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Involvement of sensory fibres in axonal subtypes of Guillain-Barré syndrome

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ABSTRACT

Background: Acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN) are due to an anti-ganglioside antibodies-mediated attack thought to be restricted to motor fibres in AMAN. Sensory symptoms and minor sensory conduction abnormalities, however, have been reported in some AMAN patients.

Objective: To verify whether sensory fibres are truly spared in AMAN and whether AMAN and AMSAN represent a continuum.

Methods: We reviewed serial conduction studies in 13 AMAN and three AMSAN patients. To evaluate the variation of sensory nerve action potential (SNAP) amplitude in serial recordings, we calculated the least significant change (LSC) in a test-retest study of 20 controls. LSCs for median, ulnar and sural nerves were 44%, 47% and 58%.

Results: In 34% of initially normal sensory nerves of six AMAN patients, SNAP amplitude significantly increased by 57-518%. In three nerves of three AMAN patients, SNAP significantly decreased by 50-69%. **Overall, serial recordings allowed to detect sensory fibres involvement in 49% of nerves and in 69% of AMAN patients.** In one AMSAN patient, SNAP increased in two nerves by 150-300%; in another patient, SNAPs, unrecordable at baseline in six nerves, reappeared during follow-up and normalize in three nerves. In five nerves of three AMAN and in eight nerves of two AMSAN patients, SNAP amplitudes increased rapidly suggesting reversible conduction failure of sensory fibres. In other nerves SNAP increased over months as for axonal regeneration.

Conclusions: Sensory fibres are often involved subclinically in AMAN. Reversible conduction failure may develop in sensory as well as in motor fibres in both AMAN and AMSAN. AMAN and AMSAN represent a continuum in axonal GBS.

INTRODUCTION

Guillain-Barré syndrome (GBS) has been divided into several subtypes according to clinical, electrophysiological and pathologic findings, infective antecedent and presence of specific antibodies.[1-2] Two primary axonal subtypes have been described: acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN).[3-7] AMAN and AMSAN have been associated with antecedent *Campylobacter jejuni* infection and autoantibodies to gangliosides, especially to GM1 and GD1a.[4-9] AMAN is clinically characterized by exclusive motor involvement although sensory symptoms have been also reported.[3-4,10-11] Immunopathological studies in humans and in the rabbit experimental model indicated that AMAN is due to a complement-mediated attack of anti-ganglioside antibodies to the axolemma of nodes of Ranvier of motor fibres with complement deposition, sodium channel cluster disruption, nodal lengthening, macrophage recruitment and final axonal degeneration in motor fibres.[12-15] The electrophysiological characteristics of AMAN are absence of demyelinating features and decreased distal compound muscle action potentials (dCMAP).[3-4] However, reduced dCMAP amplitudes, conduction block (CB) at common entrapment sites or isolated absence of F waves which promptly recover without the development of temporal dispersion or other demyelinating features have been described in some AMAN patients with anti-ganglioside antibodies and ascribed to an antibody-mediated reversible conduction impairment at the axolemma of nodes of Ranvier.[16-18] **AMSAN is quite rare (1-4% of GBS in Japan) eventhough it has been reported up to 11% in Bangladesh. [9,19-20]** AMSAN is clinically characterized by weakness, areflexia and sensory loss. Most of reported patients had severe weakness requiring mechanical ventilation,

inexcitable motor and sensory nerves and poor outcome.[21-23] In AMSAN, as in AMAN, the pathology is consistent with an antibody-mediated primary axonal damage at the node of Ranvier with the difference that the dorsal, as well as the ventral roots, are affected.[22-23] However, minor conduction abnormalities in sensory nerves have been reported in 5-12% of AMAN patients blurring the dichotomy between AMSAN and AMAN.[3,4,11]

Aim of this study was to investigate, by comparing results of serial recordings, whether sensory fibres are completely or relatively spared in AMAN and to verify whether axonal GBS subtypes form a continuous spectrum.

SUBJECTS AND METHODS

Patients

We reviewed the clinical and electrophysiological records of patients diagnosed with GBS at the University Hospital of Chieti between January 1995 and June 2009. Patients were classified as AMAN on the basis of the following criteria: 1) acute onset progressive motor weakness of more than one limb; 2) **normal sensory examination**; 3) dCMAP amplitudes <80% of lower limit of normal (LLN) in at least two nerves **without evidence of demyelination** (*AMAN with axonal degeneration*) or evidence of reversible conduction failure characterized by: reduced dCMAP amplitude **with normal or slightly prolonged distal motor latencies (DMLs)** and/or partial CB (defined as an amplitude ratio of CMAPs from proximal and distal stimulation less than 0.5) in intermediate nerve segments which, at serial recordings, recovered **within 6 weeks** without developing temporal dispersion (**increased duration of negative peak of proximal CMAP >30% compared with dCMAP**) or conduction slowing (*AMAN with reversible conduction*

failure); 4) normal or reduced sensory nerve action potential (SNAP) amplitudes not fulfilling the criteria for diagnosis of AMSAN.[5,16,22,24-25] Patients were classified as AMSAN on the basis of the following criteria: 1) acute onset progressive motor weakness of more than one limb and **loss of at least one sensory modality**; 2) results of motor nerve conduction studies as in AMAN; 3) SNAP amplitude <50% of LLN in at least two nerves.[5,22]

The final electrodiagnosis was based on the results of sequential studies and considering the whole electrophysiological history in each patient.

