Paraneoplastic peripheral neuropathy associated with anti-Hu antibodies
A clinical and electrophysiological study of 20 patients

Jean-Philippe Camdessanché,[1] Jean-Christophe Antoine,[1] Jérôme Honnorat,[2] Christophe Vial,[3] Philippe Petiot,[4] Philippe Convers[1] and Daniel Michel[1]

[1]*Department of Neurology, Hôpital Bellevue, Saint-Etienne,* [2]*Department of Neurology, Hôpital Pierre Wertheimer,* [3]*Department of Electromyography, Hôpital Pierre Wertheimer, and* [4]*Department of Electromyography, Hôpital de la Croix Rousse, Lyon, France*

Correspondence to: Jean-Christophe Antoine, Service de Neurologie, Hôpital Bellevue, Boulevard Pasteur, 42055 Saint-Etienne Cedex 02, France
E-mail: 113464.3717@compuserve.com

Summary

Although paraneoplastic subacute sensory neuronopathy is the most frequent presentation of peripheral neuropathy in patients with anti-Hu antibodies, other neuropathies have been reported. In order to investigate the clinical and electrophysiological manifestations of neuropathies associated with anti-Hu antibodies, we conducted a retrospective study of 20 patients. For the electrophysiological study, each nerve was classified as normal, demyelinating, axonal/neuronal or axonal/demyelinating. Peripheral neuropathy was the presenting symptom in 95% of patients. CNS and autonomic neuropathy were present in 40% and 30% of patients, respectively. The course of the neuropathy was acute, mimicking Guillain–Barré syndrome in one patient (5%), and subacute (55%) or progressive (40%) in the others. Clinically, the neuropathy was sensory (70%), sensorimotor (25%) or motor (5%). At onset, symptoms were symmetrical (65%), asymmetrical (25%) or multifocal (10%). Pain was a predominant manifestation (80%). Amyotrophia and fasciculations were rare. The median Rankin's score was 2, three patients having an indolent form. Electrophysiology showed the axonal/neuronal pattern to be the most frequent (46.9% of studied nerves); an axonal/demyelinating or demyelinating pattern being seen in 18.3% and 4.9% of nerves, respectively. The axonal/neuronal pattern was more frequent in sensory nerves and the mixed axonal/demyelinating pattern more frequent in motor nerves ($P < 0.01$). A higher proportion of abnormal nerves correlated with a progressive course ($P < 0.05$) or a Rankin's score between 3 and 5 ($P < 0.01$). In patients with sensory neuropathy, 88.5% of sensory nerves were abnormal, mostly with an axonal/neuronal pattern. In addition, 47% of motor nerves were abnormal so that only four out of 14 patients with a clinically pure sensory neuropathy (28.6%) had an electrophysiological pattern typical of sensory neuronopathy. In patients with a sensorimotor neuropathy, 96.6% of sensory and 71% of motor nerves were abnormal. The only statistical difference between sensory and sensorimotor neuropathies was that patients with sensorimotor neuropathy had more frequent motor nerve involvement ($P < 0.05$) without differences concerning the distribution of the abnormal patterns. Needle neuromyography showed only limited evidence of motor neurone degeneration in both sensory and sensorimotor neuropathy. The present work shows that the typical clinical and electrophysiological pattern of subacute sensory neuronopathy is rarely encountered in patients with anti-Hu antibody and that motor nerve involvement is frequently seen, even in the absence of a motor deficit. In addition to their potential pathophysiological involvement in the mechanism of the paraneoplastic neuropathy, these findings have practical consequences for the diagnosis of the disorder.

Keywords: paraneoplastic; neuropathy; anti-Hu antibodies; electrophysiology

Abbreviations: CMAP = compound motor action potential; MCV = motor conduction velocity; SCV = sensory conduction velocity; SNAP = sensory nerve action potential; SSN = subacute sensory neuronopathy

Introduction

Peripheral neuropathy is a well-known manifestation of paraneoplastic neurological anti-Hu syndrome, being seen in 60–80% of patients (Dalmau *et al.*, 1992; Lucchinetti *et al.*, 1998). Subacute sensory neuronopathy (SSN), as described by Denny-Brown (1948) is thought to be the most frequent presentation. This disorder results from the destruction of sensory neurone cell bodies in dorsal root ganglia, probably as a result of attack by the cellular immune system. However, PNS motor and autonomic neurone cell bodies can also be involved, both in isolation or in association with SSN, leading to a complex clinicopathological disorder (Dalmau *et al.*, 1992; Lucchinetti *et al.*, 1998; Molinuevo *et al.*, 1998; Graus *et al.*, 2001). In addition, rare observations of mononeuritis multiplex with vasculitis (Younger *et al.*, 1994; Oh, 1997; Eggers *et al.*, 1998) or sensorimotor demyelinating neuropathy (Antoine *et al.*, 1998) suggest that the pathological process can sometimes extend into the peripheral nerves themselves. In these conditions, the clinical manifestations of anti-Hu syndrome can differ from those of the usual well-known SSN and diagnosis becomes difficult.

Currently, electrophysiology is the first-line complementary investigation used in the diagnosis of peripheral neuropathy. Despite the large number of reports of anti-Hu-associated peripheral neuropathies, studies devoted to their electrophysiological pattern have not been published. In their series of 71 patients, Dalmau *et al.* (1992) briefly reported that the usual electrophysiological profile was a reduction or an absence of sensory nerve action potential (SNAP), with a normal or slightly reduced sensory conduction velocity (SCV) and normal motor conduction velocity (MCV), consistent with the expected lesions in dorsal root ganglia. Single case reports of patients with SSN confirm this pattern (Donofrio *et al.*, 1989; Liang *et al.*, 1994; Heidenreich *et al.*, 1995; Pourmand *et al.*, 1996). However, other studies suggest more complex electrophysiological abnormalities (Oh *et al.*, 1997, 2000).

