compound muscle action potential (CMAP), and minimal F-wave latencies were recorded for the median, ulnar, tibial, and peroneal nerves. The electrophysiological pattern of each motor nerve was classified as normal, axonal/neuronal, demyelinating, or intermediate according to the published criteria *(Camdessanché et al., 2002)*.

Statistical analysis

Statistical analyses were performed using SPSS 14® software (IBM Corporation, Armonk, NY, USA). The strategy used is summarized in Fig. 1. The study population was used to generate a model of patterns of SNN related to specific etiologies.

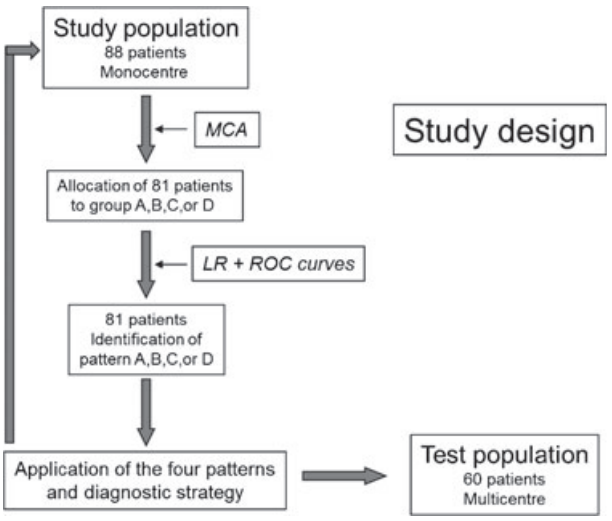

Figure 1. Flow chart for the strategy used in the study.

In the first step, multiple correspondence analysis (MCA) was used as a descriptive method to identify groups of patients in the study population who shared a similar pattern *(Benzécri, 1973; Klecka, 1980; Bécue-Bertaut and Pagès, 2006)*. MCA is a multivariate method for the exploratory study of multidimensional contingency tables. It is powered to highlight similarity and dissimilarity among a complex population by providing a synthetic analysis of categories from a battery of qualitative data. The distances between variables in a multidimensional table containing all the variable values are calculated to identify a small number (usually 2) of dimensions or axes of inertia, in which deviations from a reference value can be graphically represented as an indication of relationship between variables. The following variables were entered into the analysis: age; sex; modality of onset (acute–subacute vs. progressive); at onset, sensory manifestations involving the upper limbs with an asymmetrical distribution; and at full development, sensory manifestations restricted to the lower limbs, pain, ataxia, at least one abolished SAP in the upper limbs, and presence of motor conduction velocity abnormalities (more than one nerve with an abnormal CMAP or conduction velocities) *(Camdessanché et al., 2009)*. Etiological category was introduced as a supplementary variable, but not entered in the calculation.

In the second step, univariate and multivariate logistic regression analyses were used to identify the clinical and electrophysiological items characterizing the different types of SNN patterns based on the etiology recognized by the MCA and to obtain a model of these patterns. Receiver operating characteristic (ROC) curves were used to measure the sensitivity and specificity of the patterns. This allowed the

construction of a flowchart providing a strategy for the etiological diagnosis of SNN. In the third step, the sensitivity and specificity of the proposed strategy was checked using a prospective test population.

Results

Patients

The study and test populations consisted of 88 and 60 patients, respectively. Their characteristics and etiological diagnosis are summarized in Table 2. The two populations differed in terms of etiologies and consequently sex, because the center that recruited the study population is a reference center for paraneoplastic disorders, in which there is a higher frequency of males. Of the 148 patients, 66 fulfilled the criteria for probable SNN and 82 for possible SNN, none of the latter had electrophysiological perturbations excluding SNN. In terms of the final etiological diagnosis, 41 patients had paraneoplastic SNN (3 without onconeural antibodies), 17 toxic SNN (4 with high alcohol consumption and weight loss), and 30 dysimmune SNN (12 Sjögren's syndrome, 6 monoclonal gammopathy – including 1 with antidisialosyl ganglioside antibodies-, 1 lupus, 2 lupus anticoagulant, 1 primary biliary cirrhosis, 1 kidney graft,1 ulcerative colitis, 1 non-systemic vasculitis, and 5 unclassified dysimmune disorder). In two patients, the SNN was linked to mycoplasma pneumonia or HIV infection. Inherited SNN was seen in eight patients: one with Friedreich ataxia and one with mitochondriopathy with multiple mitochondrial DNA deletions were definite inherited SNN, while one with familial sensory neuropathy without an identified gene and five with a family history including a pair of twins corresponded to probable inherited SNN. One patient had B12 deficiency and 49 had idiopathic SNN.

