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Follow-up study and response to treatment in 23 patients with Lewis–Sumner syndrome

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Summary

Lewis–Sumner syndrome (LSS) is a dysimmune peripheral nerve disorder, characterized by a predominantly distal, asymmetric weakness mostly affecting the upper limbs with sensory impairment, and by the presence of multifocal persistent conduction blocks. The nosological position of this neuropathy in relation to multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is still debated. We report the clinical, biological and electrophysiological features, the course and the response to treatment in 23 LSS patients. The initial symptoms started in the distal part of an upper limb in 70% of patients. They were sensorimotor in 65% and purely sensory in 35% of patients. A cranial nerve involvement was observed in 26% of patients and a distal limb amyotrophy in 52%. The CSF protein level was normal in 67% of patients and mildly elevated in the remainder. None had serum anti-GM1 antibodies. There were multiple motor conduction blocks (average of 2.87/patient), predominantly located in the forearm, whereas demyelinating features outside the blocked nerves were rare. Abnormal distal sensory potentials were found in 87% of patients. The electrophysiological pattern suggests a very focal motor fibre demyelination sparing the nerve endings, whereas sensory fibre involvement was widespread. The course was chronic progressive in 71% of patients and relapsing–remitting in the others. During the follow-up study (median duration of 4 years), half of the patients progressed with a multifocal pattern and the distribution of the motor deficit remained similar to the initial presentation. The other patients showed a progression to the other limbs, suggesting a more diffuse process. Fifty-four percent of the patients treated with intravenous immunoglobulin showed an improvement, compared with 33% of the patients treated with oral steroids. Overall, 73% of patients had a positive response to immune-mediated therapy. LSS may be distinguished from MMN by the presence of sensory involvement, the absence of serum anti-GM1 antibodies and, in some cases, a positive response to steroids. In some of the patients in our study, LSS evolved into a more diffuse neuropathy sharing similarities with CIDP. Others had a clinical course characterized by a striking multifocal neuropathy, which suggests underlying mechanisms different from CIDP. Overall, whatever the clinical course, LSS responded to immune-mediated treatment in a manner similar to CIDP.

Keywords: Lewis–Sumner syndrome; multifocal acquired demyelinating sensory and motor neuropathy; multifocal motor neuropathy; chronic inflammatory demyelinating polyradiculoneuropathy

Abbreviations: CB = conduction block; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CMAP = compound muscle action potential; CV = conduction velocity; DL = distal latency; IVIg = intravenous immunoglobulin LSS = Lewis–Sumner syndrome; MMN = multifocal motor neuropathy; SNAP = sensory nerve action potential

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Introduction

In 1982, Lewis and colleagues identified, among a group of 40 patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), five patients with a chronic asymmetrical sensorimotor neuropathy mostly of the upper extremities with multifocal involvement of peripheral nerves (Lewis *et al*., 1982). They presented multifocal and persistent motor conduction block (CB). About 50 cases of Lewis–Sumner syndrome (LSS) have been reported, under various terms, upper limb predominant multifocal CIDP (Thomas *et al*., 1996; Gorson *et al*., 1999; Misra and Walker, 2000), chronic multifocal neuropathy with persistent conduction block (Gibbels *et al*., 1993), steroid-responsive multifocal demyelinating neuropathy (Liguori

et al., 1999), multifocal inflammatory demyelinating neuropathy (Van den Berg-Vos *et al*., 2000), multifocal acquired demyelinating sensory and motor neuropathy (Saperstein *et al*., 1999), and motor and sensory demyelinating mononeuropathy multiplex (Oh *et al*., 1997), underlying the difficulty of defining the nosological position of LSS among the dysimmune neuropathies, such as CIDP and multifocal motor neuropathy (MMN) (Parry, 1999). The term CIDP was coined by Dyck and co-workers in 1982 to describe an acquired peripheral neuropathy thought to be of immunological origin (Dyck *et al*., 1982). It was defined as a chronic symmetric sensorimotor polyneuropathy with loss of tendon reflexes, elevated CSF protein level, and peripheral nerve demyelination, as revealed by a slowing of nerve conduction velocities and morphological evidence of primary demyelination. A few years later, Parry and Clarke (1988) reported five patients with a motor syndrome resulting from multifocal conduction block who were very similar to those described by Lewis *et al*. They were considered to have an unusual variant of CIDP in which the demyelination is confined to motor axons. Later, the association of this condition with high titres of IgM autoantibodies directed against GM1 ganglioside (Pestronk *et al*., 1988) and the description of numerous similar cases resulted in this being considered as a separate entity (Nobile-Orazio, 2001). Clarifying the position of LSS among these chronic immune-mediated neuropathies is of therapeutic relevance (Dalakas, 1999), since CIDP shows a beneficial response to plasma exchanges, intravenous immuno globulin (IVIg) and steroids (Hughes *et al*., 2001; Van Doorn and Garssen, 2002), whereas MMN responds to IVIg (Leger *et al*., 2001), but not to steroids or plasma exchanges (Pestronk *et al*., 1988; Donaghy *et al*., 1994).