In the present work, we report a study of 20 anti-Hu patients showing that the typical SSN pattern consisting in a clinically pure and electrophysiologically almost pure sensory involvement is rarely encountered, and that motor nerve involvement is frequently observed, even in patients with a clinically purely sensory neuropathy. In addition to their pathophysiological potential implications, these findings have practical consequences for the diagnosis of these neuropathies.

Material and methods

Patient selection

Between March 1990 and March 2001, sera from 50 patients referred to our laboratories were found to be positive for anti-Hu antibodies. Twenty-seven of these patients were admitted to our hospitals (Saint-Etienne and Lyon) for a paraneoplastic neurological syndrome. For this study, we selected only those patients who had signs and symptoms of peripheral neuropathy. The most frequent other known causes of peripheral neuropathy, including diabetes mellitus, renal failure, vitamin deficiencies, thyroid dysfunction, paraproteins, cachexia or chemotherapy toxicity were excluded, as were patients with abnormal reflexes or electrophysiological abnormalities, but no clinical symptoms of peripheral neuropathy.

Clinical study

For each of the 27 patients with anti-Hu antibodies, the clinical data of the peripheral neuropathy were reviewed and analysed retrospectively. In particular, we took into account the topography and progression of motor and sensory manifestations at onset and during the course of the disease (acute ≤1 month; subacute >1 month and <6 months; progressive ≥6 months). We also analysed data concerning age, sex, central and autonomic nervous system involvement (if present), handicap assessed using Rankin's score (van Swieten *et al.*, 1988), cerebrospinal fluid analysis, type of cancer when identified, delay between onset of neuropathy and the discovery of cancer, and association with other paraneoplastic antibodies.

Paraneoplastic antibody detection

The patients' sera were tested for the presence of anti-Hu, anti-amphiphysin and anti-CV2 antibodies by immunohistochemistry, positive reactions being confirmed by Western blotting using recombinant HuD (kindly provided by Dr Josep Dalmau, Sloan Kettering Cancer Center, New York, USA), amphiphysin (kindly provided by Dr Pietro De Camilli, Department of Cell Biology, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, Conn., USA) and Ulip6/CRMP5 (GenBank AF 264015 proteins as previously reported; Antoine *et al.*, 1999).

Electrophysiological study

Data were reviewed retrospectively. Each patient underwent at least one electrophysiological examination. Six patients underwent iterative examinations (two or three). In these six patients, unless specified, we used the more representative electrophysiological recording. Similar methods were used in both centres (Saint-Etienne and Lyon). In the upper limbs, the median and ulnar nerves were studied. Compound motor action potentials (CMAPs) were recorded from the flexor pollicis and abductor digiti minimi, respectively. MCVs were measured between the wrist and elbow. SNAPs were recorded at the wrist and the SCV calculated using the orthodromic method. In the lower limbs, the tibial and peroneal motor nerves, and sural and superficial peroneal sensory nerves were studied. CMAPs were recorded from the flexor hallucis brevis and extensorum digitorum brevis, respectively. MCVs

Table 1 *Criteria for the definition of abnormal electrophysiological patterns and absolute values of the lower limits of the normal*

Demyelinating pattern	Axonal/neuronal pattern	Axonal/demyelinating pattern
	MCV or SCV >90% LLN and CMAP or SNAP <LLN	MCV or SCV 80–90% LLN and CMAP or SNAP 80–100% LLN
MCV or SCV ≤80% LLN and CMAP or SNAP≥80% LLN	or	or
		MCV or SCV below LLN without reaching values for demyelinating pattern and
or MCV or SCV ≤70% LLN	MCV or SCV >80% LLN and CMAP or SNAP <80% LLN	CMAP or SNAP in the lower range of normal values
and CMAP or SNAP <80% LLN	or Absence of CMAP or SNAP despite several stimulations	

Absolute values of LLN for motor and sensory nerves

Motor			Sensory		
Nerve	CMAP (mV)	MCV (m/s)	Nerve	SNAP (µV)	SCV (m/s)
Median	4	46	Median	8	46
Ulnar	4	46	Ulnar	8	46
Peroneal nerve	3	40	Superficial peroneal nerve	8	40
Tibial nerve	3	40	Sural nerve	8	40

CMAP = compound motor action potential; LLN = lower limit of the normal; MCV = motor conduction velocity; SCV = sensory conduction velocity; SNAP = sensory nerve action potential.

were measured between the ankle and knee. SNAPs were recorded at the leg and the SCV calculated using the antidromic method. Values for the lower limits of normal correspond to mean values minus 2 SD of a historical series of 50 healthy subjects (age range 21–82 years, mean 35 years) studied by the same methods. To take into account the fact that our population of patients was older than the reference population with a high proportion of patients aged over 60 years, we have reduced by 2 m/s the lower limit of normal of conduction velocities according to Oh (1993). Absolute values of the lower limits of normal are summarized in Table 1. When a reduced CMAP was recorded after distal nerve stimulation, a search for potentiation was systematically performed after a brief maximal voluntary contraction and, when positive, confirmed by repetitive high frequency stimulation. Distal latencies and F waves were measured for each recorded nerve and assessed as either normal or abnormal, on the basis of our normal values. In each patient, needle neuromyography was performed at least in the muscles selected for recording in the CMAP study and continued following the distribution of motor deficit as determined by clinical examination.