Electrophysiological studies

Motor conduction studies of median, ulnar, peroneal and tibial nerves were performed as previously reported.[25] Amplitude and duration of negative peak of dCMAP and CMAP from proximal stimulation (pCMAP), conduction velocities (CV), distal motor latencies (DMLs) and minimal F-wave latencies were measured. For sensory conduction, median and ulnar nerves were stimulated at the proximal wrist crease and sensory nerve action potentials (SNAPs) were antidromically recorded by ring electrodes placed at the interphalangeal joints of the third and fifth digit respectively. In selected patients median nerves were also stimulated at elbow, ulnar nerves were stimulated below elbow and above elbow, and SNAP amplitude ratios were calculated. Sural nerve was stimulated at the lateral malleolus and SNAP recorded orthodromically by a bar electrode placed slightly lateral to the midline in the lower third of the posterior aspect of the leg. SNAPs were obtained by averaging at least 8 responses to 1 Hz supramaximal stimuli, latencies were measured to the first deflection from baseline, and amplitudes were measured baseline to negative peak. Limb temperature was

maintained at 32-34 C°. For DML, CV and F wave latency we defined the upper and lower limit of normal (ULN and LLN) as the mean \pm 2.5 SD of control values of our laboratory. For CMAP and SNAP amplitudes the LLN was calculated as the mean - 2.5 SD of the logarithmically transformed amplitudes of the controls. Normal values for sensory nerve studies are: for median nerve, SNAP amplitude \geq 11 μ V and sensory conduction velocity (SCV) \geq 49 m/s; for ulnar nerve, SNAP amplitude \geq 10 μ V and SCV \geq 49 m/s; for sural nerve, SNAP amplitude \geq 6 μ V and SCV \geq 40 m/s. Control values for SNAP amplitude ratios, obtained from 20 median and 20 ulnar nerves of 10 healthy subjects (mean age 34.5 years, range 23-52) are: median, elbow to wrist = 0.49 ± 0.07 (range 0.35-0.6); ulnar, below elbow to wrist = 0.46 ± 0.09 (range 0.31-0.58); ulnar, above elbow to below elbow 0.78 ± 0.09 (range 0.6-0.93).

Definition of significant changes in serial sensory conduction studies

To evaluate the extent of variation in serial recordings of SNAP amplitudes we made a test-retest study in 20 volunteers (median age 55 years, range 23-87). In each subject, median, ulnar and sural nerve conductions were repeated one week apart by four examiners for a total of 480 recordings. We determined the root-mean-square percent coefficient of variation (RMS-%CV) of SNAP amplitude and calculated the least significant change (LSC), i.e the minimum difference between two results that can be considered to reflect a true change at a 95% statistical confidence level. The LSC was calculated by the formula: RMS-%CV x 2.77.[26] SNAP amplitudes were considered significantly increased or decreased compared to a precedent study when the value varied by at least 44% for median nerve, 47% for ulnar nerve and 58% for sural nerve.

Anti-ganglioside antibody testing

IgG and IgM to gangliosides GM1, GD1a and GD1b were tested by ELISA as previously described.[27] Serum was considered positive when showing anti-ganglioside antibodies of IgG class with a titre \geq 1:400.

Statistical analysis

Two-sided Fisher's exact test was employed to explore the association of anti-GD1b antibodies with sensory symptoms, pain, sensory signs, involvement of sensory fibres electrophysiologically demonstrated at baseline and throughout the study. Bonferroni's adjustment for multiple tests was applied and, to get an overall alpha level of 0.05, values of $p < 0.01$ in single tests were considered as significant.

RESULTS

Clinical and laboratory findings

From a series of 116 consecutive GBS patients, thirteen patients diagnosed with AMAN and three diagnosed with AMSAN had at least two examinations of motor and sensory conduction in the same nerves within 5 months from onset **and an optimal quality of sensory recordings**, and were considered for the present study (Table 1). Twelve patients were men (75%). **Median age was 63 years** (range 17-81). All patients presented with symmetric limb weakness.