In the study population, a final etiological diagnosis was made within 6 months after the first referral in 56 patients (28 paraneoplastic, 13 toxic, 10 dysimmune, 2 infectious, and 3 inherited) and between 6 months and 10 years in 10 (mean 2.3 years, median 2.8 years; 5 dysimmune and 5 paraneoplastic), the longest delay being observed in 2 patients with Sjögren's syndrome (7 and 10 years, respectively). In the case of the remaining 22 patients, no etiological diagnosis was made after a mean follow-up of 10.1 years (median 9.5, range 1–21) after onset of symptoms, and the SNN was considered idiopathic in these patients.

The time from referral to diagnosis was not recorded in the test population, but the mean follow-up was 6.2 years (median 2.8, range 0.5–45) after neuropathy onset in patients with a final etiological diagnosis and 4.6 years (median 2.7, range 1–20) in idiopathic cases.

Table 2. Demographic characteristics and etiologies of the sensory neuronopathies of the two populations used in the study.

	Study population	Test population
Number	88	60
Males/females	50/38	25/35
Age (mean + SD)	57.8 + 14.2	54.7 + 14.4
Paraneoplastic	33	8
With onconeural AB	31	7
Toxic	13	4
Platin salts	11	2
Alcohol	2	2
Dysimmune	13	17
Sjögren's syndrome	5	7
Lupus/lupus anticoagulant	2	1
Monoclonal gammopathy	2	4
Others	4	5
Infectious	2	0
Genetic/familial	3	5
Identified gene	0	2
Family history	3	3
Idiopathic	24	25
Others	0	1

AB, antibody; SD, standard deviation.

Patterns of SNN in the study population

Multiple correspondence analysis

The MCA was almost reliable, with a Chronbach's alpha value of 0.79 (reliable if $\geq$0.80). Two dimensions were identified containing 32.9% of the total variance. Dimension 1 was sensitive to age, clinical manifestations at full development, and electrophysiological abnormalities, whereas dimension 2 was sensitive to clinical manifestations at onset and the course of the disease. As shown in Fig. 2A, among the 88 patients, MCA identified two groups which almost did not overlap, group A, consisting of 41 patients with mainly paraneoplastic SNN (30 cases) or toxic SNN (10 cases), the remaining patients having dysimmune SNN, and group B, consisting of 40 patients with dysimmune SNN (10 cases), idiopathic SNN (23 cases), inherited SNN (3 cases), anti-Hu-associated paraneoplastic SNN (1 case), infectious SNN (1 case), or toxic SNN (2 cases). The remaining seven patients (two paraneoplastic, two dysimmune, one infectious, one toxic, and one idiopathic SNN) had a pattern intermediate between these two groups.

As shown in Fig. 2B, group B could be subdivided into two subgroups. Sixteen patients with genetic or idiopathic SNN formed a cluster (group C) which did not overlap with a group of 24 patients, which was a mix of idiopathic or dysimmune SNN (dysimmune/idiopathic SNN, group D).