We review the clinical, biological and electrophysiological features, and the disease course and response to treatment of 23 patients with LSS. The aims of the study were to define the main characteristics of LSS, establish an electrophysiological, and consequently a demyelinating profile of LSS, and determine the neurological prognosis and response to treatment in LSS patients. The present study provides fresh insight into the relationship between LSS, CIDP and MMN and proposes a therapeutic approach to LSS.

Patients and methods

Patients

Between November 1988 and August 2002, among 125 patients with definite CIDP and 60 patients with MMN, we identified 23 patients with LSS, which we defined as a clinical presentation of asymmetrical sensory or sensorimotor neuropathy with definite persistent conduction blocks (Olney *et al*., 2003). Extensive clinical and laboratory evaluation excluded other causes of neuropathy. Patients with pure motor neuropathy or symmetrical polyneuropathy were excluded.

Clinical assessment

Neurological examination was carried out in all patients. Patients were evaluated by a Medical Research Council (MRC) score in the eight most severely affected muscles and a modified Rankin disability scale: 0 = asymptomatic; 1 = non-disabling symptoms that do not interfere with lifestyle; 2 = minor disability symptoms that lead to some restriction to lifestyle, but do not interfere with the patients' capacity to look after themselves; 3 = moderate disability symptoms that significantly interfere with lifestyle or prevent a totally independent existence; 4 = moderately severe disability symptoms that clearly prevent an independent existence although the patient does not need constant attention day and night; and 5 = severely disabled, totally dependent, requiring constant attention day and night.

Neurophysiological investigations

The electrophysiological study was performed using a Viking Nicolet electromyograph. The motor nerve conduction study was performed with supramaximal percutaneous nerve stimulation, whereas compound muscle action potential (CMAP) was recorded with surface monopolar electrodes. The median, ulnar and peroneal nerves were examined on both sides in all patients. The median nerve was stimulated at the wrist, elbow, axilla and Erb's point. The ulnar nerve was stimulated at the wrist, below and above the elbow, at the axilla and at Erb's point. At Erb's point, the nerve was stimulated with monopolar surface electrodes. The peroneal nerve was stimulated at the ankle, below and above the fibular head. The skin temperature was maintained at 36°C during the nerve conduction study. For each nerve, distal latency (DL), conduction velocity (CV), CMAP amplitude (baseline to negative peak), areas under negative phase and CMAP duration were measured. For each nerve segment, the reduction in CMAP amplitude or area on proximal versus distal stimulation was calculated. To define CB, we used the consensus criteria of the American Association of Electrodiagnostic Medicine (Olney *et al*., 2003). A definite partial CB required a reduction in amplitude of 50% for the arm and forearm, and 60% at Erb's point and below the fibular head, without significant temporal dispersion. The CB had to be located outside the usual sites of compression. F-wave latency was recorded after distal supramaximal stimulation (at least 20 stimuli) in the median, ulnar and peroneal nerves. Reduced CV, prolonged DL and prolonged F-wave latency indicating demyelination were defined according to the criteria developed by the American Academy of Neurology Ad Hoc Task Force for CIDP (1991). Sensory nerve action potential (SNAP) amplitude (peak to peak) was measured in the median, ulnar and superficial peroneal nerves with surface recording and stimulating electrodes. A needle electromyographic examination was performed in all patients.