In the AMAN group, paresthesia were present in 2 of 13 (15%) and pain in 4 of 13 (31%) patients. **Deep tendon reflexes (DTR) were absent or hypoactive and absent distally in eight patients, preserved (diffusely hypoactive or normal) in**

four, and brisk in one. One patient had dysphagia, none had respiratory failure or dysautonomia. CSF examination showed albumino-cytological dissociation in 11 patients. Nine patients were treated with IVIg (2 g/kg in 5 days), the remainders received a course of 3-5 plasmaphereses.

All three AMSAN patients had absent or reduced DTR, paresthesia in the extremities and glove-stocking sensory loss for all modalities. Patients 14 and 15 had albumino-cytological dissociation at CSF examination and were treated with IVIg. Patient 14 developed facial diplegia, dysphagia, and respiratory failure and died during the third week of illness. Patient 16 had pain, severe gait ataxia, and involvement of facial and lower cranial nerves requiring nasogastric tube for feeding. CSF examination five days after onset was normal. This patient received a course of five plasmaphereses.

Electrophysiological findings

Baseline electrophysiological examination was performed within 15 days from onset of symptoms (median: 7 days; range: 2-15) in at least three motor and three sensory nerves. The second test was performed 2-18 days after the first examination in 13 patients, and 37-146 days after the first examination in three patients. Eight patients received further evaluations. Patients 2, 8, 15 and 16 who were admitted when this study was already in course, were prospectively studied for motor and sensory conductions. The total number of electrophysiological examinations was 48. The total number of sensory nerves re-examined in subsequent recordings was 47.

Following are the results of serial electrophysiological studies. For clearness sake we present electrophysiological findings by dividing patients in four groups:

AMAN with axonal degeneration, AMAN with reversible conduction failure, AMAN with axonal degeneration and minor sensory abnormalities, and AMSAN. Serial sensory conduction studies are fully reported in Table 2 in order to make easier to follow description and summary of results .

AMAN with axonal degeneration

In patients 1-8, baseline electrophysiological examination showed dCMAP amplitudes < 80% of LLN in at least two nerves and no signs of demyelination. In subsequent recordings, dCMAP remained stable or further decreased and moderate to abundant fibrillation potentials were found. In patients with long-term follow-up, improvement of dCMAP amplitude was seen by weeks 11-32 (median: 20 weeks). These patients had normal sensory studies at baseline and were classified as AMAN with axonal degeneration pattern.

In Patients 1 and 2, sensory conduction did not substantially change at follow-up. Six patients (Patients 3-8) showed significant changes in SNAP amplitude in re-tested nerves (Table 2). In particular, in Patients 3 and 4, median nerve SNAP decreased by 50-69% and become abnormal within the three weeks after onset (Fig 1A). In Patient 5, SNAP amplitude of the right ulnar, median and sural nerves significantly increased within 4 weeks from onset up to 518% of the baseline value (Fig 1B). In Patients 6 and 7, the amplitude of sural SNAP increased by 207% at day 52 after onset and by 138% at day 102 respectively. In Patient 8, left ulnar SNAP amplitude decreased by 64% nine days after onset to recover in 80 days and be increased by 57% compared to baseline at day 191. SNAP amplitude of left median nerve gradually increased by 59% compared to

baseline, and SNAP amplitude of right median and ulnar nerves was found significantly increased by 63-105% at day 191 (Fig 1C).

AMAN with reversible conduction failure

Patients 9,10,11 showed, at the baseline electrophysiological examination, low-amplitude dCMAPs in at least two nerves, mildly prolonged DML in six nerves (median: 122% of ULN; range: 109-132) and partial motor CB in nine nerves.

MCV was normal except for the site of CB in five nerves. Within six weeks amplitude and latency of dCMAPs normalized, CB and conduction slowing at the site of CB resolved without development of excessive temporal dispersion of CMAPs. At follow-up, little or no signs of denervation were seen at EMG. These three patients, classified as AMAN with reversible conduction failure pattern, had normal sensory studies at the first examination performed within the first week.[16,23]

In the left median nerve of Patient 9, SNAP amplitude increased by 220% in eight weeks along with normalization of dCMAP amplitude, whereas proximal SNAP amplitude increased by 139% along with improvement of proximal CMAP amplitude and disappearance of motor CB (Fig 2). At day 23, because of the greater increase of SNAP amplitude from wrist stimulation compared to SNAP from elbow stimulation, the SNAP ratio decreased from 0.75 to 0.42. The SNAP ratio increased to 0.56 at day 59. In the remaining two patients no significant changes were observed in SNAPS, and SNAP ratios remained within the normal range throughout the follow-up.

AMAN with axonal degeneration and minor sensory abnormalities

Patients 12 and 13 had an axonal degeneration pattern in motor fibres, no sensory signs and minor baseline abnormalities of sensory conductions not fulfilling the criteria for AMSAN.