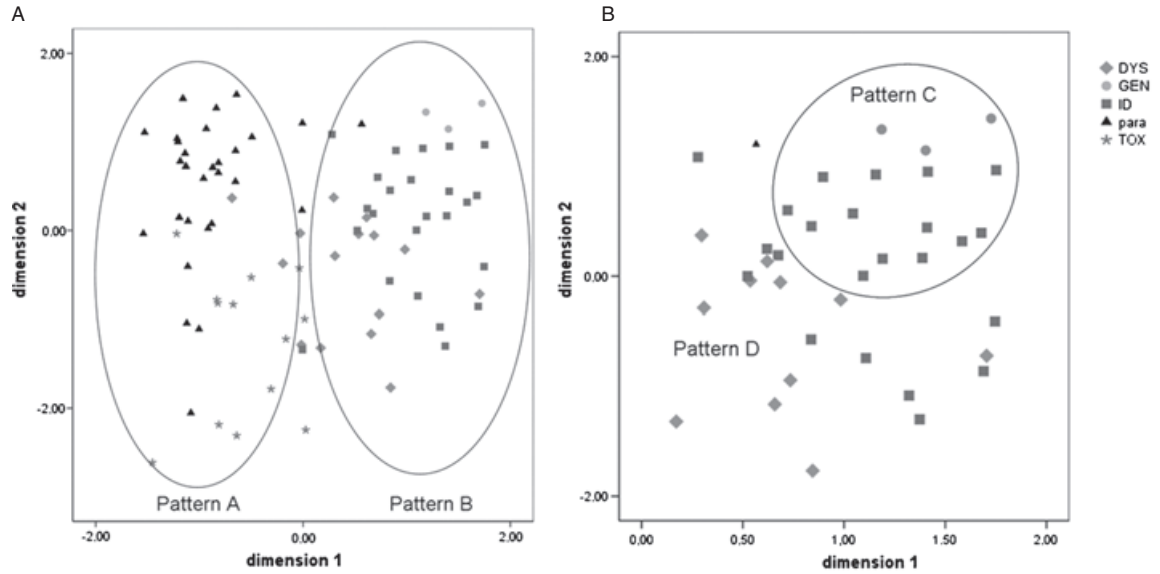

Figure 2. Multiple correspondence analysis. (A) Distribution of the 88 patients in the study population in two-dimensional space and identification of patients conforming to pattern A or pattern B. (B) In the patients conforming to pattern B, identification of patients conforming to pattern C; pattern D corresponds to those patients with pattern B who do not conform to pattern C. DYS, dysimmune; GEN, genetic; ID, idiopathic; PARA, paraneoplastic; TOX: toxic.

Logistic regression analysis

Logistic regression analysis was then used to determine the clinical and electrophysiological characteristics that distinguished pattern A from pattern B and pattern C from pattern D (Tables 3 and 4). The analysis was performed on 81 patients after exclusion of the 7 patients with a pattern intermediate between A and B.

Patterns A and B. Patients with pattern A (mostly paraneoplastic and toxic SNN) were more frequently males and were older than patients with pattern B (mainly dysimmune and idiopathic SNN). In group A, comparatively to group B, onset was frequently acute or subacute with involvement of all four limbs or only the arms and with pain as an early manifestation, while at full development, pain and dysesthesia were predominant, and in patients with paraneoplastic disorders, the CSF results and motor conduction velocities were frequently abnormal. Multivariate analysis identified an older age (odds ratio [OR] 1.13: 1.0–1.27 95% confidence interval [CI], $p < 0.05$), male sex (OR 44.4: 10.02–197.4 95% CI, $p < 0.01$), acute or subacute onset (OR 189.9: 18.8–1896.4 95% CI, $p = 0.001$), and painful onset (OR 7.9: 2.4–25.7 95% CI, $p < 0.05$) less frequently restricted to the lower limbs (OR 0.07: 0.002–0.19 95% CI, $p < 0.01$) as factors characteristic of pattern A that distinguished it from pattern B. The CSF was not included in the analysis, as not all of the patients underwent a spinal tap. Using ROC curves (Fig. 3A), the presence of at least two of these items distinguished pattern A from pattern B with 90% sensitivity and 75% specificity. When these criteria established on the 81 patients with either pattern A or B were applied to the whole study population of 88 patients (Fig. 4), 100% of cases of toxic SNN (13/13) and of infectious SNN (2/2), 85% of cases of paraneoplastic SNN (28/33), and 0% of cases of inherited SNN (0/3) were correctly identified. The overall positive predictive value of these criteria for these etiologies was 90%. However, only 59% of patients with idiopathic SNN (14/24) and 29% of those with dysimmune SNN (4/13) were identified, with an overall positive predictive value of 38%, indicating clinical heterogeneity in these two forms of SNN, for which the criteria characterizing patterns C or D need to be applied to accurately identify the etiology.

Patterns C and D. Compared to patients in the overlapping group of idiopathic and dysimmune SNN (pattern D), patients with pattern C (idiopathic or inherited SNN) tended to be older. In group C, compared to D, onset was more frequently progressive, with ataxia as a predominating manifestation, and onset in the lower limbs and absence of pain were marginally significant. Extension of sensory loss to the trunk was more frequent. Electrophysiologically, SAPs in the four limbs were more severely abnormal. Multivariate analysis confirmed that this variety of SNN was characterized by older age (OR 1.1: 1.01–1.20 95% CI, $p < 0.05$), a slowly progressive course (OR 39.8: 2.84–558.9 CI, $p < 0.01$), and an electrophysiologically

Table 3. Univariate logistic regression analysis showing the differential characteristics of the sensory neuronopathy patterns identified by the multiple correspondence analysis.

