Nerve conduction studies in polyneuropathy : practical physiology and patterns of abnormality

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Abstract

Nerve conduction studies are an essential part of the work-up of peripheral neuropathies. Many neuropathic syndromes can be suspected on clinical grounds, but optimal use of nerve conduction study techniques (in combination with needle electromyography) allows diagnostic classification and is therefore crucial to understanding and separation of neuropathies. Multifocal motor neuropathy, for example, may clinically present as ALS. Detection of evidence of demyelination (conduction blocks) leads to the correct diagnosis and to proper treatment.

Nerve conduction studies provide essential information on (1) the spatial pattern of neuropathy, (2) the pattern of abnormalities distinguishing between primarily axonal and demyelinating pathology, and (3) the severity of neuropathic damage. This information is very comprehensive since many nerves and long segments of individual nerves can be sampled. Moreover, the information is extremely detailed to the extent that the cellular pathology of a patient's neuropathy is usually defined best by physiological testing rather than by biopsy.

Neuropathies can be generalized, focal, or multifocal ; they can be symmetric or asymmetric ; they can be distally predominant or proximal and distal. Primarily axonal neuropathies mainly affect sensory nerve and compound muscle action potential amplitudes, whereas demyelinating neuropathies lead to slowing of nerve conductions, and to increased temporal dispersion or conduction block. Usually, the pattern of demyelination allows to distinguish hereditary (uniform demyelination) from acquired (segmental demyelination) neuropathies. Electrodiagnostic criteria for primary demyelination are helpful to identify acquired demyelinating neuropathies.

Key words : Nerve conduction ; conduction velocity ; conduction block ; temporal dispersion ; demyelination ; polyneuropathy ; MMN ; CIDP.

Introduction

The goal of this contribution is to provide insight into the distinction between axonal and demyelinating neuropathies by means of nerve conduction studies. For this purpose, we will explain how pathophysiological events in single axons are reflected by a nerve conduction study in which hundreds of axons are assessed simultaneously. This will be done for a normal nerve, a nerve affected by loss of axons and a nerve affected by demyelination. Criteria for axonal degeneration and for the several features of demyelination will be discussed as well as electrophysiological criteria for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Also, the typical distribution of nerve conduction abnormalities for the most important demyelinating neuropathies will be presented. Finally, two case reports will be presented.

Nerve conduction studies

In a typical motor nerve conduction study, a mixed nerve containing motor and sensory axons, is stimulated at a given site along its course. The stimulus is a brief electrical pulse which will induce a sufficient depolarization in all the axons under this site to generate action potentials. The evoked potentials in motor axons will travel in distal and proximal directions from the stimulus site. The action potentials travelling towards the muscle innervated by that nerve, will reach the neuromuscular synapses after some milliseconds and will induce there neuromuscular transmission and eventually action potentials along the muscle fibers. The summation of these muscle fiber action potentials is recorded by surface electrodes placed on the skin over the muscle and is known as compound muscle action potential (CMAP). Variables that can be measured from the CMAP are its latency after the stimulus, amplitude, area under the curve and duration. The onset latency of the CMAP reflects the conduction time along the fastest conducting axons of the nerve. When the nerve is stimulated at increasing distances from the muscle (e.g. wrist, elbow, axilla, and Erb's point), CMAPs of increasing latencies are recorded. Dividing the distance between the two sites at each end of a nerve segment (e.g. wrist-elbow) by the latency difference between the CMAPs evoked at these sites, yields

the conduction velocity (CV) of the fastest conducting axons in that segment. This is known as the maximal motor conduction velocity or, simply but slightly wrong, "the" motor conduction velocity (MCV). The amplitude and area of the CMAP reflect the number of muscle fiber action potentials and therefore indirectly, the number of axons which can be stimulated. However, as in nerve pathology some axons may be affected whereas other axons are normal, it is more convenient to describe the CMAP as the summation of motor unit action potentials (MUPs) rather than as the summation of muscle fiber action potentials. A MUP is the summation of the muscle fiber action potentials of one motor unit. A motor unit is one motor neuron, including its axon, and the muscle fibers it innervates. As surface electrodes are used to record the CMAP, the CMAP in this description is the summation of the surface recorded MUPs which are evoked after stimulation of a nerve.