For each nerve, three abnormal patterns were considered as defined in Table 1. To summarize: (i) a demyelinating pattern corresponded to the criteria used by Cornblath *et al*. (1991) for the diagnosis of chronic inflammatory demyelinating polyneuropathy; (ii) an axonal/neuronal pattern defined as when the CMAP or SNAP amplitude was reduced and the MCV or SCV slowed corresponding to this reduction, or when recordings could not be made in spite of several attempts; and (iii) a mixed axonal/demyelinating pattern defined as when the reduction in MCV or SCV exceeded that expected from the reduction in CMAP or SNAP amplitude without reaching the values for the demyelinating pattern, or when MCV or SCV was below the lower limits of normal, but without reaching the values of the demyelinating pattern and CMAP or SNAP were in the range of normal values.

In addition, we studied several factors that could have influenced the frequency and distribution of electrophysiological abnormalities. These were the clinical pattern (sensory or sensorimotor), age (below or above the median age), course of the neuropathy (acute, subacute or progressive), the Rankin's score (0–2 versus 3–5), delay between onset of clinical symptoms of neuropathy as reported by the patient and the electrophysiological study (<4 months, 4–6 months and >6 months), and the presence of another paraneoplastic antibody.

Statistical studies
These were performed using the χ^2-squared test and the Fisher's exact test as appropriate.

Results

Clinical study

Of the 27 patients with anti-Hu syndrome, 20 had a clinically overt peripheral neuropathy (74.1%) and seven had CNS disorder only corresponding to encephalomyelitis (25.9%). Details of the data for our 20 patients are given in Table 2. The patients consisted of 17 males and three females (median age 64 years, range 42–80 years, mean 63.25 years). Peripheral neuropathy was the presenting symptom of the paraneoplastic neurological syndrome in 19 out of 20 (95%) of cases, and the only manifestation in six out of 20 (30%). CNS involvement was present in eight patients (40% of cases), corresponding to cerebellar degeneration (10%), limbic encephalitis (5%), brainstem encephalitis (5%) or encephalomyelitis (10%). Autonomic neuropathy was present in six patients (30% of cases) including blood pressure instability (20%), constipation (10%), intestinal obstruction (10%) and urine retention (10%). Cancer was found in 17 patients (85%). The mean delay between onset of neuropathy and tumour detection was 7.7 months (median 5 months; SD 9.7). The tumour was a small cell lung cancer in 13 out of 17 patients (76.5%).

The neuropathy was clinically purely sensory in 14 patients (70%), sensorimotor in five (25%) and purely motor in one (5%). At onset, the neuropathy was acute in one patient (5%), subacute in 11 (55%) and progressive in eight (40%). Symptoms were symmetrical in 13 patients (65%), asymmetrical in five (25%) and multifocal, suggesting mononeuritis multiplex, in two (10%). Signs and symptoms of the neuropathy were present in the four limbs in six patients (30%) and restricted to the upper limbs in five patients (25%) or the lower limbs in nine patients (45%). During the course of the neuropathy, signs and symptoms extended to the four limbs in 11 patients (55%). They were predominant in upper limbs in four patients (20%) and in lower limbs in five patients (25%). Hypoaesthesia, paraesthesia and pain were predominant manifestations occurring in 17 (85%), 16 (80%) and 15 patients (75%), respectively. Deep tendon reflexes were decreased or absent in 18 patients (90%). Sensory ataxia was noted in six patients (30%) and postural tremor in two (10%). Mild to severe amyotrophia occurred in three patients (15%) and fasciculations in one (5%).

Fourteen patients (70%) had a clinically pure sensory neuropathy similar to that reported with anti-Hu antibody (Dalmau *et al.*, 1992; Graus *et al.*, 2001). Five patients (25%) had a sensorimotor neuropathy. For Patient 16, sensory manifestations were severe with slight predominantly proximal motor deficit in the lower limbs. Motor weakness was moderate to severe in the four other patients. In the first, sensorimotor manifestations were restricted to the left upper limb with severe proximal and distal motor deficit, amyotrophia, pain and mild hypoaesthesia (Patient 15). The second patient (Patient 17) had motor weakness in the four limbs, predominating in proximal lower limbs with diffuse fasciculations and diffuse amyotrophia particularly severe in the

hands. Sensory manifestations were limited to distal dysaesthesia and hypoaesthesia in the four limbs. At the end of the course, bulbar muscles were involved. The third patient (Patient 18) had an acute ascending sensorimotor neuropathy resulting in complete paraplegia and severe proximal upper limb motor deficit associated with dysautonomic involvement. The disorder resembled Guillain–Barré syndrome but showed no improvement with follow-up. The fourth patient (Patient 19) had a severely disabling lower limb proximal and upper limb distal motor deficit with pain and paraesthesia in three of the four limbs. The neuropathy was clinically purely motor in one patient (Patient 20). At the onset, this patient had a distal right upper limb motor weakness extending within a few weeks to a severe tetraparesia. Weakness predominated in proximal limb muscles. A mild amyotrophia developed in the hand. Fasciculations were not noted during the course of the disease. Orthostatic hypotension was present.

Rankin's score was 0–2 in 11 patients (55%) and 3–5 in nine patients (45%). Three patients (15%) had an indolent neuropathy, which did not progress after 2, 5 or 10 years of follow-up (Patients 4, 12 and 5, respectively), while one patient had a severe motor neuropathy leading to death within 3 months (Patient 20). Rankin's score was not statistically different in patients with sensory or sensorimotor neuropathy.