Biological investigations

Protein electrophoresis was performed and CSF was examined. IgM anti-ganglioside antibodies were detected and titrated by immunodot using commercially available purified gangliosides (Sigma, St Louis, MO). Each serum sample was tested against a panel of gangliosides (GM3, GM2, GM1, GD1a, GD1b and GT1b) already coated on a PVDF membrane

(Millipore, Bedford, MA). Patients' serum reactivity was tested at the first dilution of 1 : 100 (reaction cut-off) and titrated by serial 2-fold dilution until negative. After incubation of diluted serum with the strip and washes, peroxidase goat anti-human IgM was added to bind specific antibodies. After washing, 4-chloro-1-naphthol substrate solution allowed purple coloration of the antibody-reacted antigen spots. When positive, anti-light chains κ and λ were used following the same dilution process.

Treatment procedures

Treated patients received either a course of IVIg (2 g/kg over 3–5 days) once a month for 2 months, or prednisone (1 mg/kg/day for 4 weeks followed by tapering therapy for 6 weeks). Patients who did not respond well to this first-line treatment subsequently received the alternative treatment. Patients were considered to have responded to either treatment if motor strength improved by at least two MRC grades in any muscle and/or by a one-point gain in the disability score. The frequency of treatment administration during the follow-up was tailored to each patient on the basis of clinical examination and functioning in daily life.

Results

Clinical features

The main clinical features of LSS patients are summarized in Table 1. There were 17 men and six women. The age at onset ranged from 22 to 72 years, with a median age of 44 years. The median duration of symptoms was 24 months at the time of diagnosis (range 2–168). The initial symptom occurred in an upper limb in 16 patients (70%). The site of the neurological deficit was always distal, mostly in the median or ulnar territories. One-third (30%) of the patients initially presented a sensorimotor deficit affecting a lower limb with foot drop and distal paraesthesia. Three patients had an associated proximal deficit (weakness and amyotrophy of quadriceps in cases 13 and 15 and lateral femoral cutaneous nerve sensory involvement in case 12). Onset of symptoms was unilateral in 17 patients (74%) and bilateral though asymmetrical in six (26%). Five patients presented a unifocal onset affecting the median nerve territory (case 1), the ulnar nerve territory (case 9), the radial nerve territory (case 5) or the peroneal nerve territory (cases 14 and 17). The first symptom was sensorimotor in 15 patients (65%) and sensory in eight (35%). The most common sensory symptom was numbness and paraesthesia. Five patients (22%) also presented neuropathic pain (cases 3, 8, 9, 13 and 16).

Laboratory findings

The CSF protein content was normal in 12 out of 18 patients (67%) and mildly elevated in six (ranging from 52 to 100 mg/dl with an average of 71 mg/dl) (Table 1). Thirteen patients were tested for IgM and IgG anti-GM1 antibodies and all were negative. None of the patients had monoclonal gammopathy.

Electrophysiological data

Conduction blocks

The number and topography of CBs are shown in Table 2. Twenty-one patients had definite partial CB, and two had

Table 1 *Clinical and biological characteristics of 23 patients with Lewis–Sumner syndrome*

Patient	Age at onset (years)/sex	Duration of symptoms (months)	Initial symptom	Upper limb involvement	Lower limb involvement	Distal amyotrophy	Cranial nerve palsy	CSF protein level (mg/dl)
1	54/F	108	SM	+	−	−	−	ND
2	70/M	12	SM	+	−	−	−	ND
3	40/M	24	S	−	+	+	−	38
4	54/M	4	SM	+	−	+	−	40
5	48/M	72	SM	+	−	+	−	52
6	22/M	120	SM	+	−	+	III, IV	35
7	42/M	48	S	+	+	−	−	ND
8	46/M	24	SM	+	−	+	−	ND
9	40/M	24	S	+	−	−	−	36
10	29/M	4	SM	+	−	+	II, V	95
11	72/M	2	SM	+	−	+	−	40
12	37/M	8	SM	+	−	−	VII	36
13	28/F	168	S	−	+	+	−	ND
14	68/M	48	SM	−	+	−	VII	54
15	56/M	6	SM	+	+	+	−	42
16	60/F	72	S	−	+	−	−	57
17	42/M	60	SM	−	+	+	−	70
18	31/F	48	S	+	−	+	V	40
19	46/M	24	SM	+	−	+	−	38
20	44/M	24	S	+	−	−	−	100
21	22/F	36	S	+	−	−	−	35
22	39/F	8	SM	+	−	−	−	37
23	46/M	23	SM	+	+	+	−	39

F = female; M = male; S = sensory; SM = sensorimotor; + = present; − = absent; ND = not determined.

