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Original articles

Electrodiagnosis of demyelinating neuropathies

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Abstract

The inflammatory demyelinating neuropathies constitute a significant proportion of the acquired polyneuropathies. Major progress in finding the causes and in the treatment of these neuropathies has been made over the last decade. Early recognition is of paramount importance, because timely and appropriate treatment can largely reduce morbidity and disability. Electrodiagnosis plays a key role in the detection and characterization of the inflammatory demyelinating neuropathies. Electrodiagnostic criteria for primary demyelination have therefore been developed. They are empirically based on changes of nerve conduction parameters in populations of patients with a confirmed clinical and laboratory diagnosis of inflammatory demyelinating neuropathy. The challenge consists of defining criteria sets that are highly specific but also as sensitive as possible. Most of the hereditary demyelinating neuropathies are part of Charcot-Marie-Tooth disease type 1. The pattern of nerve conduction abnormalities usually provides valuable clues for the distinction from chronic inflammatory demyelinating neuropathies.

Key words : Demyelinating neuropathy ; inflammatory ; hereditary ; electrodiagnosis ; nerve conduction.

Spectrum of demyelinating neuropathies

Demyelinating neuropathies can be divided into two broad categories : acquired and hereditary. Most acquired demyelinating neuropathies are of presumably inflammatory origin. They include the classical demyelinating form of Guillain-Barré syndrome (GBS) or acute inflammatory demyelinating polyradiculoneuropathy (AIDP), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and two CIDP variants : multifocal motor neuropathy (MMN) and multifocal demyelinating neuropathy with persistent conduction block, also known as Lewis-Sumner syndrome (Table 1). AIDP and CIDP are characterized by areflexic symmetric tetraparesis, sensory symptoms and signs, and elevated spinal fluid protein (Barohn and Saperstein, 1998). Most patients with AIDP reach the nadir of symptoms and signs by 4 weeks and a significant proportion presents with cranial nerve (mainly facial nerve) palsy, autonomic involvement, and respiratory failure. In contrast, patients with CIDP present with a progressive or relapsing course of at least 2 months duration ; facial palsy is rare and autonomic or respiratory involvement is exceptional. MMN and Lewis-Sumner syndrome are chronic neuropathies, predominantly affecting the distal upper limbs asymmetrically and in a peripheral nerve distribution (Lewis *et al.*, 1982 ; Parry, 1993). The main difference between the two conditions is the absence of sensory involvement, the relative preservation of deep tendon reflexes, and the common occurrence of fasciculations in MMN, which may therefore be confused with amyotrophic lateral sclerosis.

Most hereditary neuropathies are part of the genetically heterogeneous group of disorders, known as Charcot-Marie-Tooth disease (CMT) (De Jonghe *et al.*, 1997 ; Pareyson, 1999). The CMT clinical phenotype consists of distal limb muscle weakness and wasting with or without sensory loss, pes cavus, and reduced or absent deep tendon reflexes. CMT is subdivided in two main categories, demyelinating CMT1 and axonal CMT2. CMT1 comprises autosomal dominant, autosomal recessive, and X-linked forms (Table 2). The majority of CMT1 cases are associated with mutations in the genes encoding peripheral myelin protein 22 (PMP22) (CMT1A) and myelin protein zero (P0) (CMT1B), both of which are autosomal dominantly transmitted, and connexin 32 (Cx32) (CMTX), which is chromosome X-linked. Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder, characterized by recurrent painless mononeuropathies, most commonly affecting the ulnar, radial, and peroneal nerves and the brachial plexus. HNPP is usually associated with a deletion of the region in the PMP22 gene that is duplicated in CMT1A patients. Autosomal recessive CMT1 neuropathy patients are rare. As compared to autosomal dominant and X-linhed CMT1, age of onset is earlier and distal weakness is more pronounced. Several genetic loci have been documented, but only 2 genes have been identified, the MTMR2

Table 1

Differential diagnostic features of acquired demyelinating neuropathies. SNAP = sensory nerve action potential, CMAP = compound muscle action potential, MCV = motor conduction velocity