In addition to anti-Hu antibodies, four patients (20%)—of whom three had been described previously (Antoine *et al.*, 2001)—had anti-CV2 antibodies and one (5%), anti-amphiphysin antibodies. In the 15 patients with only anti-Hu antibodies, the neuropathy was purely sensory in 10 (66.65%), sensorimotor in four (26.65%) and purely motor in one (6.7%). In the four patients with both anti-CV2 and anti-Hu antibodies, the neuropathy was sensory in three and sensorimotor in one. The patient with both anti-Hu and anti-amphiphysin antibodies had a purely sensory neuropathy.

Electrophysiological study

Two hundred and seventy-two nerves, consisting of 145 motor and 127 sensory nerves, were studied. The mean number of studied nerves per patient was 11.2 (3.29 SD), corresponding to 6 motor nerves (2.05 SD) and 5.2 sensory nerves (1.58 SD). None of the patients with a reduced CMAP amplitude exhibited potentiation suggestive of Lambert–Eaton myasthenic syndrome.

Distribution and frequency of electrophysiological patterns

Results of the distribution of MCV and SCV according to CMAP and SNAP for each studied nerve in the upper and lower limbs are presented as a scattergram in Fig. 1. When the results for sensory and motor nerves were pooled, axonal/neuronal and normal patterns were the most frequently encountered, being present in 46.9% and 29.9% of nerves, respectively. Axonal/demyelinating and demyelinating

Table 2 *Clinical and electrophysiological data of the 20 patients with peripheral neuropathy and anti-Hu antibody*

No.	Sex/age (years)	Other AB	Cancer	CSF	CNS involvement and other	Autonomic neuropathy	Rankin	Peripheral paraneoplastic neuropathy						
								Course	Distribution (onset)	Topography	Clinical pattern	Sensory signs and symptoms	Motor signs	Delay (months)
1	M/65	–	SCLC	ND	–	–	2	Progressive	Symmetrical	4L	Sensory	Paraesthesia/pain Hypoaesthesia Mild sensory ataxia	-	36
2	M/56	–	SCLC	2 54 wbc 14% IgG	Deafness Cerebellar ataxia Nystagmus	–	4	Progressive	Asymmetrical	4L	Sensory	Paraesthesia/pain Hypoaesthesia Mild sensory ataxia	-	5
3	M/73	CV2	SCPrC Kidney carcinoma	0.78 1 wbc	Cerebellar ataxia	–	2	Subacute	Symmetrical	LL	Sensory	Hypoaesthesia Pseudo athetotic limb movements	–	6
4	F/75	–	ND	ND	–	–	2	Progressive	Symmetrical	UL>LL	Sensory	Paraesthesia/pain Hypoaesthesia	–	5
5	M/42	–	Ethmoid carcinoma	0.84 3 wbc	Uveitis and papillitis	–	1	Progressive	Multifocal	4L	Sensory	Paraesthesia/pain Hypoaesthesia	–	26
6	M/77	CV2	SCLC	ND	–	Constipation	2	Subacute	Symmetrical	4L	Sensory	Paraesthesia/pain	–	8
7	M/71	Amphi	SCLC	1.33 3 wbc	–	Orthostatic hypotention	2	Subacute	Symmetrical	4L	Sensory	Paraesthesia/pain Hypoaesthesia	–	3
8	M/56	–	SCLC	1.14 35 wbc oligoclonal	Temporal lobe epilepsy Deafness Nystagmus	–	3	Progressive	Symmetrical	UL>LL	Sensory	Paraesthesia/pain Hypoaesthesia Mild sensory ataxia	–	5
9	M/59	–	Large cell neuroendocrine carcinoma	ND	–	–	2	Subacute	Symmetrical	LL>UL	Sensory	Paraesthesia/pain Hypoaesthesia Hand tremor	–	2
10	M/80	–	SCLC	0.59 3 wbc 16% IgG oligoclonal	Cerebellar ataxia	–	2	Subacute	Symmetrical	4L	Sensory	Pain Hypoaesthesia	–	3
11	M/61	–	SCLC	ND	Temporal lobe epilepsy	Intestinal obstruction	4	Progressive	Asymmetrical	LL	Sensory	Paraesthesia/pain Hypoaesthesia Severe sensory ataxia	–	8
12	M/50	–	SCLC	1.2 1 wbc	–	Intestinal obstruction Orthostatic hypotension	1	Subacute	Multifocal	UL>LL	Sensory	Paraesthesia/pain	–	1
13	M/61	CV2	Not diagnosed	0.86 13 wbc	–	–	2	Subacute	Symmetrical	4L	Sensory	Paraesthesia/pain Hypoaesthesia Mild sensory ataxia	–	2
14	H/63	–	SCLC	1.6 10 wbc	–	–	4	Subacute	Asymmetrical	4L	Sensory	Paraesthesia/pain Hypoaesthesia Severe sensory ataxia	–	4
15	M/52	–	SCLC	0.81 9 wbc	Cerebellar ataxia Cranial nerve palsy	–	3	Subacute	Asymmetrical	Left UL	Sensorimotor	Pain Hypoaesthesia	Amyotrophia Left UL weakness	3