	Pattern A vs. B	p-Value	Pattern C vs. D	p-Value
Age	1.03 (0.99–1.06)	0.07	1.04 (0.99–1.09)	0.07
Sex (males)	5.93 (2.23–15.76)	**0.0004**	2.57 (0.72–9.17)	0.14
Onset	40/41	22/26	16/27	—
Progressive	0.043 (0.01–0.16)	**0.043**	5.42 (1.25–23.49)	**0.024**
Dysesthesia	3.08 (0.88–10.82)	0.079	0.38 (0.09–1.54)	0.17
Ataxia	0.64 (0.27–1.54)	0.32	8.67 (1.96–38.41)	**0.0045**
Pain	2.93 (1.18–7.27)	**0.020**	0.29 (0.07–1.25)	0.097
Four limbs	5.48 (1.78–16.82)	**0.003**	NA	0.98
LL only	0.10 (0.03–0.32)	**<0.0001**	3.20 (0.87–11.82)	0.08
UL only	1.83 (0.73–4.56)	0.20	0.91 (0.24–3.42)	0.89
Four limbs + LL only	0.61 (0.25–1.52)	0.29	1.29 (0.35–4.82)	0.70
Four limbs + UL only	10.80 (3.49–33.41)	**<0.0001**	0.36 (0.10–1.34)	0.13
Full development				
LL only	0.22 (0.02–2.11)	0.19	1.79 (0.23–14.1)	0.58
UL only	2.0 (0.17–22.9)	0.56	NA	0.98
Four limbs	1.81 (0.40–8.14)	0.44	0.35 (0.05–2.34)	0.27
Face	0.32 (0.08–1.29)	0.11	2.67 (0.51–13.9)	0.24
Trunk	0.51 (0.14–1.90)	0.51	11.82 (1.24–113.26)	**0.032**
Pain	4.04 (1.60–10.23)	**0.0032**	0.18 (0.03–0.94)	0.18
Dysesthesia	4.80 (1.24–18.82)	**0.024**	0.29 (0.07–1.17)	0.08
Dysautonomia	0.82 (0.27–2.53)	0.73	1.92 (0.41–9.05)	0.41
Small fiber involvement	0.85 (0.35–2.07)	0.71	0.54 (0.15–1.96)	0.35
Large fiber involvement	1.58 (50.25–10.01)	0.63	NA	0.97
Ataxia	0.79 (0.29–2.18)	0.79	NA	0.97
Rankin	1.43 (0.95–2.16)	0.085	1.03 (0.60–1.68)	0.99
CSF				
Number	22/26	—	8/18	—
Abnormal*	13.7 (1.54–125.0)	0.07	1.5 (0.25–8.98)	0.66
Nerve conduction study				
>1 SAP = 0 in UL	1.04 (0.42–2.59)	0.94	18.7 (2.16–162.9)	**0.008**
>2 SAP = 0 in UL	0.41 (0.16–1.02)	**0.055**	3.67 (0.99–13.6)	**0.052**
>1 SAP = 0 in LL	0.93 (0.36–2.37)	0.88	6.5 (1.22–34.7)	**0.028**
>2 SAP = 0 in LL	0.41 (0.16–1.02)	**0.051**	10.40 (1.92–56.11)	**0.0065**
Minor motor abnormalities	0.17 (0.06–0.49)	**0.001**	0.37 (0.07–1.95)	0.37

The values shown are the odds ratio and 95% confidence interval. Significant values are shown in bold. CSF, cerebrospinal fluid; LL, lower limb; NA, not available; SAP, sensory action potential; UL, upper limb.
*CSF abnormalities were a protein concentration >0.5 g/l, a white cell count >5/mm^3, or an oligoclonal pattern.

Table 4. Summary of the main characteristics of the 4 patterns of SNNs. Patterns C and D are the two variants of pattern B.

	Pattern A	Pattern B	Pattern C	Pattern D
Clinical features	Acute/subacute, onset in all four limbs or only the arms, early pain, frequently males, and over 60 years	Progressive course, onset in the LL, rare pain and dysesthesia, early ataxia, possible face or trunk involvement	Onset at early or late age, slow progression, marked ataxia	More rapid progression, less severe involvement, possible asymmetrical distribution
Most frequent etiologies	Paraneoplastic and toxic	Inherited, dysimmune, and idiopathic	Inherited and idiopathic	Idiopathic and dysimmune
Specific paraclinical abnormalities	Abnormal CSF and MCV point to paraneoplastic SNN	—	Severe reduction of SAP with at least one SAP abolished in the upper limbs	SAP less severely altered

CSF, cerebrospinal fluid; LL, lower limb; MCV, motor conduction velocity; SAP, sensory action potential; SNN, sensory neuronopathy.

more severe disease marked by at least one abolished SAP in the upper limbs (OR 27.1: 7.1–267.8 95% CI, $p < 0.01$). Using the ROC curve (Fig. 3B), the presence of at least three of these criteria identified patients in group C with 93% sensitivity and 78% specificity. On applying these criteria to those patients in the