Table 2 *Electrophysiological data in patients with Lewis–Sumner syndrome*

Patient	No. of CBs	Topography of CB*			Demyelinating features on motor nerves			SNAP
		Median nerve	Ulnar nerve	Peroneal nerve	Reduced CV†	Abnormal F waves‡	Prolonged DL§	No. of nerves with abnormal distal SNAP
1	1	1 (D)						1
2	2		1 (D)	1				6
3	2		1 (I)	1	+			2
4	3	1 (I)	2 (I)		+			3
5	4		3 (D, P)					4
6	4	2 (D)	1 (D)	1	+		+	4
7	2	2 (D, I)						3
8	1		1 (D)			+		4
9	2		2 (D)			+	+	2
10	6	3 (2D, I)	3 (D)		+			1
11	2	2 (P)					+	4
12	5	3 (2D, I)	2 (I, P)				+	1
13	2	1 (D)	1 (D)		+			2
14	1		1 (D)					4
15	1		1 (P)					6
16	2		2 (D, I)			+		3
17	3	2 (D, P)	1 (P)			+		1
18	5	1 (D)	2 (D)	2			+	4
19	2	1 (P)	1 (I)					3
20	3	2 (D)	1 (I)			+	+	4
21	4		4(D, 2I, P)					0
22	6	4 (2D, 2P)	2 (D)				+	0
23	3	1 (D)	2 (D, I)			+		0

*D = distal (forearm); I = intermediate (axillary-elbow); P = proximal (Erb's point-axillary); † + indicates the presence of a reduced CV, indicating demyelination outside blocked nerves in at least one nerve; ‡ + indicates the presence of a prolonged F-wave latency or an absent F wave outside blocked nerves in at least one nerve; § + indicates the presence of a prolonged DL in at least one nerve.

probable partial CB. The degree of CB ranged from 40 to 97%, with a mean of 61%. Four patients (17%) had only one CB, and 11 patients (48%) had three or more CBs. The average number of CBs per patient was 2.87. All patients had CB in an upper limb. Four patients also had CB in the lower limbs. In the upper limbs, 53% of CBs were found on the ulnar nerve, and 40% on the median nerve; in the lower limbs, 7% of CBs were located on the peroneal nerve. In the upper limbs, 59% of CBs were distal (in the forearm), 23% were intermediate (between the axilla and elbow) and 18% were proximal (between Erb's point and the axilla). The majority of patients had at least one distal CB, but 22% of patients had only proximal or intermediate CBs. In the lower limbs, all CBs were located below the fibular head on the peroneal nerve.

Motor nerve conduction velocity

Slowing of CV, indicating demyelination, was found in at least one nerve in 19 patients (83%), but reduced CV was observed predominantly in the territory of the blocked nerves. Only five patients had a reduction in CV in one nerve segment outside the territory of the blocked nerves (Table 2). CV was reduced across the blocked segment in 76% of nerves with CB. Every nerve studied had at least one segment with normal CV, and diffuse reduced CV was not observed along any of the examined nerves.

F-wave latency

A prolonged F-wave latency or an absent F wave in at least one nerve was observed in 19 patients (83%), but few patients had an abnormal F wave outside the blocked nerve territory (Table 2). F-wave latency was abnormal in 58% of nerves with CB and in only 17% of nerves without CB. The frequency of abnormal F-wave latency was higher (75%) on nerves with reduced CV than on nerves with normal CV (9%). None of the patients presented abnormal F waves and reduced CV in any of the nerves without CB.