In a sensory nerve conduction study, a nerve is stimulated in the same way as in motor conduction studies and a sensory nerve action potential (SNAP) is usually recorded from a site distal from the stimulation site with surface electrodes. This so-called antidromic recording is possible because, after a stimulus, the evoked action potentials will travel in proximal as well as distal directions along the nerve. The SNAP is the summation of the action potentials in sensory nerve axons evoked by the stimulus ; its amplitude reflects indirectly the number of axons that can be activated. To record a SNAP uncontaminated by CMAPs, a mixed nerve can be stimulated and the SNAP recorded from a purely sensory branch or a pure sensory nerve can be investigated for stimulation and recording. The purpose of sensory conduction studies in the diagnosis of polyneuropathy is to assess whether there is loss of peripheral sensory axons rather than to detect demyelination.

Normal nerve

Stimulation at a distal site (e.g. the median nerve at the wrist) evokes action potentials in all motor axons to the thenar muscle yielding a CMAP consisting of summated MUPs. Stimulation at a more proximal site (e.g. the median nerve at the elbow) also evokes action potentials in the axons to the thenar, again yielding a CMAP. Due to the difference in conduction times (some axons conduct slightly faster than others), the MUPs do not arise completely synchronously after stimulation at the elbow, thereby slightly reducing the CMAP amplitude. The difference in conduction times between the fastest and slowest conducting axons in a nerve is known as temporal dispersion (TD).

In a normal nerve, TD is limited so that the CMAP evoked at the most proximal stimulation site of a nerve is almost as large as the CMAP

evoked at the most distal stimulation site. In a normal nerve, the amplitude of the negative CMAP phase is typically above 3 mV and the motor conduction velocity (MCV) is above 50 m/s for upper extremity and above 40 m/s for lower extremity nerves. The SNAP amplitude is above 7 µV. It should be stressed that these values are not absolute as they are affected by age, height and temperature (De Jesus *et al.* 1973, Rivner *et al.* 2001).

Axonal degeneration

If axons are lost, the CMAP amplitude and area are reduced after distal and after proximal stimulation because both CMAPs consist of a less than normal amount of MUPs. The conduction velocity may be normal (if some of the remaining axons are fast conducting) or slightly reduced (if all fast conducting axons are lost).

The distally and proximally evoked CMAPs are of approximate equal amplitude because the same reduced number of MUPs are recorded after distal and proximal stimulation. The SNAP amplitudes are reduced, reflecting loss of sensory axons.

Criteria for axonal degeneration and axonal polyneuropathy

Nerve conduction criteria for axonal degeneration usually include a decrease in the distally evoked CMAP or SNAP. This is because a decreased distal CMAP is most likely due to loss of axons although occasionnally it may be caused by other mechanisms such as a very distal conduction block, a neuromuscular transmission deficit (especially Lambert-Eaton myasthenic syndrome) and a severe distal myopathy (Kimura 2001). Proximally evoked CMAPs are not suitable for this purpose as these may be affected by demyelination (see below).

There are no internationally accepted criteria for axonal polyneuropathy. However, in most publications, axonal polyneuropathy is assumed if there are decreased distal CMAPs and SNAPs and no evidence of demyelination (Eurelings *et al.* 2001, Vrancken *et al.* 2002). Decreased SNAPs are a requisite to prove the existence of an axonal polyneuropathy as decreased CMAPs only can also be the result of other disorders such as motor neuron disease. However, in some axonal polyneuropathies, such as diabetic neuropathy or CMT type 2, SNAPs are within normal limits so that other evidence is required to make a diagnosis of polyneuropathy (Logigian *et al.* 1994, Andersen *et al.* 1997).