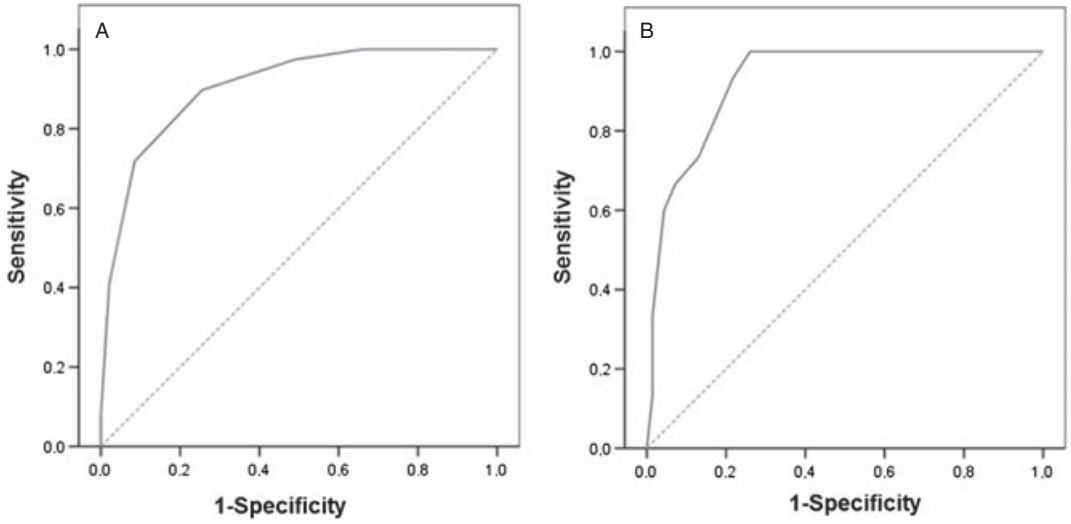

Figure 3. Receiver operating characteristic curves for the sensitivity and specificity of the two sets of criteria distinguishing pattern A from pattern B (A) and pattern C from pattern D (B) in the study population. The area under the curve is 0.906 (0.854–0.968 95% confidence interval [CI]) and 0.927 (0.871–0.983 95% CI), respectively.

	DYS	GEN	ID	INF	PARA	TOX	OTHER	TOTAL
SP	13	3	24	2	33	13	0	88
CP	17	5	25	0	8	4	1	60

Pattern B

	DYS	GEN	ID	INF	PARA	TOX	OTHER	TOTAL
SP	6	3	17	0	5	0	0	31
CP	12	5	16	0	0	0	0	34

Pattern A

	DYS	GEN	ID	INF	PARA	TOX	OTHER	TOTAL
SP	7	0	7	2	28	13	0	57
CP	5	0	9	0	8	4	0	26

Pattern C

	DYS	GEN	ID	INF	PARA	TOX	OTHER	TOTAL
SP	1	3	8	0	1	0	0	13
CP	3	5	12	0	0	0	0	20

Pattern D

	DYS	GEN	ID	INF	PARA	TOX	OTHER	TOTAL
SP	5	0	9	0	4	0	0	18
CP	9	0	4	0	0	0	1	14

Figure 4. Distribution of cases in the two populations after application of the different patterns of criteria elaborated by logistic regression. DYS, dysimmune sensory neuronopathy (SNN); GEN, genetic SNN; ID, idiopathic SNN; INF, infectious SNN; OTHER, other etiologies of SNN; PARA, paraneoplastic SNN; SP, study population; TOX, toxic SNN; CP, control/test population.

study population not identified in the previous step as conforming to pattern A (Fig. 4), pattern C identified 100% of cases of inherited SNN (3/3) and 47% of cases of idiopathic SNN (8/17), while pattern D identified 53% of cases of idiopathic SNN (9/17) and 83% of cases of dysimmune SNN (5/6).

Elaboration of a strategy for the etiological diagnosis of SNN

Using the results obtained above, a strategy was developed with the study population and checked against the test population, with the aim of allocating each patient to the correct etiological group. This