Distal latency and distal CMAP amplitude

Prolonged DL was found in seven patients (30%) and was observed mostly on nerves with CB (Table 2). A reduced distal CMAP amplitude in at least one nerve was found in 13 patients (56%) and was correlated with muscle atrophy in nine of these patients. The distal CMAP amplitude was reduced on 22% of nerves with CB and 26% of nerves without CB. However, CB was difficult to demonstrate in the presence of a marked reduction of distal CMAP amplitude.

Sensory nerve action potential

Distal SNAP was abnormal (amplitude reduction or absence) in 20 patients (87%). The sensory involvement was diffuse and asymmetrical. Overall, a mean of 50% of SNAPs were altered

per patient. An abnormal sensory potential was found in 57% of nerves with CB, and in 38% of nerves without CB. Most patients (65%) had at least one abnormal sensory potential on a nerve without CB. Three patients had normal distal SNAP: case 21 had only sensitive symptoms, and cases 22 and 23 had a sensorimotor deficit with prominent sensory manifestations and an alteration of the proximal sensory evoked potential.

Needle EMG findings

Needle EMG showed fibrillation potentials, at rest, in distal muscles in six patients.

Follow-up study

Disease course and response to treatment are summarized in Table 3.

Disease course

Two patients (cases 2 and 11) died due to cardiovascular failure just after the diagnosis. The disease course in the remaining 21 patients was studied with a median duration of follow-up of 4 years (range 1–14). During the course of the disease, atrophy of weak muscles was observed in 13 patients (52%). Six patients (26%) had a cranial nerve involvement, namely trigeminal sensory neuropathy in three cases, facial neuropathy in two, oculomotor palsy in two and optic neuritis in one. The disease was progressive in 15 patients (71%) and the course was relapsing–remitting in six patients (29%). Spontaneous stabilization occurred early in the history of the disease in six patients (cases 3, 4, 7, 13, 15 and 21). In one group of nine patients (cases 1, 3, 8, 14, 16, 17, 18, 20 and 23), the neurological deficit progressed to the other limbs, suggesting a diffuse process. In this group, the mean duration of the follow-up study was 5.4 years (range 1–14). The sensory deficit became symmetrical in all patients but one (case 23). Four patients had ataxia (cases 14, 17, 20 and 23). The weakness remained distal and asymmetrical in four patients (cases 14, 18, 20 and 23). The weakness became symmetrical and distal in two patients (cases 8 and 17). One patient had symmetrical proximal weakness of the lower limbs (case 1), and in two patients the disease progressed with pure sensory symptoms (cases 3 and 16). All these patients had generalized areflexia, except for two patients with asymmetrical absent reflexes (cases 18 and 20). In another group of nine patients (cases 4, 5, 6, 7, 9, 13, 15, 19 and 21), the clinical pattern remained similar to the initial presentation despite a mean course of 5.8 years (range 1–14). The deficit was distal and asymmetrical in all these patients. An extension to the proximal region of the affected limb was observed in two patients (cases 6 and 19). In two other patients, the symptoms remained purely sensory (cases 7 and 21). In this group, tendon reflexes were either normal or absent in a multifocal distribution (cases 6, 7, 13 and 19). Three patients (cases 12, 22 and 10) had complete remission after treatment, as determined at the last follow-up.

Table 3 *Follow-up study and response to treatment in patients with Lewis–Sumner syndrome*

Patient	Duration of follow-up (months)	Course	First-line treatment	Response to treatment	Second-line treatment	Response to treatment	Third-line treatment	Response to treatment
1	168	Progressive	IVIg	Yes	Prednisone	No	IVIg + Az	Yes
2		Progressive	Untreated*					
3	24	Progressive	Prednisone	No	IVIg	Stabilization		
4	7	Relapsing	Untreated‡					
5	78	Progressive	IVIg	No	Prednisone	No	IVIg	Yes
6	120	Progressive	Untreated†					
7	60	Progressive	Untreated‡					
8	27	progressive	IVIg	No				
9	46	Progressive	IVIg	Yes	prednisone	No	IVIg	Yes
10	36	Relapsing	prednisone	Yes				
11	2	Unknown	Untreated*					
12	12	Progressive	IVIg	No	Prednisone	Yes		
13	168	Progressive	IVIg	No	Prednisone	No		
14	60	Progressive	IVIg	No	Prednisone	Yes		
15	22	Relapsing	Untreated‡					
16	78	Progressive	IVIg	Yes	Prednisone	No		
17	96	Progressive	Prednisone	No	IVIg	Yes	IVIg + Az	Yes
18	48	Progressive	Prednisone	Yes				
19	84	Progressive	Untreated‡					
20	60	Relapsing	IVIg	Yes				
21	36	Relapsing	Untreated‡					
22	12	Relapsing	IVIg	Yes				
23	36	Progressive	IVIg	Stabilization	Prednisone	No	IVIg + Cyclo	Yes