	Acute Inflammatory Demyelinating Polyradicucloneuropathy (GBS)	Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	Multifocal Demyelinating Neuropathy with Persistent Conduction Block (Lewis-Sumner syndrome)	Multifocal Motor Neuropathy (MMN) (ALS)	Amyotrophic Lateral Sclerosis
Age of onset	all ages	all ages	23-72 yrs	15-70 yrs	40-70 yrs
Weakness	symmetric	symmetric	Asymmetric	asymmetric	asymmetric
Distribution	Distal-Proximal Lower>Upper Extremity	Distal-Proximal Lower>Upper Extremity	Distal>Proximal Upper>Lower Extremity	Distal>Proximal Extremity Upper>Lower	Distal>Proximal Extremity, Bulbar Upper-Lower
Progression	acute	insidious/stepwise	Insidious/stepwise	stepwise/insidious	rapid
Fascicul./Cramps	rare	rare	Rare	common	very common
Deep tendon reflexes	reduced/absent	reduced/absent	Reduced/absent	reduced/normal	increased
Sensory loss	present	present	Present	absent/minor	absent
SNAP	absent/reduced	absent/reduced	absent/reduced	normal/reduced	normal
CMAP	reduced	reduced	Reduced	reduced/normal	reduced
Conduction block	present	present	Present	present	absent
MCV	slowed	slowed	slowed/normal	slowed/normal	normal
CSF protein	increased	often increased	often increased	normal	normal
GM1 Antibodies	+/–	+/–	+/–	22-84% ; mean 50%	+/–
Sural nerve biopsy	abnormal	abnormal	Abnormal	minor abnormalities	normal

Table 2

Classification and features of hereditary demyelinating neuropathies. CMT = Charcot-Marie-Tooth disease, HNPP = hereditary neuropathy with liability to pressure palsies, HMSN = hereditary motor and sensory neuropathy, PMP22 = peripheral myelin protein 22, P0 = myelin protein 0, EGR2 = early growth response element 2 transcription factor

	Age of onset	Weakness and sensory loss	Gene location	Gene product
Autosomal dominant				
CMT1A	1st or 2nd decade	Distal	17p11.2	PMP22
CMT1B	1st or 2nd decade	Distal	1q22-23	P0
CMT1C	1st or 2nd decade	Distal	?	?
CMT1D	1st or 2nd decade	Distal	10q21-22	EGR2
HNPP	Variable	Isolated peripheral nerves	17p11.2	PMP22
CMT3 (Dejerine-Sottas/ Congenital hypomyelination)	Infancy	Generalized, severe	17p11.2, 1q22-23, 10q21-22	PMP22, P0, EGR2
Autosomal recessive				
CMT4A	Infancy	Distal and proximal, severe	8q13-21	?
CMT4B1	Infancy	Distal and proximal, severe	11q23 (*MTMR*2)	Myotubularin-related protein-2
CMT4B2	1st or 2nd decade	Distal and proximal	11p15	?
CMT4C	Infancy	Distal, severe	5q23-33	?
CMT4D (HMSN-Lom)	1st decade	Distal, severe, deafness	8q24 (*NDRG*1)	N-myc downstream-regulated gene 1-related protein
CMT4E (HMSN-Russe)	Infancy	Distal, severe	10q21-22	?
CMT4F	Infancy	Distal, severe	19q13	?
X-linked dominant (CMTX)	1st or 2nd decade	Distal	Xq13.1 (*GJB*1)	Connexin 32

gene and the NDRG1 gene. The MTMR2 gene is mutated in one of the CMT4B subtypes, whereas mutations in the NDRG1 gene are responsible for HMSN-LOM, the hereditary motor and sensory neuropathy, first described in Gypsies of the Bulgarian town Lom, with deafness as a constant feature.

The diagnosis of demyelinating neuropathies is based on 1) clinical features and mode of inheritance and 2) electrodiagnostic (nerve conduction) studies, spinal fluid examination, molecular genetic analysis, and in selected cases peripheral nerve biopsy.

Physiology of nerve conduction

Nerve and muscle cells are charcterized by excitability of their plasma membrane. At rest, the membrane potential is determined by the sodium, potassium, chloride, and anorganic ion equilibrium potentials by means of their respective electrical and concentration gradients and permeabilities.