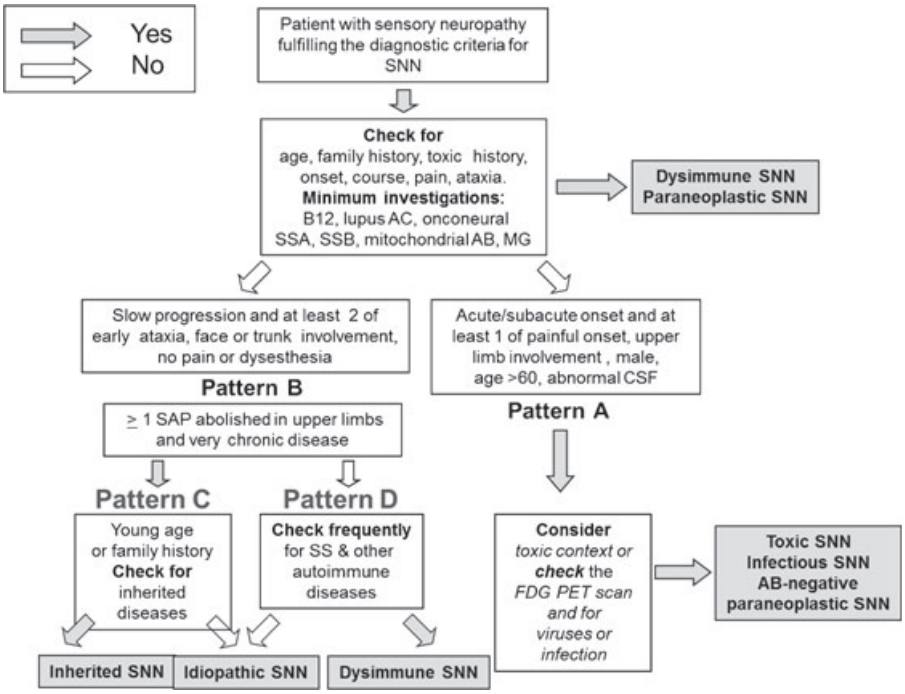

Figure 5. Proposed strategy for the etiological diagnosis of sensory neuronopathies (SNNs). AB, antibodies; AC, anticoagulant; CSF, cerebrospinal fluid; MG, monoclonal gammopathy; SAP, sensory action potential; SS, Sjögren's syndrome.

strategy was based on the different clinical patterns identified above and on the facts that (1) some patients did not follow these patterns, in particular patients with seronegative or slowly evolving paraneoplastic SNN, in whom the underlying tumor must not be missed and (2) a dysimmune etiology sometimes appeared years after the first referral. The number of patients identified at each step is presented as a flow chart in Fig. S1 and the final strategy is summarized in Fig. 5. In all, 95.4% (84/88) of the patients in the study population and 97% (58/60) patients in the test population were correctly allocated to their final etiological diagnosis. The four patients in the study population who were misclassified (one with pattern C and three with pattern A) developed an autoimmune context after an initial negative workup, whereas the two patients in the test population who were misclassified had either an acute idiopathic SNN that did not follow pattern A or a subacute SNN associated with Biermer's disease that was missed, as B12 levels were not initially included in the laboratory investigations.

If we consider the group of 10 patients in the study population for whom the time between onset and etiological diagnosis was 1–10 years, the use of this strategy would have led to the correct etiological diagnosis in 5/5 cases of paraneoplastic SNN (4 with Hu antibodies not initially tested and 1 seronegative patient) and 3/5 cases of dysimmune SNN. Of the 22 patients with an initial negative workup and a final diagnosis of idiopathic SNN after a follow-up of up to 20 years, a diagnosis of chronic idiopathic SNN would have been predicted after the first referral in 59% (13 patients).

Discussion

Although different types of SNN share clinical and electrophysiological features that allow them to be distinguished from other sensory neuropathies *(Camdessanché et al., 2009)*, they show identifiable differences related to the etiology. A better knowledge of the clinical and electrophysiological patterns of SNN may help to determine the best strategy for searching for the underlying etiology *(Graus et al., 2004)*. Such a strategy has to take into account several difficulties. First, some etiological groups are heterogeneous, for example, idiopathic SNN can sometimes involve immunity *(Colli et al., 2008)* and dysimmune SNN can follow an acute, subacute, or progressive course, implying different mechanisms. Second, in the case of paraneoplastic or dysimmune SNN, the cause of the neuropathy may only be revealed months or years later. Third, for a given etiology, some patients deviate from the expected pattern, as is the case in paraneoplastic SNN, which sometimes follows a protracted and indolent course *(Graus et al., 1994)*. It is therefore important to identify, as soon as possible, those patients for whom a frequent check is recommended and this implies that the developed strategy relies on

clinical characteristics available at onset or early in the evolution of the neuropathy.

MCA, which does not identify groups of patients from an a priori point of view, but by whether their clinical characteristics are similar or dissimilar, allowed the characterization of four clinical patterns that are clearly linked to underlying causes of the neuropathy. Interestingly, multivariate logistic regression showed that items observable early in the evolution could identify these patterns with good sensitivity and specificity. For example, 64% of patients with an acute or subacute onset involving the upper limbs, with pain, and an age over 60 (pattern A) had paraneoplastic or toxic SNN and this pattern identified 91% of patients with these etiologies. However, this pattern also occurs with infectious SNN and sometimes with idiopathic or dysimmune SNN. An abnormal CSF is typically indicative of a paraneoplastic or infectious origin. Conversely, 91% of patients with a progressive and painless evolution (pattern B) had inherited, dysimmune, or idiopathic SNN and this pattern identified 100%, 60%, and 67% of cases with these respective etiologies. Patterns C and D are subgroups of pattern B. Pattern C characterizes patients with a very slow progressive course, an early marked ataxia without pain or dysesthesia, and a severe and diffuse alteration of SAPs. Especially if the lower limbs are affected first, this pattern typically indicates idiopathic SNN in older patients, while, in younger patients, it is suggestive of an inherited disorder. Conversely, pattern D characterizes patients with a more rapid course, mild ataxia, and sometimes asymmetric symptoms, and 56% of patients with this pattern have dysimmune, or occasionally paraneoplastic, SNN *(Graus et al., 1994)*, while, in 40.6%, no etiology is found. Thus, as some cases of idiopathic SNN are indistinguishable from dysimmune SNN, patients with pattern D should be frequently investigated for the appearance of a dysimmune context, which developed in 31% of cases in the study population. At present, it is not known whether this dysimmune context, mainly Sjögren's syndrome, is the true cause of the neuropathy or whether this results from the association of two autoimmune diseases *(Dyck, 2005)*. Conversely, the probability that patients with pattern C have an autoimmune disease does not exceed 12%, suggesting that close checking may not be warranted.