In Patient 12, baseline electrophysiological examination showed normal sensory conduction in right ulnar nerve, abnormal right median SNAP amplitude (70% of LLN), and abnormal SNAP amplitude and SCV in right sural nerve (respectively 88% and 90% of LLN). Nine days later SNAP amplitude increased by 51% becoming normal in the sural nerve and was significantly increased (by 239%) in the ulnar nerve.

In Patient 13, who had at baseline only abnormal median SNAP amplitude and SCV (respectively 73% and 88% of LLN), the re-examination five months after onset showed, in the median nerve, the persistence of low-amplitude SNAP but normalization of SCV, whereas there was a significant decrease of SNAP amplitude in sural nerve (-61%) and a non significant decrease of SNAP amplitude in ulnar nerve (by 42%). At 9 months median nerve SNAP was increased by 128% compared to baseline becoming normal.

AMSAN

Three patients (Patients 14-16) had dCMAP amplitudes < 80% of LLN in at least two nerves, SNAP amplitude <50% of LLN in at least two nerves, and were classified as AMSAN.

Patient 14 showed no significant changes of motor and sensory conductions during the first two weeks.

In Patient 15, baseline CMAP amplitudes were markedly decreased in both median and ulnar nerves and at lower limit of normal in peroneal nerves,

whereas SNAP amplitudes were < 50% of LLN in both ulnar nerves and normal in both median nerves and in right sural nerve. At follow-up, distal CMAP disappeared or further decreased in amplitude in upper limb nerves, remained stable in left peroneal nerve and improved by 59% in right peroneal nerve by day 55. Conversely, SNAP amplitude of ulnar nerves significantly improved by 150-300% and normalized within one week during IVIg administration (Fig 3).

In Patient 16 baseline electrophysiological examination showed low-amplitude distal CMAP in right median, ulnar and peroneal nerves, and a partial motor CB in the forearm segment of the right ulnar nerve. DMLs and MCVs were normal. SNAPs were not recordable in median, ulnar and sural nerves bilaterally. Within four weeks distal CMAP amplitudes normalized in upper limb nerves and partial CB resolved in the right ulnar nerve without development of excessive temporal dispersion of proximal CMAP, indicating reversible conduction failure in motor fibres. During follow-up SNAPs early reappeared in all nerves and finally normalized in three nerves. (Fig 4).

Summary of serial sensory conduction findings

In the AMAN group, one sensory nerve showing minor abnormalities at baseline significantly recovered at follow up, and 11 of 32 initially normal sensory nerves (34%) of 6 patients (five with baseline normal sensory conduction, one with minor sensory abnormalities at baseline) showed an increase of SNAP amplitude (median increase by 106%, range 57-518%). Conversely, in three initially normal nerves of three AMAN patients (two with baseline normal sensory conduction, one with minor sensory abnormalities at baseline) a decrease of SNAP amplitude was found (median decrease by 60%, range 50-69). In summary,

in the AMAN group we found that: 1) two patients had minor sensory changes in three nerves at baseline; 2) 14 of 32 initially normal nerves (44%) and seven of 11 patients with baseline normal sensory conductions (64%) showed significant changes in SNAP amplitude; 3) overall sensory fibres were involved in 49% of nerves and in 69% of AMAN patients.

In one AMSAN patient, SNAP amplitude increased by 150-300% in two nerves. In six nerves of another AMSAN patient, SNAPs were unrecordable at baseline but reappeared during follow-up normalizing in three nerves.

Overall eleven of 16 patients with axonal GBS (69%) showed significant changes in SNAP amplitudes in 23 of 47 (49%) re-tested nerves (Table 1 and Table 2).

Antiganglioside antibodies

Antibodies to at least one of the examined gangliosides were found in 13 of 15 tested patients (87%) (Table 1). There was no difference in the immunological profile of AMAN and AMSAN patients. Anti-GD1b antibodies were not associated with paresthesias ($p=0.026$), pain ($p=0.315$), sensory loss ($p=0.077$), electrophysiological involvement of sensory fibres at baseline ($p=0.119$) or at follow-up ($p=1.000$).

DISCUSSION

Axonal GBS is a term derived from pathology but electrophysiologically defined axonal GBS subtypes are not only the expression of axonal degeneration. Three AMAN and one AMSAN patients we report showed at serial recordings reversible conduction failure in motor fibres. Reversible conduction failure, described in

some patients with anti-ganglioside antibodies and in a GBS subtype named acute motor conduction block neuropathy, is ascribed to an antibody-mediated reversible conduction impairment at the axolemma of nodes of Ranvier.[16,28] According to experimental studies, anti-ganglioside antibodies attack primarily the axolemma of motor fibres at the nodes of Ranvier sequentially inducing complement activation, disruption of sodium channel clusters and nodal architecture and finally Wallerian-like degeneration.[15] In some patients, this pathological cascade may arrest to the stage of sodium channel derangement resulting in transient and reversible failure of axonal function.[2] The occurrence of reversible conduction failure in motor fibres has not been reported in AMSAN before and may explain why some AMSAN patients do not have poor outcome.