Table 2 *Continued*

No.	Sex/age (years)	Other AB	Cancer	CSF	CNS involvement and other	Autonomic neuropathy	Rankin	Peripheral paraneoplastic neuropathy						
								Course	Distribution (onset)	Topography	Clinical pattern	Sensory signs and symptoms	Motor signs	Delay (months)
16	M/65	CV2	SCLC	1.62 56 wbc	Cerebellar ataxia Mood change Buccofacial dyskinesia	–	2	Progressive	Symmetrical	LL>UL	Sensorimotor	Paraesthesia/pain Hypoaesthesia	LL weakness	2
17	M/68	–	SCLC	ND	Temporal lobe epilepsy Myoclonia	–	3	Progressive	Symmetrical	4L	Sensorimotor	Hypoaesthesia	Severe hand amyotrophia Slight teraparesia Fasciculations	36
18	M/74	–	Hepatocellular carcinoma	0.99 4 wbc	–	Blood pressure instability Urine retention	4	Acute	Symmetrical	LL>UL	Sensorimotor	Paraesthesia Hypoaesthesia	Severe tetraparesia	1
19	F/48	–	SCLC Breast	0.84 4 wbc oligoclonal	–	–	4	Subacute	Asymmetrical	4L	Sensorimotor	Paraesthesia Pain/hypoaesthesia	Severe tetraparesia	9
20	F/69	–	Not diagnosed	0.76 32 wbc oligoclonal	–	Constipation Urine retention Orthostatic hypotension Mouth dryness	5	Subacute	Symmetrical	4L	Motor	–	Slight amyotrophia Severe tetraparesia	2

AB = antibodies; Amphi = anti-amphiphysin antibodies; CV2 = anti-CV2 antibodies; F = female; LL = lower limbs; M = male; ND = not done; SCLC = small cell lung cancer; SCPrC = small cell prostate cancer; Topography = topography of signs and symptoms of the neuropathy during the course of the disease; UL = upper limbs; wbc = white blood cell; 4L = four limbs.
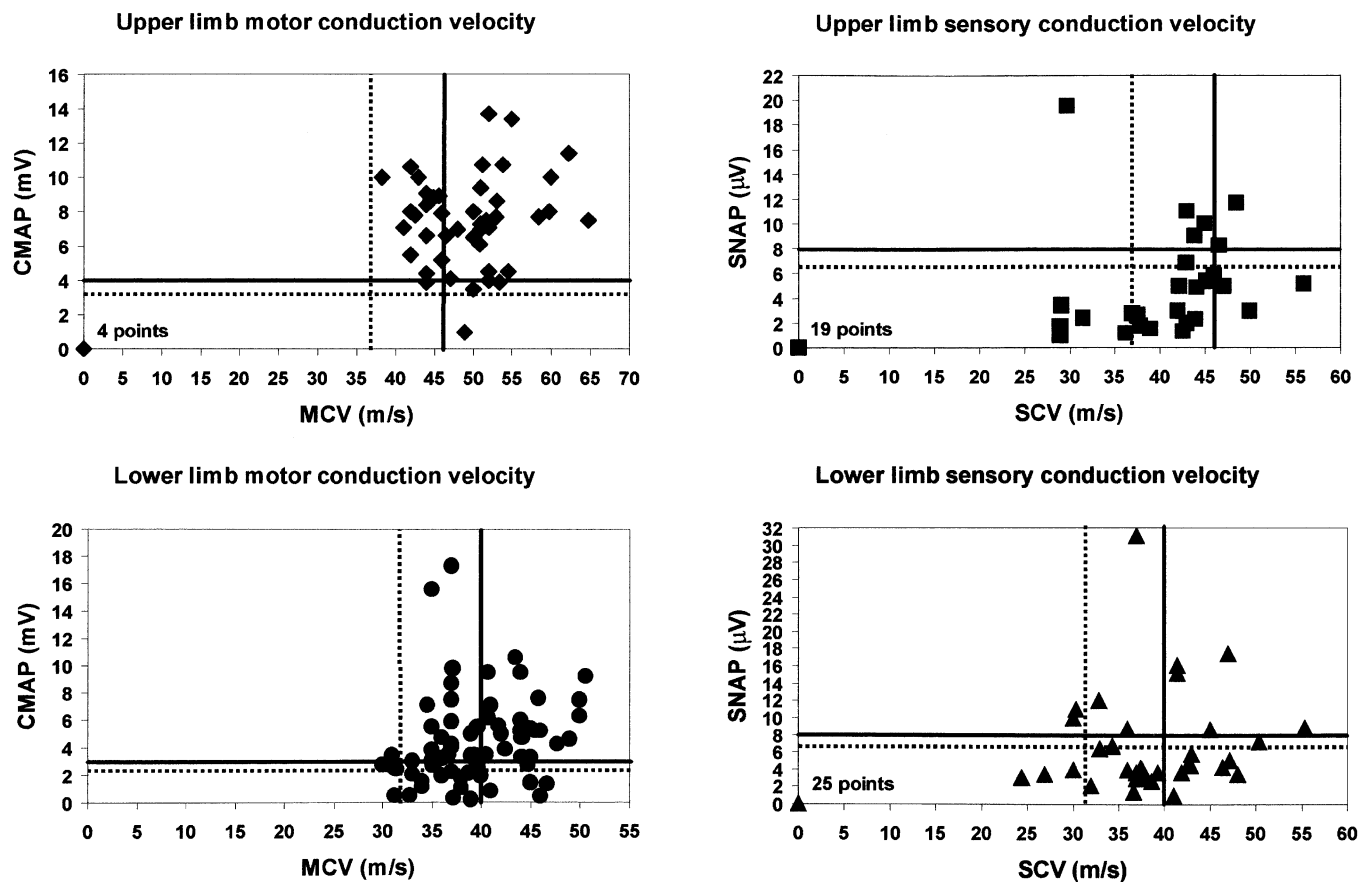
Upper limb motor conduction velocity