The complexity of SNN points to the need for a diagnostic strategy that takes into account the different issues discussed above. The strategy proposed here can be summarized as follows (Fig. 5): in a patient with possible SNN, it is necessary to take into account age at onset, family history, toxic habits, including alcohol consumption, and treatments, such as chemotherapy and chronic B6 intake. Whatever the evolution, the initial laboratory investigations should systematically include a search for anti-nuclear (ANA), SSA, or SSB antibodies and B12 vitamin deficiency. Screening for onconeural antibodies is also necessary to allow the identification of the majority of paraneoplastic SNN cases, including those with an atypical clinical presentation (e.g., with an indolent or protracted course). If one of these investigations is positive, an etiological diagnosis can be made. In our series, 40% of the study patients were diagnosed at this stage. If the workup is negative, the pattern of the neuropathy is determinant. Patients with pattern A should be investigated for toxic causes. If the CSF is abnormal, a check for an infectious disease, including HIV, is recommended and, if this is negative, the 18 fluorodesoxyglucose-positron emission tomography (FDG-PET), scanner must be used to exclude a seronegative paraneoplastic disorder *(Antoine et al., 2000)*. In those patients who do not conform to pattern A, if the evolution is progressive and the patient fits to pattern D, a young age or family history points to an inherited disease, while older age probably suggests an idiopathic form. With pattern C, a frequent checkup for autoimmunity is warranted, especially if the patient is a young female. The presence of monoclonal gammopathy may point to a dysimmune disorder and monoclonal IgM should be tested for anti-disialosyl ganglioside reactivity. Finally, one interesting finding is that some patients with apparently idiopathic SNN show a pattern identical to that of dysimmune SSN, which may suggest that these neuropathies also involve autoimmune mechanisms.

Appendix

The French CIDP Study Group: Other members of the French CIDP group who provided cases for the study are, in alphabetical order: Françoise Bouhour, CHU de Lyon, France; Pierre Clavelou, CHU de Clermont-Ferrand, France; Andoni Echaniz-Laguna, CHU de Strasbourg, France; Hélène Gervais-Bernard, CHU de Lyon, France; Joerg Kleeberg, CHUV Lausanne, Switzerland; Emeline Lagrange, CHU de Grenoble, France; Jean-Pascal Lefaucheur, CHU de Créteil, France; Jean-Marc Léger, Hôpital de la Salpetrière, Paris, France; Stephane Mathis, CHU de Poitiers, France; Guillaume Nicolas, CHU Angers, France; François Ochsner, La Chaux-de-Fond, Switzerland; Yann Péréon, CHU de Nantes, France; Philippe Petiot, CHU Lyon, France; Pierre Soichot, CHU de Dijon, France; Guillaume Taïeb, CHU de Nimes, France; Jean-Michel Vallat, CHU de Limoges, France; Christophe Vial, CHU Lyon, France; Karine Viala, Hôpital de la Salpetrière, Paris, France.

References

Antoine JC, Camdessanché JP (2007). Peripheral nervous system involvement in patients with cancer. Lancet Neurol 6:75–86.

Antoine JC, Cinotti L, Tilikete C, Bouhour F, Camdessanché JP, Confavreux C, Vighetto A, Renault-Mannel V, Michel D, Honnorat J (2000). [18F]fluorodeoxyglucose positron emission tomography in the diagnosis of cancer in patients with paraneoplastic neurological syndrome and anti-Hu antibodies. Ann Neurol 48:105–108.

Bécue-Bertaut M, Pagès J (2006). Multiple Factor Analysis for Contingency Tables. Chapman and Hall, London, pp 300–326.

Benzécri JP (1973). L'Analyse des Données. Volume II. L'Analyse des Correspondences. Dunod, Paris, pp 1–619.

Camdessanché JP, Antoine JC, Honnorat J, Vial C, Petiot P, Convers P, Michel D (2002). Paraneoplastic peripheral neuropathy associated with anti-Hu antibodies. A clinical and electrophysiological study of 20 patients. Brain 125:166–175.