*Died before treatment; †lost to follow up; ‡not severe enough to be treated. Az = aziathioprine; Cyclo = cyclophosphamide.

Response to treatment

Five patients (22%) (cases 4, 7, 15, 19 and 21) were not treated because their neurological state was not considered severe enough. Two patients (cases 2 and 11) died before receiving any treatment. One patient (case 6) was lost to follow-up. Overall, 15 patients were treated.

Eleven patients (cases 1, 5, 8, 9, 12, 13, 14, 16, 20, 22 and 23) were treated with IVIg as first-line therapy. Two patients (cases 20 and 22) fully recovered after the first infusion, for 1 and 2 years, respectively. Three patients (cases 1, 9 and 16) experienced a transient response and became IVIg dependent. One patient (case 23) was stabilized but with a handicap that required regular, repeated infusions. One patient (case 5) responded to IVIg only after four infusions. Four patients (cases 8, 12, 13 and 14) did not respond to IVIg treatment. They were treated subsequently with prednisone, and two (cases 12 and 14) improved with this treatment. Two patients (cases 3 and 17) were treated with IVIg as second-line therapy; one (case 17) improved but became dependent on IVIg, and the other case (case3), with repeated infusions, was stabilized but with a handicap. Four patients (cases 3, 10, 17 and 18) received prednisone as first-line therapy. Two (cases 10 and 18) made a recovery lasting 3 years and 1 year, respectively. The other two experienced no improvement and were treated subsequently with IVIg. Only one of them (case 17) improved with this treatment. Eight patients (cases 1, 5, 9, 12, 13, 14, 16 and 23) received prednisone as second-line therapy. These patients had received IVIg as first-line therapy but were non-responders, were dependent on IVIg or had persistent neuropathic pain. One made a full recovery (case 12) and another improved (case 14) but with steroid dependence. The others did not improve, and case 5 showed a moderate deterioration. The association of azathioprine (150 mg/day) and IVIg was tried in two patients (cases 1 and 17), which allowed the IVIg infusions to be delayed in one case (case 17). Case 23 had a 9 month treatment with cyclophosphamide (100 mg/day) and was stabilized during this period. However, he developed a thrombocytopenic purpura and needed splenectomy; he died 15 days later from acute infectious respiratory distress.

Overall, 11 out of 15 patients (73%) responded to immune-mediated therapy. One-third of the responders experienced a prolonged recovery, whereas the others developed dependence on the treatment. Two patients were stabilized but with a handicap. Two patients (cases 8 and 13) did not respond either to IVIg therapy or to steroids. Fifty-four percent of the patients treated with IVIg showed an improvement, compared with 33% of the patients treated with oral steroids.