Upper limb sensory conduction velocity

Lower limb motor conduction velocity

Lower limb sensory conduction velocity

Fig. 1 Bivariate scattergram of motor and sensory conduction velocities (MCV and SCV) according to compound motor action potential (CMAP) and sensory nerve action potential (SNAP) for each studied nerve in the 20 patients with peripheral neuropathy and anti-Hu antibodies. Full lines indicate the lower limit of normal and dotted lines 80% of the lower limit of normal.

patterns were noted in 18.3% and 4.9% of nerves, respectively. The distribution of the three most frequent patterns (axonal/neuronal, axonal/demyelinating and normal) was different in sensory and motor nerves, the axonal/neuronal pattern being significantly more frequent in sensory nerves (74% versus 23.3%; $P < 0.01$) and the mixed axonal/demyelinating pattern more frequent in motor nerves (26.7% versus 8.7%; $P < 0.01$). Motor nerves were significantly more frequently recorded as normal than sensory nerves (46.7% versus 10.6%; $P < 0.01$). Abnormalities were more frequent in lower than in upper limbs (76% versus 62.1%; $P < 0.05$). All of the studied sensory nerves were abnormal in 14 patients (70%) and a minimum of two-thirds of the studied sensory nerves were abnormal in 17 patients (85%). Similarly, all of the studied motor nerves were abnormal in three patients (15%) and at least two-thirds were abnormal in eight patients (40%).

When taking into account variables that could interfere with the frequency and distribution of electrophysiological patterns, there appeared to be no statistical difference with age. In terms of the course, an abnormal electrophysiological pattern was significantly more frequent when the neuropathy was progressive rather than subacute (78.2% versus 61.9%;

$P < 0.05$), but there was no difference in the distribution of the abnormal electrophysiological patterns. An abnormal electrophysiological pattern was significantly more frequent with a Rankin's score of 3–5 than with Rankin's score 0–2 (79.7% versus 59.4%; $P < 0.01$), but there was no difference concerning the distribution of the abnormal patterns. With an increasing delay between onset and the electrophysiological study, the frequency of the axonal/neuronal pattern increased significantly (especially from 4 months onward), while the frequency of the mixed axonal/demyelinating pattern did not change or tended to decrease after 6 months ($P < 0.05$). The frequency of normal pattern decreased with time ($P < 0.05$).

Electrophysiological abnormalities as a function of the clinical presentation of the neuropathy

In patients with a clinically pure sensory neuropathy ($n = 14$), 88.5% of the studied sensory nerves were abnormal. In these nerves, the main electrophysiological abnormal pattern was axonal/neuronal (78.3%). In addition, 47% of the studied motor nerves were abnormal, the main abnormal pattern being axonal/demyelinating (24.2%). On needle neuromyo-

graphy, widespread abnormal potentials were detected in only one patient (7.1%). As a whole, only four out of 14 patients with a clinically pure sensory neuropathy had no or only slight abnormal motor conduction velocities resulting in a typical pattern of sensory neuronopathy (28.6%).

In patients with a clinically sensorimotor neuropathy (*n* = 5), 96.6% and 71% of sensory and motor nerves, respectively, were abnormal. The main abnormal pattern was axonal/neuronal in sensory nerves (69%) and axonal/demyelinating in motor nerves (38.7%). Needle neuromyography showed fibrillation, denervation or fasciculation potentials in three patients (60%), a frequency not statistically different from that seen in patients with a pure sensory neuropathy. In the patient with a purely motor neuropathy, all of the studied sensory nerves had an axonal/neuronal pattern. No spontaneous activities were recorded during needle neuromyography.

When comparing the frequency and distribution of abnormal patterns in patients with a clinically sensory or sensorimotor neuropathy, there was no statistical difference in the sensory nerves (88.4% versus 96.5%). Motor nerves were more frequently abnormal in patients with a sensorimotor neuropathy (71% versus 47%; $P < 0.05$), but there was no difference in the distribution of the abnormal electrophysiological patterns. Distal latencies and F waves were recorded as abnormal in 45.4% and 68.1%, respectively, of the recorded motor nerves. Abnormal values were more frequent in sensorimotor neuropathies than in sensory neuropathies (61.3% versus 40.2% and 83.9 versus 63.4%, respectively; $P < 0.05$).

Electrophysiological pattern as a function of the presence of anti-CV2 antibodies

There was no statistical difference in the frequency of normal and abnormal patterns in patients with or without anti-CV2 antibodies. In patients with anti-CV2 antibodies, the distribution of the axonal/demyelinating pattern was 42.1% in motor nerves and 29.4% when pooling motor and sensory nerves, the corresponding values in patients without anti-CV2 antibodies being 23.8% and 16.3%. These differences were not significant, but tended to reach the level of significance ($P = 0.0689$ and $P = 0.097$), in contrast to all the other non-significant values found in the study.

Discussion

We report a combined clinical and electrophysiological study of peripheral neuropathy in a series of patients with anti-Hu antibodies. The clinical manifestations of the peripheral neuropathy were similar to those reported in other published series and were dominated by sensory signs and symptoms (Dalmau *et al*., 1992; Molinuevo *et al*., 1998; Graus *et al*., 2001). Motor weakness was far less frequent, but when present, usually contributed severely to the handicap. At

onset, an asymmetrical or multifocal distribution that could mislead to the diagnosis of mononeuropathy multiplex or radiculopathy was frequent. Finally, peripheral neuropathy was the only clinical manifestation of the paraneoplastic neurological syndrome in 30% of cases, an additional 25% having an associated autonomic neuropathy. The remaining patients had a combination of CNS and PNS disorders.