Camdessanché JP, Jousserand G, Ferraud K, Vial C, Petiot P, Honnorat J, Antoine JC (2009). The pattern and diagnostic criteria of sensory neuronopathy: a case-control study. Brain 132:1723–1733.

Colli BO, Carlotti CG Jr, Assirati JA Jr, Lopes Lda S, Marques W Jr, Chimelli L, Neder L, Barreira AA (2008). Dorsal root ganglionectomy for the diagnosis of sensory neuropathies. Surgical technique and results. Surg Neurol 69:266–273; discussion 273.

Dalmau J, Furneaux HM, Rosenblum MK, Graus F, Posner JB (1991). Detection of the anti-Hu antibody in specific regions of the nervous system and tumor from patients with paraneoplastic encephalomyelitis/sensory neuronopathy. Neurology 41:1757–1764.

Dyck PJ (2005). The clinical heterogeneity of immune sensory and autonomic neuropathies with (or without) sicca. Brain 128:2480–2482.

Esiri MM, Morris CS, Millard PR (1993). Sensory and sympathetic ganglia in HIV-1 infection: immunocytochemical demonstration of HIV-1 viral antigens, increased MHC class II antigen expression and mild reactive inflammation. J Neurol Sci 114:178–187.

Graus F, Ribalta T, Campo E, Monforte R, Urbano A, Rozman C (1990). Immunohistochemical analysis of the immune reaction in the nervous system in paraneoplastic encephalomyelitis. Neurology 40:219–222.

Graus F, Bonaventura I, Uchuya M, Valls-Sole J, Rene R, Leger JM, Tolosa E, Delattre JY (1994). Indolent anti-Hu-associated paraneoplastic sensory neuropathy. Neurology 44:2258–2261.

Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, Honnorat J, Smitt PS, Vedeler C, Verschuuren JJ, Vincent A, Voltz R (2004). Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 75:1135–1140.

Griffin JW, Cornblath DR, Alexander E, Campbell J, Low PA, Bird S, Feldman EL (1990). Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjogren's syndrome. Ann Neurol 27:304–315.

Hainfellner JA, Kristoferitsch W, Lassmann H, Bernheimer H, Neisser A, Drlicek M, Beer F, Budka H (1996).T-cell-mediated ganglionitis associated with acute sensory neuronopathy. Ann Neurol 39:543–547.

Klecka WR (1980). Discriminant Analysis. Sage Publications, Beverly Hills, CA, p 88.

Kuntzer T, Antoine JC, Steck AJ (2004). Clinical features and pathophysiological basis of sensory neuronopathies (ganglionopathies). Muscle Nerve 30:255–268.

Kurokawa K, Noda K, Mimori Y, Watanabe C, Katayama S, Nakamura S, Sannomiya K, Yamamoto S, Tahara E (1998). A case of pandysautonomia with associated sensory ganglionopathy. J Neurol Neurosurg Psychiatry 65: 278–279.

Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, Katsuno M, Fujita A, Aiba I, Ogata A, Saito T, Asakura K, Yoshida M, Hirayama M, Sobue G (2005).The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. Brain 128:2518–2534.

Okajima T, Yamamura S, Hamada K, Kawasaki S, Ideta T, Ueno H, Tokuomi H (1983). Chronic sensory and autonomic neuropathy. Neurology 33:1061–1064.

Scaravilli F, Sinclair E, Arango JC, Manji H, Lucas S, Harrison MJ (1992).The pathology of the posterior root ganglia in AIDS and its relationship to the pallor of the gracile tract. Acta Neuropathol (Berl) 84:163–170.

Sghirlanzoni A, Pareyson D, Lauria G (2005). Sensory neuron diseases. Lancet Neurol 4:349–361.

Sobue G, Yanagi T, Hashizume Y (1988). Chronic progressive sensory ataxic neuropathy with polyclonal gammopathy and disseminated focal perivascular cellular infiltrations. Neurology 38:463–467.

Wanschitz J, Hainfellner JA, Kristoferitsch W, Drlicek M, Budka H (1997). Ganglionitis in paraneoplastic subacute sensory neuronopathy: a morphologic study. Neurology 49:1156–1159.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow chart showing the results of the diagnosis strategy for the etiology of sensory neuronopathy (SNN). Figures associated with the arrows indicate the number of patients selected at each step of the procedure. Those of the study population are in normal font, while bold and italic font indicates the control population. Black arrows indicate patients with a final diagnosis of dysimmune (DYS) SNN obtained with follow-up in the study population. A-SA, acute–subacute; AB, antibodies; CSF, cerebrospinal fluid; MG, monoclonal gammopathy; P, progressive; SAP, sensory action potential; SS, Sjögren syndrome.