Demyelination

At the level of one internode, demyelination and especially paranodal demyelination, may result in an enlarged node (Kaji 2003). This may result in

severe disruption of normal saltatory conduction. With normal saltatory conduction, the inward current at one node associated with the action potential at that node, induces an outward current at the next node (i.e., the node which is next to be activated) where this outward current yields depolarization and sodium channel opening. If the depolarization at the next node reaches a certain threshold, an action potential arises which is associated with an inward current. In paranodal demyelination, the initial outward current at the next node is dissipated over a larger area. If the next node can be depolarized to threshold after a larger duration current, saltatory conduction is slowed but preserved ; with more severe demyelination insufficient current is available to depolarize the next node to threshold and the action potential will extinguish. This is known as conduction block (CB). Thus, at the level of one internode, demyelination may give rise to conduction slowing or CB. At the level of a nerve which contains many axons each with many internodes, nerve conduction studies may reveal slowing of MCV, increased TD and CB.

Demyelinative slowing and increased temporal dispersion

If the axons in the nerve are demyelinated but are still able to conduct (albeit more slowly), the CV will be reduced ; the maximal CV may then be that of the least demyelinated axon. When some axons are more demyelinated than others, the difference in conduction times will be increased. This increased TD will lead to desynchronized MUPs, especially with more proximal stimulation. In addition, the positive phase of one MUP may neutralize the negative phase of the other MUP (phase cancellation). Due to these two mechanisms the CMAP on proximal stimulation will be lower and broader than the CMAP on distal stimulation. This is known, respectively, as CMAP (amplitude or area) reduction on proximal versus distal stimulation (P/D) and duration prolongation P/D.

Criteria for demyelinative slowing were developed which require a maximal CV that is slower than can be explained by axonal degeneration. Buchtal and Behse (1977) compared CVs between patients with demyelinating Charcot-Marie-Tooth (CMT) neuropathy and patients with axonal CMT neuropathy as diagnosed by nerve biopsy. In the demyelinating form, CV was below 60% of the normal mean whereas in the axonal form, it was above 60% of the normal mean. From these findings criteria for demyelinative slowing were subsequently derived which required nerve conduction to be slower than a given percentage beyond the limit of normal ; criteria were defined for MCV, distal motor latency (DML) and F wave latency (Albers and Kelly 1989, Cornblath 1990, American Academy of Neurology 1991, Saperstein et al.

2001). These latter criteria were shown to be in agreement with investigations carried out in patients with different types of polyneuropathy (Logigian et al. 1994). Globally, a MCV below 38 m/s in an arm nerve and below 30 m/s in a leg nerve are consistent with demyelination, provided that the distal CMAP exceeds 1 mV.

Temperature is an important variable to take into account as CV will become slower when temperature decreases (de Jesus et al. 1973). As the decrease in CV with temperature is different in patients with a polyneuropathy than in normal controls, recalculation of the CV to the expected value at 37°C should be discouraged as it leads to significant errors (Notermans et al. 1994, Franssen et al. 1999). Criteria for demyelinative slowing at 37°C were defined recently (Van Asseldonk et al. 2005). It should be stressed that ; when the distal CMAP amplitude is below 1 mV (negative phase), criteria for demyelination should not be applied or stricter criteria should be used (American Academy of Neurology 1991, Van Asseldonk et al. 2005).

Criteria for increased TD require a duration prolongation P/D that is larger than can be explained by axonal degeneration.Criteria were derived from the maximal duration prolongation P/D found in patients with motor neuron disease (Cappellari et al. 1997, Van Asseldonk et al. 2005). Globally, a duration prolongation P/D of more than 30-40% in arm nerves or more than 100% in leg nerves indicates increased TD due to demyelination.

Recently, a criterium for increased TD in the distalmost segment of a nerve was developed and subsequently determined for 37 degrees C : a distal CMAP duration of about 9-10 ms or more indicates demyelination (Thaisetthawatkul et al. 2002, Van Asseldonk et al. 2005).

Conduction block

Suppose that all axons in the nerve are structurally intact but some are severely demyelinated (or affected by other pathophysiological mechanisms) at a site between, for instance, the wrist and elbow. A wrist stimulus will then evoke action potentials in all axons yielding a normal CMAP. An elbow stimulus will also evoke action potentials in all axons but, due to CB, some will be extingsuihed at the severely demyelinated site so that the CMAP after the elbow stimulus will be reduced because it consists of less MUPs. Thus, CB may, like increased TD, also result in CMAP reduction P/D.