Several clinical aspects should be emphasized in our study. First, in contrast to the results from another series (Molinuevo *et al*., 1998), the Rankin's score indicated mild handicap in half of our patients. This may be explained, in part, by a significant proportion (15%) of patients with an indolent neuropathy (Graus *et al*., 1994). Secondly, several patients had a bizarre distribution of the neuropathy that was very uncommonly encountered in non-paraneoplastic neuropathies such as sensorimotor monomelic involvement or severe distal deficit in the hand combined with severe proximal weakness in the leg. Thirdly, one patient presented with a Guillain–Barré-like syndrome. Although an autopsy was not performed on this patient, the clinical and electrophysiological data suggested a pure peripheral neuropathy and not encephalomyelitis, as previously reported (Graus *et al*., 1987). Interestingly, this patient had slowing of the MCVs that fell in the range for primary demyelination. Fourthly, in our series, pure motor neuropathy (Verma *et al*., 1996) was extremely rare and, as in most reported cases, electrophysiological sensory involvement was present (Dalmau *et al*., 1992; Forsyth *et al*., 1997).

As regards electrophysiology, the commonly accepted idea is that the electrophysiological pattern in patients with anti-Hu antibodies corresponds to sensory neuronopathy with reduced or absent sensory responses and almost normal MCV (Anderson *et al*., 1988; Dalmau *et al*., 1992). In our series, most of the sensory nerves were abnormal. The predominant electrophysiological pattern was axonal/neuronal with a high proportion of nerves with absent SNAPs, corresponding to the expected lesion in the sensory ganglia in these patients. However, motor nerves were also frequently abnormal. Patients with a sensorimotor neuropathy had more frequent electrophysiological abnormalities in their motor nerves, but half of the motor nerves were also abnormal in patients with a clinically pure sensory neuropathy. In motor nerves, the electrophysiological pattern indicated a mixed axonal/demyelinating process with frequent slowing of MCV that nevertheless did not usually reached the values of primary demyelination.

These findings have two implications. First, from the clinical point of view, only four patients corresponded perfectly to the concept of sensory neuronopathy, while all the others had significant abnormalities in their motor nerves, even when the neuropathy was clinically purely sensory. Thus, in the management of patients with sensory neuropathy, the diagnosis of anti-Hu antibody-associated neuropathy should not be ruled out when MCVs are altered. Secondly, the motor nerve abnormalities suggest that, in anti-Hu syndrome, the pathological process is frequently not

restricted to dorsal root ganglia and is probably more complex. As there was no significant difference in the distribution of electrophysiological patterns in motor nerves as a function of the clinical presentation of the neuropathy, the motor deficit probably resulted from an increased number of affected motor fibres, rather than different mechanisms of nerve lesion.

The mechanisms of motor fibre involvement in our patients remain unclear. Motor neurone degeneration in the spinal cord has been reported in several autopsy studies (Henson and Ulrich, 1982; Dalmau *et al.*, 1992; Verma *et al.*, 1996) and is considered to be the usual cause of motor deficit in the anti-Hu neuropathy. However, in our series, only a limited number of patients had clinical and electrophysiological evidences of motor neurone disease. In contrast, the high frequency of an axonal/demyelinating pattern and its early occurrence suggest a dysfunction of axon–Schwann cell relationships and is more suggestive of peripheral neuropathy than nerve remodelling consecutively to motor neurone disease. There have been only a limited number of pathological studies of peripheral nerve lesions in patients with anti-Hu antibodies, since most autopsy studies are restricted to the spinal cord and sensory ganglia. Nerve vasculitis, reported in at least three patients (Younger *et al.*, 1994; Oh, 1997; Eggers *et al.*, 1998), shows that direct peripheral nerve involvement can occur in addition to neurone degeneration in anti-Hu syndrome. An autopsy study of our Patient 16 showed, in addition to damage of the dorsal root ganglia, the presence of axonal degeneration and demyelinating and remyelinating lesions (Antoine *et al.*, 1998). Demyelination was also associated with vasculitis in an additional patient (Eggers *et al.*, 1998). These data give pathological support to the slowing of MCVs seen in our series.

As Hu proteins are not present in peripheral nerves (Antoine *et al.*, 2001), other nerve proteins may be the targets of the paraneoplastic immune process. Twenty per cent of our patients also had anti-CV2 antibodies. Recently, we observed that patients with this antibody have predominantly sensorimotor axonal/demyelinating neuropathy (Antoine *et al.*, 2001). In the present study, patients with both anti-Hu and anti-CV2 antibodies tended to have an axonal/demyelinating pattern, but this did not reach statistical significance, probably because the number of patients with both antibodies was too low. However, an axonal/demyelinating electrophysiological pattern was also encountered in patients without anti-CV2 antibodies. In these patients, peripheral nerve involvement may be explained by a specific immune response directed against still unknown peripheral nerve antigens, or depend on non-specific inflammatory mechanisms, such as those mediated by cytokines, which can have various effects on axons or Schwann cells (Redford *et al.*, 1995).

In conclusion, our study emphasizes the high frequency of electrophysiological motor nerve involvement in the paraneoplastic peripheral neuropathy associated with anti-Hu syndrome. The mechanism of these changes remains unclear,

but may involve peripheral nerve remodelling consecutive to neurone dysfunction or nerve inflammatory lesions. From the practical point of view, this study shows that the typical pattern of sensory neuronopathy is rare and that the presence of an axonal/demyelinating pattern does not exclude the diagnosis of paraneoplastic anti-Hu neuropathy.