The 13 patients with AMAN we report had clinically pure motor GBS with no sensory signs. DTR were preserved in four patients and brisk in one.

According to Asbury and Cornblath (1990) universal areflexia is the rule in GBS although distal areflexia with definite hyporeflexia of the biceps and knee jerks will suffice for diagnosis if other features are consistent.[29] DTR may be preserved throughout the disease course in patients with AMAN.[30] Moreover, 48% of Chinese and 33% of Japanese patients with AMAN showed hyperreflexia in the recovery phase.[16,31] Moderate weakness and the normal afferent branch of the myotatic reflex arch could account in our patients for the preservation of DTR but they do not explain hyperreflexia. Electrophysiologic evidence of lower motor neuron hyper-excitability has been reported in some patients with AMAN with hyperreflexia.[32-33] In conclusion, preserved DTR and even hyperreflexia may occur in patients with AMAN and are not inconsistent with the diagnosis.

Paresthesia was present in 15% and pain in 31% of patients. Two patients (15%)

had mild sensory abnormalities at baseline electrophysiological examination. As for preserved DTR, these features are not inconsistent with AMAN diagnosis. Paresthesia has been reported in 10-40 % of patients and pain, even severe, accompanies AMAN in up to 66% of patients.[3,10,11,34] The sensory conduction abnormalities we found at baseline in two patients did not satisfy the electrophysiological criteria to define AMSAN, and have been reported in 5-12% of AMAN patients.[3,4,5,11,22]

Serial recordings of sensory conduction demonstrated that sensory fibres were subclinically involved in most AMAN patients, even when baseline sensory conduction appeared normal. In fact, SNAP amplitudes significantly increased in 34% of initially normal nerves of 6 patients indicating that, at baseline, sensory fibres were involved although not enough to produce a decrease of SNAP below the LLN. Similarly, in eight nerves of two AMSAN patients initially absent or reduced SNAPs recovered at follow-up. In three AMAN patients, SNAP amplitude decreased in three initially normal nerves indicating a later involvement of sensory fibres. Overall, in our series, baseline and subsequent serial recordings allowed to detect sensory fibres involvement in 49% of nerves and in 69% of AMAN patients.

The improvement of SNAPs followed two courses. In five nerves of three AMAN and in eight nerves of two AMSAN patients SNAP amplitudes increased rapidly (within 2-4 weeks from onset). Similar features have been reported in one AMAN patient with reversible conduction failure pattern and antibody to GM1/GalNAc-GD1a complex and in patients with acute sensory ataxic neuropathy and antibodies to GD1b suggesting that reversible conduction failure may occur not only in motor but also in sensory fibres.[35,36] In other patients,

SNAP amplitudes increased over months according to an axonal regeneration process.

We did not find different immunological profiles in electrophysiologically pure motor GBS, AMAN with minor sensory involvement, and AMSAN. In particular, we could not confirm the hypothesis that anti-GD1b antibodies were associated with clinical or electrophysiological involvement of sensory fibres.

Although our findings demonstrate that AMAN is not an exclusively motor neuropathy, there is no doubt that the involvement of motor fibres is predominant and determinant for clinical severity. The bases of this phenomenon are not clear. Biochemical studies demonstrated that sensory and motor nerves express similar quantities of GM1 and GD1a gangliosides.[37,38] However, serum from an AMAN patient with anti-GD1a antibodies selectively stained nodes of Ranvier of motor fibres and an anti-GD1a monoclonal antibody (mAb) preferentially stained motor spinal roots in humans and rodents.[38,39] A study employing several mAbs and GD1a derivatives suggested that both fine specificity of antibodies and different orientation/exposure of ganglioside in motor and sensory fibres contribute to target recognition by anti-ganglioside antibodies.[40] Moreover a number of biophysical differences between human sensory and motor axons have been reported. Sensory axons have less supernormality and late subnormality, longer strength-duration time constant and a lower rheobase than motor nerves.[41-44] Sensory axons accommodate more than motor axons to long-lasting hyperpolarizing currents suggesting a greater expression of the hyperpolarization-activated inward rectifier channels and greater expression of persistent Na⁺ channels.[42,45] Lastly, the electrogenic Na⁺-K⁺ -ATPase is more active in sensory nerves.[46] These differential biophysical features may explain

the fact that motor fibres are more affected than sensory fibres by the attack of the same antibody and the coexistence of positive sensory symptoms such as paresthesias in some AMAN patients.