Discussion

In this study, the inclusion criteria were both clinical and electrophysiological, and were closely related to the initial description by Lewis and Sumner (Lewis *et al*., 1982). Patients with a clinical pattern of CIDP and multifocal CB were excluded. Patients with a pure motor neuropathy who developed a secondary sensory involvement were also excluded. We identified 23 LSS patients over a 14 year period. In our experience, LSS is five times less frequent than CIDP. We found a male predominance (sex ratio M/F: 2.83), which is a constant feature of LSS (Oh *et al*., 1997; Gorson *et al*., 1999; Saperstein *et al*., 1999; Van den Berg-Vos *et al*., 2000), except in the first description by Lewis and colleagues (sex ratio M/F: 0.2) (Lewis *et al*., 1982). The mean age at onset ranged between 40 and 50 years (Oh *et al*., 1997; Gorson *et al*., 1999; Saperstein *et al*., 1999; Van den Berg-Vos *et al*., 2000) as in CIDP (Maisonobe *et al*., 1996) and MMN patients (Bouche *et al*., 1995). The initial symptoms usually affected an upper limb with a distal topography. Symptoms were sensorimotor in two-thirds of our patients. A pure sensory onset with numbness and paraesthesia in the median or ulnar territory was observed in only one-third of our patients, whereas this presentation concerned 50% (Van den Berg-Vos *et al*., 2000) or 80% (Lewis *et al*., 1982) of patients in other reports. Pain was a rare symptom (22% of our patients), as reported elsewhere (Saperstein *et al*., 1999; Van den Berg-Vos *et al*., 2000), whereas others have reported it to be a prominent symptom (Lewis *et al*., 1982; Gorson *et al*., 1999). A lower limb onset with a distal and asymmetrical sensorimotor deficit was found in one-third of our patients. An electrophysiological study limited to the lower limbs may therefore lead to a misdiagnosis. During the course of the disease, cranial nerve involvement was present in 26% of our patients, a similar result to that reported elsewhere (Saperstein *et al*., 1999; Van den Berg-Vos *et al*., 2000), whereas 40% of the patients in the study by Lewis *et al*. had cranial nerve palsy (Lewis *et al*., 1982). Trigeminal, facial and oculomotor nerve involvement was observed. One patient had optic neuritis, a finding also noted in the study by Lewis *et al*. Distal amyotrophy was observed in half of our patients (Lewis *et al*., 1982). Proximal weakness was rare and affected only five patients. Four patients had a pure sensory form of the disease.

The course of the disease followed one of two distinct patterns. In half of the patients, the disease progressed with a multifocal pattern and the distribution of the deficit remained similar to that of the initial presentation. In the other half of the patients, the disease progressed to other limbs, suggesting a more diffuse process. In the latter group, the sensory deficit became more symmetrical. Weakness became symmetrical, distal or proximal, in three patients. Four patients presented bilateral but asymmetrical weakness. This feature was also observed by Lewis *et al*. and Oh *et al*., who described generalized neuropathy with superimposed multifocal nerve trunk abnormalities (Lewis *et al*., 1982) or asymmetrical polyneuropathy (Oh *et al*., 1997) at the patients' maximal disability. The course was progressive in two-thirds of our patients and relapsing–remitting in the remaining third. Van den Berg-Vos *et al*. found a high proportion of the relapsing form (66%) (Van den Berg-Vos *et al*., 2000), whereas Gorson *et al*. observed a predominantly progressive course (90%) (Gorson *et al*., 1999).

In line with most reports, all of the patients tested were negative for IgM anti-GM1 antibodies. CSF protein levels

were normal in the majority of our patients, whereas Saperstein *et al*. and Oh *et al*. (Oh *et al*., 1997; Saperstein *et al*., 1999) reported a frequent occurrence of elevated CSF protein levels; however, the elevation they reported was moderate, with a mean value of 70 mg/dl, as in our study.

Electrophysiologically, our LSS patients were characterized by an elevated number of marked CBs, which were predominantly located in the upper limbs, even in patients with predominantly lower limb involvement. They were mostly located in the forearm, although 22% of the patients had only proximal CB, emphasizing the importance of stimulating the nerves as proximal as Erb's point. Demyelinating features outside the blocked nerves were rare, and no patients had a widespread alteration of nerve conduction. The pattern of demyelination in LSS seemed relatively to spare the nerve endings, as prolonged DL or isolated F-wave abnormalities were not frequent. Normal CSF protein in the majority of patients was an additional argument in favour of the rarity of very proximal nerve segment demyelination. These observations suggest a very focal or multifocal pattern of demyelination affecting the middle nerve segment in LSS. Unlike motor fibre demyelination, sensory involvement was widespread and exceeded the blocked nerve territories. Distal sensory potential was abnormal in most cases. In a few cases, it was normal, contrasting with the presence of sensory symptoms suggesting a more proximal sensory involvement, as demonstrated by abnormal sensory evoked potential.