Criteria for CB require that the CMAP reduction P/D is more than can be explained by increased TD. All factors which may lead to CMAP reduction P/D, such as CB, increased TD and polyphasia of MUPs contributing to the CMAP, may be present in patients with immune-mediated neuropathies (Brown and Feasby 1984, Van den Berg-Vos et al. 2002, Van Asseldonk et al. 2003, 2006).

For this reason, comparative studies between these patients and control groups are not suitable for deriving criteria that are specific for CB, making simulation studies necessary. On the basis of computer simulation studies in which CMAPs were reconstructed from MUPs recorded in rat muscles, it was shown that the maximal effects of TD could yield a CMAP amplitude reduction P/D of up to 80% and a CMAP area reduction P/D of up to 50% (Rhee *et al.* 1991). It was concluded that CMAP amplitude is not suitable for the detection of CB as it was too much influenced by TD and that a CMAP area reduction P/D of 50% or more indicates CB in at least some axons of the nerve. Very detailed criteria for CB were defined by the American Association of Electrodiagnostic Medicine (AAEM) (Olney *et al.* 1999) but these are not based on evidence but on expert opinion. Recently, criteria for CB were developed that were also based on computer simulation albeit with surface recorded MUPs in humans ; these criteria were defined for different degrees of duration prolongation P/D so that, with limited TD, criteria for CB can be less strict (Van Asseldonk *et al.* 2003). These criteria are yet to be validated.
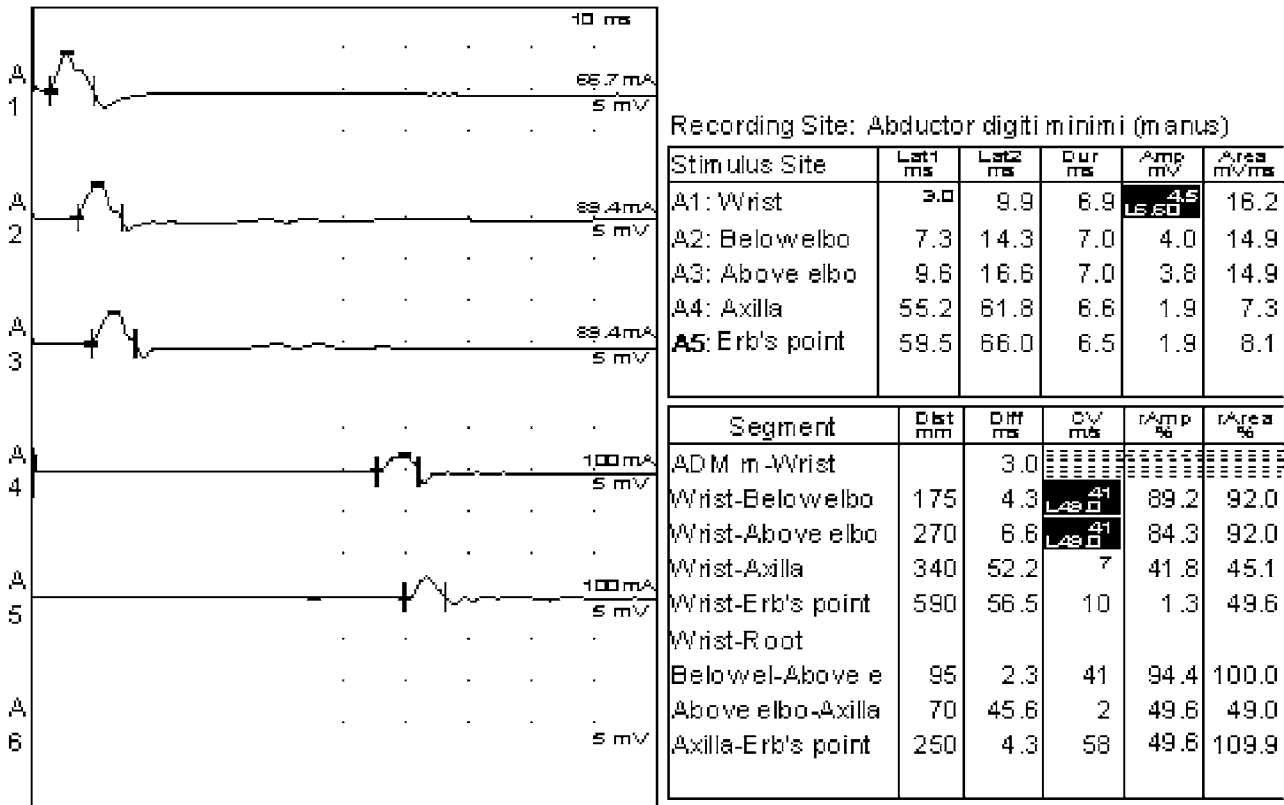
Criteria-sets for CIDP