Whatever is the reason of differential involvement of motor and sensory fibres in axonal GBS subtypes this study shows that: 1) sensory fibres are involved in AMAN although to a lesser extent than motor fibres and not enough to produce a clinical correlate; 2) reversible conduction failure is present in motor and sensory fibres both in AMAN and AMSAN; 3) AMAN and AMSAN having in common immunological profile, electrophysiological features and pathophysiology are a continuum, with AMSAN with axonal degeneration representing the more severe end of the spectrum.

COMPETING INTERESTS

Dr. Margherita Capasso: none

Dr. francesca Notturmo: none

Dr. Claudia Manzoli: none

Prof. Antonino Uncini: received research support from Kedrion and payment for lectures by Pfizer

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FIGURE LEGENDS

Figure 1

Linear graphs of electrophysiological findings in three patients with AMAN and axonal degeneration pattern and normal sensory studies at baseline (A, Patient 4; B, Patient 5; C, Patient 8). In ordinates are amplitudes of sensory nerve action potentials (SNAP) and of distal compound muscle action potential (CMAP). In abscissae are days after onset. The numbers beside the symbols indicated decreased (-) or increased (+) percentages of SNAP amplitude compared to baseline evaluation.

Figure 2

Patient 9, left median nerve. Upper tracings: serial recordings of compound muscle action potential from abductor pollicis brevis muscle after stimulation at wrist and elbow. Lower tracings: serial recordings of sensory nerve action potential from digit III after wrist and elbow stimulation.

Figure 3

Patient 15, left ulnar nerve. Upper tracings: serial recordings of compound muscle action potential from abductor digiti minimi muscle after stimulation at wrist, below-elbow, and above-elbow. Lower tracings: serial recordings of sensory nerve action potential recorded from digit V after wrist stimulation.

Figure 4

Linear graphs of serial electrophysiological findings in **Patient 16** with AMSAN and reversible conduction failure pattern. In ordinates are amplitudes of distal compound muscle action potential (dCMAP) and of sensory nerve action potentials (SNAP). In abscissae are days after onset.

TABLE 1. Clinical features, electrophysiological patterns at final diagnosis, and laboratory findings

Patientt	Paresthesia	Pain	Sensory loss	DTR	Neurophysiological Classification	Significant SNAPa changes	Antecedent infectious symptoms	Anti-ganglioside IgG		
								GM1	GD1a	GD1b
1	-	-	-	-	AMAN/AD	-	diarrhea/fever	-	-	-
2*	-	-	-	-	AMAN/AD	-	diarrhea	51,200	-	800
3	+	-	-	-	AMAN/AD	+	diarrhea/fever	ND	ND	ND
4	-	-	-	-	AMAN/AD	+	diarrhea	-	12,800	-
5	-	+	-	-	AMAN/AD	+	flu	1,600	6,400	-
6	-	-	-	+	AMAN/AD	+	diarrhea/fever	-	1,600	-
7	-	+	-	+	AMAN/AD	+	diarrhea/fever	1,600	51,200	-
8*	-	-	-	-	AMAN/AD	+	diarrhea	3,200	12,800	-
9	-	+	-	++	AMAN/RCF	+	diarrhea	51,200	102,400	102,400
10	-	-	-	+	AMAN/RCF	-	diarrhea	51,200	102,400	-
11	+	-	-	+	AMAN/RCF	-	diarrhea/fever	-	-	400
12	-	-	-	-	AMAN/AD/MSA	+	diarrhea	-	-	-
13	-	+	-	-	AMAN/AD/MSA	+	diarrhea	6,400	1,600	400
14	+	-	+	-	AMSAN/AD	-	URTI	400	400	800
15*	+	-	+	-	AMSAN/AD	+	diarrhea	51,200	-	12,800
16*	+	+	+	-	AMSAN/RCF	+	diarrhea/fever	400	-	400

An asterisk indicates patients who were prospectively evaluated. Paresthesia and pain were reported to be present (+) or absent (-). Deep tendon reflexes (DTR) were absent/hypoactive (-), preserved (+) or brisk (++). AMAN = acute motor axonal neuropathy; AMSAN= acute motor and sensory axonal neuropathy; AD= axonal degeneration pattern in motor fibres; RCF= reversible conduction failure pattern in motor fibres; MSA= minor sensory abnormalities at baseline, SNAPa= sensory nerve action potential amplitude. URTI= upper respiratory tract infection. **The titre of IgG to gangliosides is reported.**

TABLE 2. Serial sensory conduction studies in patients with acute motor axonal neuropathy (Patients 1-13) and acute motor and sensory axonal neuropathy (Patients 14-16)