In a review of the literature, we assessed the therapeutic responsiveness of LSS in a number of isolated cases or small series (Lewis *et al*., 1982; Oh *et al*., 1997; Gorson *et al*., 1999; Saperstein *et al*., 1999; Van den Berg-Vos *et al*., 2000). About two-thirds of patients responded to steroids and 50–70% of patients showed a beneficial response to IVIg (Pouget *et al*., 2001). In our study, based on a larger cohort, 54% of patients responded to IVIg and 33% responded to steroids. Overall, we observed a beneficial response to immune-mediated treatment in 73% of patients.

In our study, the long duration of follow-up allowed an assessment to be made of the prognosis of LSS. The disease was not necessarily severe initially. An initial spontaneous stabilization was even observed in 26% of patients. Half of our patients presented a good outcome: five needed no treatment and five had a prolonged recovery after therapy. About 40% of patients were treatment dependent because of persistent neurological disorders requiring maintenance of therapy. The non-responder rate was $\sim$10%.

Our study of the main characteristics of LSS provides fresh insight into its relationship with CIDP and MMN. LSS and CIDP have similar features. Both are demyelinating sensorimotor neuropathies with possible cranial nerve palsy and a progressive or remitting course. Responsiveness to IVIg and corticosteroids is nearly identical in LSS and CIDP. Sural nerve biopsies in LSS show elements consistent with primary demyelination, indistinguishable from those seen in typical CIDP (Lewis *et al*., 1982; Oh *et al*., 1997; Bouchard *et al*., 1999; Gorson *et al*., 1999; Saperstein *et al*., 1999; Van den Berg-Vos *et al*., 2000; Vallat *et al*., 2003). The clinically distinct features concern the predominance of upper limb involvement and the asymmetrical and distal topography in LSS, even if asymmetry may also be encountered in CIDP. The CSF protein level is normal or mildly elevated in LSS, whereas 50% of CIDP patients presented a CSF protein level >100 mg/l (Maisonobe *et al*., 1996). The pattern of demyelination in LSS seems to be more focal, principally affecting the middle nerve segment, and distinguishes it from the diffuse pattern commonly observed in CIDP. In fact, the pattern of demyelination in CIDP may be heterogeneous, with diffuse, multifocal, distal or proximal demyelination (Kuwabara *et al*., 2002). The neurological progression towards a diffuse pattern in half of our patients suggests that LSS might be an initially focalized variant of CIDP. In contrast, the pattern that remained multifocal after a disease course of several years in the other patients rather suggests an inflammatory and demyelinating process restricted to some areas of the PNS. This focal pattern may suggest that some local immunological determining factors, especially in the upper limbs, are involved in the physiopathological mechanisms of LSS. This particular pattern could also be due to a self-limiting process induced by an appropriate anti-inflammatory response that limits the diffusion of lesions.

MMN is a pure motor neuropathy whereas LSS has a clinical and electrophysiological sensory involvement. Even though MMN patients may have mild distal paraesthesia (Nobile-Orazio, 2001), the clinical pattern is dominated by the motor deficit. In LSS, sensory manifestations frequently are the presenting symptoms and they are at least as severe as the motor involvement. This vulnerability of the sensory fibres to the demyelination process in LSS is a major difference from MMN. The absence of anti-GM1 antibodies in the sera of LSS patients is another argument to suggest that MMN and LSS are physiopathologically different. The positive response to corticosteroids in some LSS patients is another substantial difference between LSS and MMN. However, some MMN patients may develop a multifocal sensorimotor syndrome later in the disease course (Parry and Clarke, 1988), indicating that a continuum may exist between MMN and LSS.

In conclusion, LSS appears to be a sensory or a sensorimotor asymmetrical neuropathy with an upper limb predominance, in which the sensory and motor manifestations have an equal importance. Sensory symptoms are present at the onset of the disease. The predominant electrophysiological features are the presence of motor CB contrasting with a mild degree of demyelination outside the blocked nerve territory. In addition, there is a multifocal alteration of the sensory potentials. LSS could be considered as a variant of CIDP. In order to justify a nosological distinction between LSS and CIDP, it will have to be proven that there are differences in the pathological mechanisms underlying them. For LSS patients, we propose a therapeutic approach similar to that of CIDP, with a first-line treatment with IVIg (2 g/kg/course). Patients who do not respond after two or three courses should be switched to

prednisone (1 mg/kg/day), which should be maintained for 4–6 weeks, then slowly tapered.

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