CIDP is a progressive or relapsing polyneuropathy characterized by multifocal demyelination (Dyck *et al.* 1975, Barohn *et al.* 1989). Differentiation from other neuropathies is important as CIDP may improve with immunological treatment (Dyck *et al.* 1982, Van Doorn *et al.* 1990, Vermeulen *et al.* 1993, Hahn *et al.* 1996). As an aid to the diagnosis of CIDP several sets consisting of clinical and electrophysiological criteria for demyelination were developed and are often employed (American Academy of Neurology 1991, Nicolas *et al.* 2002, Molenaar *et al.* 2002, Magda *et al.* 2003). A typical set of electrophysiological criteria requires at least 3 out of the following 4 items : (1) CB or increased TD in at least 1 nerve, (2) MCV consistent with demyelination in at least 2 nerves, (3) DML consistent with demyelination in at least 2 nerves, and (4) minimal F wave latency consistent with demyelination in at least 2 nerves (American Academy of Neurology 1991). These sets pose several problems. They are based on expert opinion and not on a formal analysis of parameters which should be tested. Furthermore, although the specificity of all sets is high, their sensitivity is low which limits the identification of patients with a potentially treatable neuropathy (Bromberg 1991, Latov 2002). Finally, the use of a set in a patient suspected of CIDP only yields whether the patient has or has no CIDP ; the probability of CIDP cannot be determined. Several attempts were made to solve this problem. Recently, the number of required abnormalities was optimized (Van den Bergh and Piéret 2005). Other groups are working on computerized optimization and validation of criteria (International Study Group for Validation of CIDP Criteria) or on the estimation of the probability for CIDP on the basis of clinical criteria and the subsequent contribution of electrophysiological criteria (Neuromusclar Research Group, UMC Utrecht).

Distribution of abnormalities in demyelinating neuropathies

CMT 1a neuropathy, the most common form of hereditary demyelinating polyneuropathy, is characterized by uniformly slowed conduction consistent with demyelination without CB ; in CIDP, conduction slowing consistent with demyelination, increased TD and CB may all be present ; these demyelinative abnormalities may be generalized, multifocal and symmetrical, or mainly distal with increased DMLs (Lewis and Sumner 1982, Kuwabara *et al.* 2002). The polyneuropathy associated with anti-myelin associated glycoprotein (MAG) antibodies and the demyelinating polyneuropathies associated with IgM monoclonal gammopathy without anti-MAG antibodies are characterized by demyelinative slowing mainly at distal and common entrapment sites ; recently it was shown that slowing and axonal degeneration are length-dependent (Kaku *et al.* 1994, Chassande *et al.* 2001, Cocito *et al.* 2001, Franssen and Notermans in press). In MMN, multifocal CB occurs mainly in arm nerves ; in the segments with conduction block MCV is often, but not always, slowed and consistent with demyelination ; sensory conduction is usually normal, also in segments with CB (Parry and Clarke 1985, Chaudhry *et al.* 1994, Bouche *et al.* 1995, Katz *et al.* 1997, Van Asseldonk *et al.* 2003, 2005). The Lewis-Sumner syndrome is characterized by multifocal, asymmetrical demyelinative slowing and CB on motor and sensory conduction studies (Lewis *et al.* 1982, Saperstein *et al.* 1999, Van den Bergh *et al.* 2000, Van den Berg-Vos *et al.* 2000) (Case report A). In hereditary neuropathy with liability to presssure palsies, MCV over common entrapment sites can be consistent with demyelination ; in addition, there are generalized features including slowing of DMLs and distal sensory CVs and decreased SNAP amplitudes (Andersson *et al.* 2000, Li *et al.* 2002)