	MEDIAN NERVE SNAP				ULNAR NERVE SNAP				SURAL NERVE SNAP						
	Basal (μ V)	% variation			Basal (μ V)	% variation			Basal (μ V)	% variation					
PATIENT 1															
day					<u>10</u> 14.9	<u>18</u> -2%			<u>10</u> 26.2	<u>18</u> -37%					
PATIENT 2															
day	<u>7</u> R 22.2	<u>14</u> +27%	<u>224</u> +32%		<u>7</u> R 25.3	<u>14</u> -28%	<u>224</u> +32%		<u>7</u> 11.2	<u>14</u> -36%	<u>224</u> -36%				
	L 23.1	+9%	+17%		L 33.1	-18%	+15%								
PATIENT 3															
day	<u>2</u> 29.5	<u>7</u> -50%			<u>2</u> 19.3	<u>7</u> -25%									
PATIENT 4															
day	<u>3</u> 30.3	<u>21</u> -69%	<u>143</u> -54%		<u>3</u> 17.7	<u>21</u> +17%	<u>143</u> -23%		<u>3</u> 9.8	<u>21</u> +29%	<u>143</u> +2%				
PATIENT 5															
day	<u>5</u> 25.2	<u>12</u> +98%	<u>27</u> ND		<u>5</u> 12.6	<u>12</u> +157%	<u>27</u> +518%		<u>5</u> 16.9	<u>12</u> -27%	<u>27</u> +106%				
PATIENT 6															
day	<u>15</u> 13.7	<u>52</u> +25%	<u>92</u> +2%	<u>226</u> -7%	<u>15</u> 10.5	<u>52</u> ND	<u>92</u> ND	<u>226</u> +3%	<u>15</u> 6.7	<u>52</u> +207%	<u>92</u> ND	<u>226</u> +149%			
PATIENT 7															
day									<u>11</u> 10.1	<u>102</u> +138%					
PATIENT 8															
day	<u>4</u> R 24.2	<u>9</u> ND	<u>21</u> +13%	<u>80</u> -4%	<u>191</u> +63%	<u>4</u> R 22.1	<u>9</u> ND	<u>21</u> ND	<u>80</u> +9%	<u>191</u> +105%	<u>4</u> 11.9	<u>9</u> -17%	<u>21</u> ND	<u>80</u> ND	<u>191</u> 28%
	L 31.1	+10%	+23%	+61%	+59%	L 36.2	-64%	-42%	+56%	+57%					

PATIENT 9

day	<u>7</u>	<u>23</u>	<u>59</u>
R	36.2	-17%	+27%
L	23.4	+111%	+220%

PATIENT 10

day	<u>7</u>	<u>15</u>	<u>7</u>	<u>15</u>
	26.3	+19%	12.4	+21%

PATIENT 11

day	<u>6</u>	<u>12</u>
	22	-13%

PATIENT 12

day	<u>5</u>	<u>14</u>	<u>5</u>	<u>14</u>
	7.7 *	ND	5.3 *	+51%

PATIENT 13

day	<u>7</u>	<u>153</u>	<u>266</u>	<u>7</u>	<u>153</u>	<u>266</u>	<u>7</u>	<u>153</u>	<u>266</u>
	8 *	+11%	+128%	24.3	-42%	-32%	13.9	-61%	ND

PATIENT 14

day	<u>8</u>	<u>13</u>
R	4.5 §	+37%
L	3.1 §	+20%

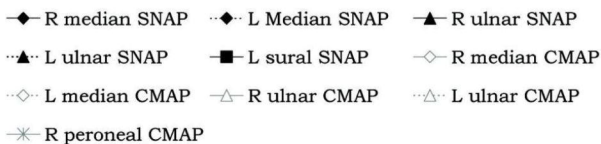
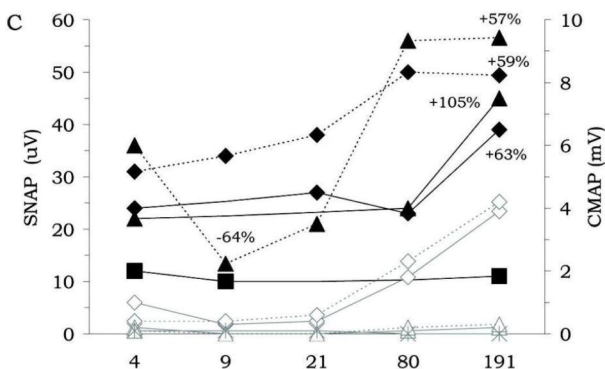
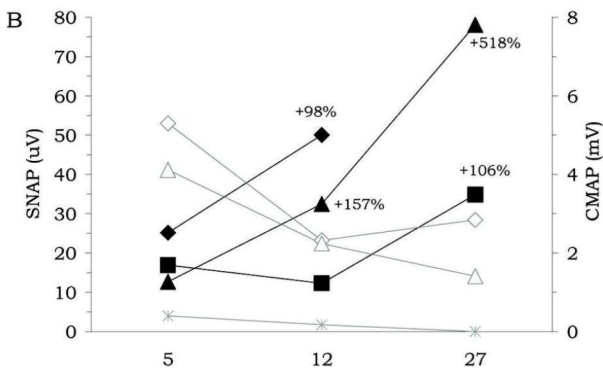
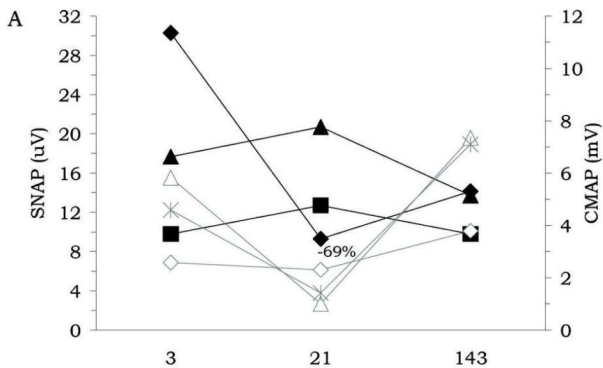
PATIENT 15