Acknowledgements

References

Anderson NE, Rosenblum MK, Graus F, Wiley RG, Posner JB. Autoantibodies in paraneoplastic syndromes associated with small-cell lung cancer. Neurology 1988; 38: 1391–8.

Antoine JC, Mosnier JF, Honnorat J, Convers P, Absi L, Lapras J, et al. Paraneoplastic demyelinating neuropathy, subacute sensory neuropathy, and anti-Hu antibodies: clinicopathological study of an autopsy case. Muscle Nerve 1998; 21: 850–7.

Antoine JC, Absi L, Honnorat J, Boulesteix JM, de Brouker T, Vial C, et al. Anti-amphiphysin antibodies are associated with various paraneoplastic neurological syndromes and tumors. Arch Neurol 1999; 56: 172–7.

Antoine JC, Honnorat J, Camdessanché JP, Magistris M, Absi L, Mosnier JF, et al. Paraneoplastic anti-CV2 antibodies react with peripheral nerve and are associated with a mixed axonal and demyelinating peripheral neuropathy. Ann Neurol 2001; 49: 214–21.

Cornblath DR, Asbury AK, Albers JW, Feasby TE, Hahn AF, McLeod JG, et al. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Neurology 1991; 41: 617–18.

Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu–associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. Medicine (Baltimore) 1992; 71: 59–72.

Denny-Brown D. Primary sensory neuropathy with muscular changes associated with carcinoma. J Neurol Neurosurg Psychiatry 1948; 11: 73–87.

Donofrio PD, Alessi AG, Albers JW, Knapp RH, Blaivas M. Electrodiagnostic evolution of carcinomatous sensory neuronopathy. Muscle Nerve 1989; 12: 508–13.

Eggers C, Hagel C, Pfeiffer G. Anti-Hu-associated paraneoplastic sensory neuropathy with peripheral nerve demyelination and microvasculitis. J Neurol Sci 1998; 155: 178–81.

Forsyth PA, Dalmau J, Graus F, Cwik V, Rosenblum MK, Posner JB. Motor neuron syndromes in cancer patients. Ann Neurol 1997; 41: 722–30.

Graus F, Elkon KB, Lloberes P, Ribalta T, Torres A, Ussetti P, et al. Neuronal antinuclear antibody (anti-Hu) in paraneoplastic

encephalomyelitis simulating acute polyneuritis. Acta Neurol Scand 1987; 75: 249–52.

Graus F, Bonaventura I, Uchuya M, Valls-Sole J, Rene R, Leger JM, et al. Indolent anti-Hu-associated paraneoplastic sensory neuropathy. Neurology 1994; 44: 2258–61.

Graus F, Keime-Guibert F, Rene R, Benyahia B, Ribalta T, Ascaso C, et al. Anti-Hu associated paraneoplastic encephalomyelitis: Analysis of 200 patients. Brain 2001; 124: 1138–48.

Heidenreich F, Schober R, Brinck U, Hartung HP. Multiple paraneoplastic syndromes in a patient with antibodies to neuronal nucleoproteins (anti-Hu). J Neurol 1995; 242: 210–16.

Henson RA, Urich H. Encephalomyelitis with carcinoma. In: Henson RA, Urich H. Cancer and the nervous system. Oxford: Blackwell Scientific; 1982. p. 314–45.

Liang BC, Albers JW, Sima AA, Nostrant TT. Paraneoplastic pseudo-obstruction, mononeuropathy multiplex, and sensory neuronopathy. Muscle Nerve 1994; 17: 91–6.

Lucchinetti CF, Kimmel DW, Lennon VA. Paraneoplastic and oncologic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology 1998; 50: 652–7.

Molinuevo JL, Graus F, Serrano C, Rene R, Guerrero A, Illa I. Utility of anti-Hu antibodies in the diagnosis of paraneoplastic sensory neuropathy. Ann Neurol 1998; 44: 976–80.

Oh SJ. Clinical electromyography. Nerve conduction studies. 2nd ed. Baltimore: Williams & Wilkins; 1993.

Oh SJ. Paraneoplastic vasculitis of the peripheral nervous system. In: Younger DS, editor. Vasculitis and the nervous system. Neurologic Clinics, Vol. 15, No. 4. Philadelphia: W.B. Saunders; 1997. p. 849–63.

Oh SJ, Dropcho EJ, Claussen GC. Ant-Hu-associated paraneoplastic sensory neuropathy responding to early aggressive immunotherapy: report of two cases and review of literature. [Review]. Muscle Nerve 1997; 20: 1576–82.

Oh SJ, Gurtekin Y, Dropcho E, King P, Claussen GC. Diverse electrophysiological spectrum of anti-Hu antibody positive neuropathy [abstract]. Neurology 2000; 54 Suppl 3: A384.

Pourmand R, Maybury BG. AAEM case report 31: paraneoplastic sensory neuronopathy. Muscle Nerve 1996; 19: 1517–22.

Redford EJ, Hall SM, Smith KJ. Vascular changes and demyelination induced by the intraneural injection of tumour necrosis factor. Brain 1995; 118: 869–78.

van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19: 604–7.

Verma A, Berger JR, Snodgrass S, Petito C. Motor neuron disease: a paraneoplastic process associated with anti-Hu antibody and small-cell lung carcinoma. Ann Neurol 1996; 40: 112–6.

Younger DS, Dalmau J, Inghirami G, Sherman WH, Hays AP. Anti-Hu-associated peripheral nerve and muscle microvasculitis. Neurology 1994; 44: 181–3.