It is important to realize that in most of these demyelinating neuropathies, except HNLPP, features of axonal degeneration may also be present, especially in lower limb nerves (Gosselin *et al.* 1991, Van Asseldonk *et al.* 2003, Franssen and Notermans in press). In MMN, features of axonal degeneration are widespread even on concentric needle electromyography of arm muscles (Van Asseldonk *et al.* 2006). The first consequence of

Recording Site: Abductor digiti minimi (manus)

Stimulus Site	Lat1 ms	Lat2 ms	Dur ms	Amp mV	Area mVms
A1: Wrist	3.0	9.9	6.9	4.5 LS 6.6	16.2
A2: Belowelbo	7.3	14.3	7.0	4.0	14.9
A3: Above elbo	9.6	16.6	7.0	3.8	14.9
A4: Axilla	55.2	61.8	6.6	1.9	7.3
A5: Erb's point	59.5	66.0	6.5	1.9	8.1

Segment	Dist mm	Diff ms	CV m/s	rAmp %	rArea %
ADM m-Wrist		3.0			
Wrist-Belowelbo	175	4.3	41 LS 49	89.2	92.0
Wrist-Above elbo	270	6.6	41 LS 49	84.3	92.0
Wrist-Axilla	340	52.2	7	41.8	45.1
Wrist-Erb's point	590	56.5	10	1.3	49.6
Wrist-Root					
Belowel-Above e	95	2.3	41	94.4	100.0
Above elbo-Axilla	70	45.6	2	49.6	49.0
Axilla-Erb's point	250	4.3	58	49.6	109.9

Case report A. Fɪɢ. 1. — Right ulnar motor nerve conduction study. The distal negative peak CMAP amplitude is reduced (4.5 mV, lower limit of normal is 6.6 mV). In the nerve segment between the axilla and the elbow, partial conduction block occurs (amplitude and area reduction of 50%) and the nerve conduction velocity is considerably slowed (2 m/s), which is characteristic of a focal demyelinating lesion. Below and above this lesion, slowing is moderate (41 m/s, lower limit of normal is 49 m/s).

this is that these neuropathies still have to be classified into the group of demyelinating neuropathies and not in a group of mixed neuropathies with uncertain classification. The other consequence is that, in order to detect demyelination reliably, nerve conduction has to be assessed in arm nerves.
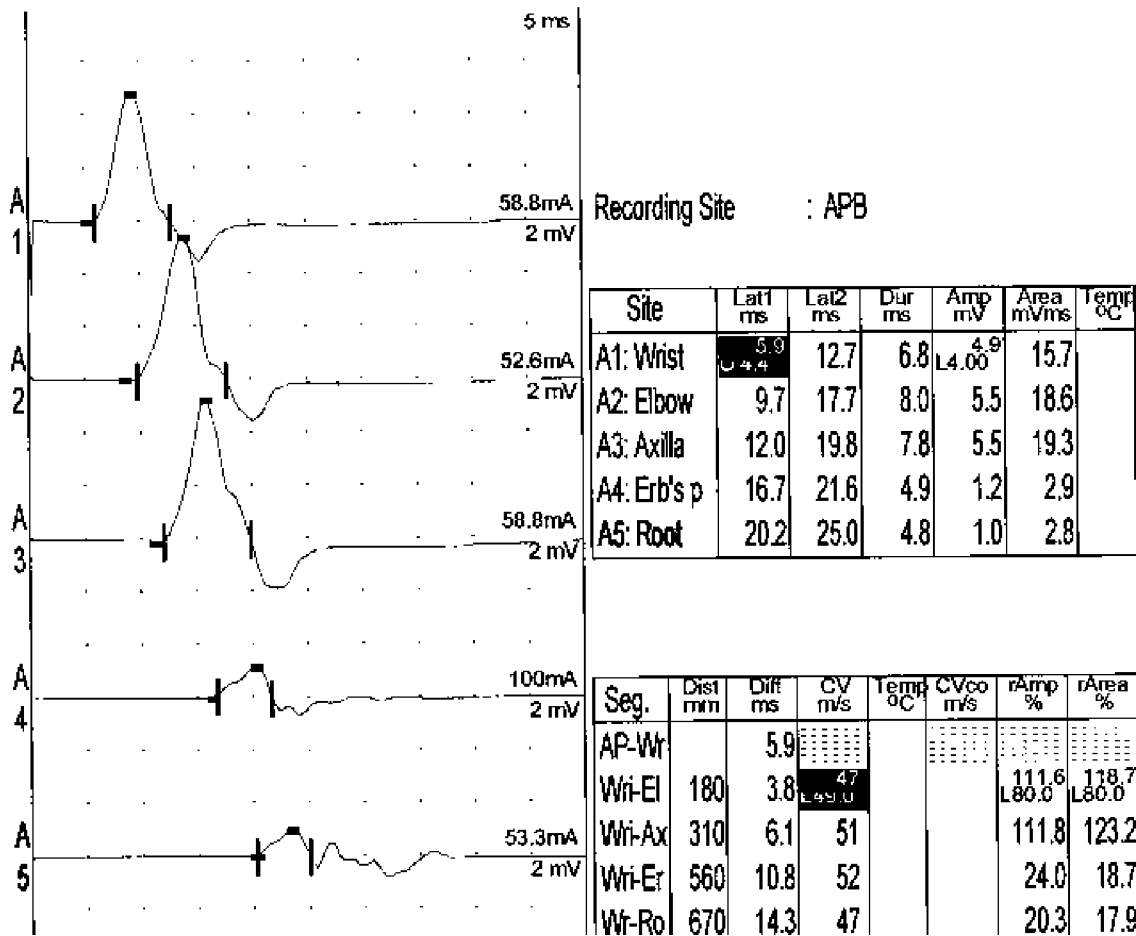
Case report A