day	<u>15</u>	<u>17</u>	<u>21</u>	<u>28</u>	<u>36</u>	<u>15</u>	<u>17</u>	<u>21</u>	<u>28</u>	<u>36</u>	<u>15</u>	<u>17</u>	<u>21</u>	<u>28</u>	<u>36</u>
R	11.1	+1%	+2%	-10%	-22%	4.1 §	+31%	+150%	+128%	+145%	13.9	-28%	-35%	-28%	-14%
L	15.8	+12%	+14%	-6%	+8%	3.0 §	+163%	+270%	+300%	+293%					

PATIENT 16[#]

day	<u>6</u>	<u>16</u>	<u>29</u>	<u>45</u>	<u>109</u>	<u>6</u>	<u>16</u>	<u>29</u>	<u>45</u>	<u>109</u>	<u>6</u>	<u>16</u>	<u>29</u>	<u>45</u>	<u>109</u>
R	0	0	6	6.8	11	0	0	2	3	2	0	ND	5	ND	ND
L	0	0	7	14	14	0	2	2.1	7.2	7.8	0	1	8	8	8.5

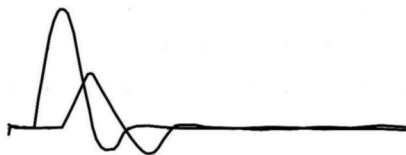
SNAP = sensory nerve action potential. Percentage variations are calculated compared with basal values. In bold are significant changes, that is variations \geq the least significant change calculated in the test-retest study. ND= not done; * = minor sensory changes; § = SAP amplitude <50% of LLN. # = for patient 16, absolute values are reported, as percentage is not calculable.



day 7



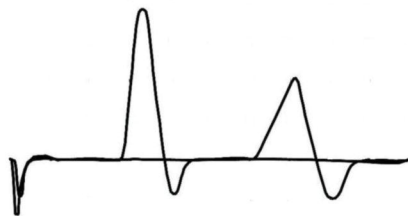
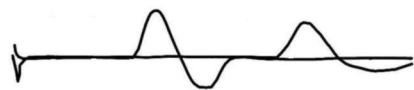
day 23



day 59



2 mV
5 ms



20 μ V
1 ms

day 15



day 17



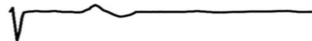
day 21



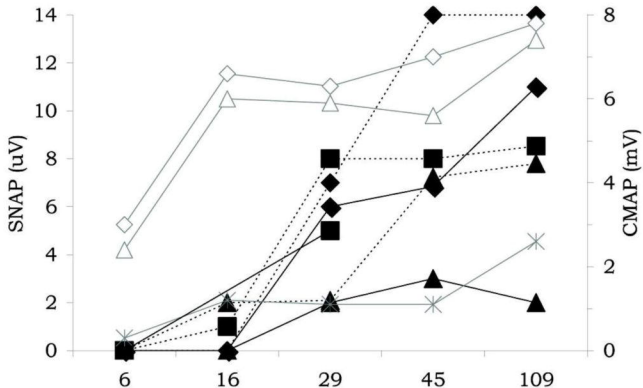
day 28



1 mV
5 ms



10 μ V
1 ms



—◆— right median SNAP

—▲— right ulnar SNAP

—■— right sural SNAP

—◇— right median CMAP

—*— right peroneal CMAP

··◆·· left median SNAP

··▲·· left ulnar SNAP

··■·· left sural SNAP

—△— right ulnar CMAP