At age 25, a female schoolteacher began complaining of numbness and tingling in both hands as well as of weakness of left hand grip. Seven months later, during an episode of low-grade fever with vomiting and diarrhea, she experienced difficulty moving her tongue and was found to have a right-sided hypoglossal nerve palsy, which spontaneously disappeared a few days later. A year after symptom onset, following an episode of viral pharyngitis, the patient developed hoarseness due to left vocal cord palsy, lasting for a few days. Three years after symptom onset, transient right vocal cord palsy occurred. At that time, significant weakness of the hand muscles was noted in an ulnar more than median nerve distribution. Touch, temperature, and pain sensation were reduced in the ulnar nerve skin territories. Marked hypertrophy of the ulnar nerves between the axilla and elbow was noted on palpation (thick and hard as a
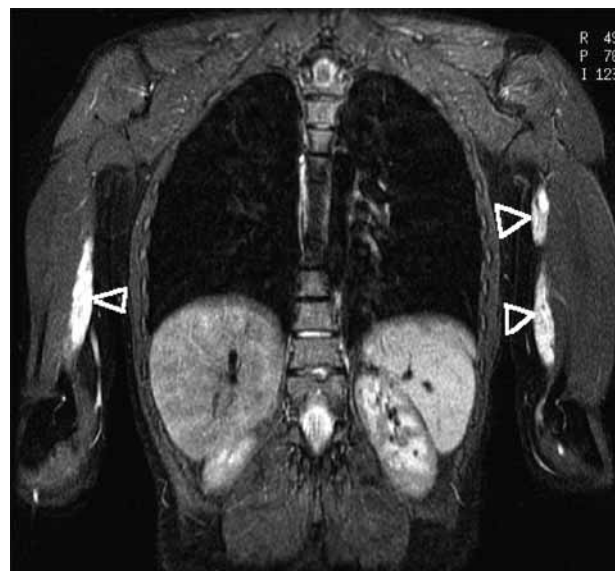
Case report A. Fɪɢ. 2. — Coronal short tau inversion recovery (STIR) image of thorax and arms, showing irregular and focal hyperintense enlargement of the ulnar nerves (from A. P. Jeanjean et al., Acta Neurol. Belg., 2001, 101, 237, with permission).

wooden pencil). Deep tendon reflexes were normal, except the flexor carpi ulnaris reflexes, which were absent.

Recording Site   : APB

Site	Lat1 ms	Lat2 ms	Dur ms	Amp mV	Area mVms	Temp °C
A1: Wrist	5.9 / 4.4	12.7	6.8	4.00 / 4.9	15.7	
A2: Elbow	9.7	17.7	8.0	5.5	18.6	
A3: Axilla	12.0	19.8	7.8	5.5	19.3	
A4: Erb's p	16.7	21.6	4.9	1.2	2.9	
A5: Root	20.2	25.0	4.8	1.0	2.8	

Seg.	Dist mm	Diff ms	CV m/s	Temp °C	CVco m/s	rAmp %	rArea %
AP-Wr		5.9					
Wri-El	180	3.8	47 / L49.0			111.6 / L80.0	118.7 / L80.0
Wri-Ax	310	6.1	51			111.8	123.2
Wri-Er	560	10.8	52			24.0	18.7
Wr-Ro	670	14.3	47			20.3	17.9

Case report B. FIG. 3. — Right median motor nerve conduction study. APB : abductor pollicis brevis muscle. The distal motor latency is prolonged. Marked partial conduction block between Erb's point and the axilla is observed (distal negative peak CMAP amplitude and area reduction of 80 and 70%, resp.). C8-Th1 nerve root stimulation (A5) confirms the results obtained after Erb's point stimulation (A4).

Nerve conduction studies showed that the sensory nerve action potential (SNAP) of the median and ulnar nerves was absent on the right and the amplitude was reduced on the left. Sensory conduction of the radial and sural nerves was normal. The compound muscle action potential (CMAP) amplitude of the right median nerve was significantly reduced and partial motor conduction block was observed in the elbow to wrist segment, where the motor conduction velocity was very slow (7 m/s). Partial conduction block was observed in the axilla to elbow segment of the right ulnar nerve, together with extreme focal slowing of the motor conduction velocity (Fig. 1). Motor conduction was normal in the radial, peroneal, and posterior tibial nerves. Needle electromyography showed evidence of chronic denervation in distal muscles, especially those innervated by the ulnar nerves.

MRI showed considerable hypertrophy of the brachial nerves from the brachial plexus level down to the peripheral nerves at the wrist. Massive enlargement was multifocal, irregular, and asymmetric (Fig. 2). MRI of the lumbosacral plexuses, the cranial ; nerves, and the brain was normal.

Case report B. FIG. 4. — Coronal short tau inversion recovery (STIR) image of cervical spine and brachial plexuses shows enlargement and signal hyperintensity of right cervical roots C6-C8 and of the middle and lower trunks of the brachial plexus.

This patient presents with relapsing-remitting 12th and 10th cranial nerve palsies and upper limb demyelinating neuropathy, asymmetrically involving the ulnar and median nerves. The clinical, electrodiagnostic, and MRI findings are characteristic of multifocal upper limb demyelinating neuropathy, initially described by Lewis *et al.* (1982) and referred to as Lewis-Sumner syndrome.

Case report B

At age 40, a healthy housewife started complaining of a dull ache throughout the right arm. Soon thereafter, weakness of the right hand followed. The aching disappeared and no sensory symptoms were noted. Hand weakness progressively increased together with proximal extension to forearm and upper arm muscles. Three years after onset, the patient could barely write, she dropped objects, and she could not lift objects with the right arm. On examination at that time, significant weakness of right interossei, the finger and wrist flexors and extensors, and the brachioradialis muscles was found. There was no amyotrophy. Sensation was completely normal. Deep tendon reflexes were abolished in the right upper limb and normal in all other limbs.

Electromyography revealed evidence of chronic denervation in C5 < C6-C7 < C8-innervated muscles. Sensory nerve conduction studies were completely normal. Motor nerve conduction studies revealed very significant partial motor conduction blocks in the right median, ulnar, and radial nerves in the Erb's point to above elbow nerve segments (Fig. 3). MRI of the cervical spine was non-contributory, but the right C6-C8 nerve roots and the right brachial plexus were hypertrophic (Fig. 4).
The findings were indicative of a diagnosis of multifocal motor neuropathy, limited to the right brachial plexus. Treatment with intravenous immunoglobulin led to rapid and very significant improvement, which could be maintained by repetitive perfusions every 3 weeks.

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