The polarisation condition of the membrane is continuously changing because of neurotransmitter-mediated inhibitory and excitatory postsynaptic potentials, leading to local and graded hyper- and depolarisation. When a critical depolarisation threshold is reached, opening of voltage-dependent sodium channels initiates a regenerative cycle with explosive depolarisation of the membrane and generation of an action potential. The membrane rapidly repolarizes by respective inactivation and activation of voltage-dependent sodium- and potassium channels, thus restoring the resting membrane potential. The action potential is propagated away from the neuronal soma via a local electrotonic current, created by a cloud of positive charges perturbing the equilibrium of the resting potential. The conduction velocity of the action potential is proportional to the axonal diameter and the characteristics of the myelin sheath (thickness and internodal length). Whereas in unmyelinated nerve fibers, nerve conduction is a slow process (up to 1 m/sec), sodium channels in myelinated fibers are located only at the nodes of Ranvier. The sodium current jumps from node to node ; depolarisation is therefore discontinuous. The processs of saltatory conduction is much faster (up to 100 m/sec) and much less energy-consuming than the process of continuous conduction in non-myelinated axons.

Nerve conduction studies allow to record the propagated action potential (Kimura, 1989). By inducing focal nerve depolarisation, electrical stimulation evokes a propagating nerve action potential, which can be recorded by surface plate- of ring-electrodes following the laws of the volume conduction theory. Propagated action potentials create a moving electrical dipole field. The amplitude of the recorded signal depends on the distance from and the density and surface of the dipole. The configuration of the signal depends on the montage of the active and reference recording electrodes. On supramaximal nerve stimulation, all axons depolarize and a compound action potential is recorded, the sensory nerve action potential (SNAP) from sensory nerves and the compound muscle action potential (CMAP) from muscle. Intervening steps in CMAP generation are the neuromuscular junction and the sarcolemma. The amplitude and area of the negative peak of the SNAP or CMAP correlate with the number of axons constituting the nerve. Compound action potentials are composed of multiple peaks, representing the range of sizes of axons and myelin sheaths ; their duration, therefore, is a measure of temporal dispersion. On distal and proximal stimulation of a nerve, the negative peak amplitude and area of the proximal as compared to the distal compound action potential is often smaller because of temporal dispersion and phase-cancellation. Under normal circumstances and over relatively short distances, this phenomenon does not significantly affect the CMAP, dispersion of which mainly occurs at the neuromuscular junction and the sarcolemma. However, it is pronounced in sensory nerves. Whereas distal stimulation leads to summation of the action potentials of slow- and fast-conducting axons, the conduction delay between these axons after proximal stimulation causes phase cancellation of the negative and positive peaks of the action potentials of slow- and fast-conducting axons, respectively. This may lead to up to 50% reduction of the SNAP negative peak amplitude and area (Kimura *et al.*, 1986). Latencies and conduction velocity of the signal are determined by the largest and fastest conducting axons. Nerve conduction studies, therefore, only measure the speed of the largest-diameter myelinated fibers. Evaluation of proximal nerve segments is more difficult and depends on late response (F- and H-wave) studies and nerve root stimulation techniques.

Consequences of demyelination

In myelinated axons, the amount of current generated by an impulse is severalfold larger than necessary for the excitation of consecutive nodes of Ranvier. In demyelinating neuropathies, loss of functional myelin leads to current leakage out of the affected axons. This first leads to an increased excitation time and consequent slowing of conduction. As demyelination progresses, residual current falls below the depolarization threshold and conduction block occurs. During nerve conduction studies, uniform slowing of conduction in all axons leads to prolongation of distal and proximal latencies and slowing of the conduction velocity. Differential slowing of conduction in the axons that constitute the nerve leads to abnormal temporal dispersion of the compound action potential, which becomes polyphasic and of increased duration (Fig. 1a). Reduction in amplitude and area of the compound action potential is proportional to the number of axons that fail to conduct. Depending on whether conduction failure occurs in part of or in all axons, partial or complete conduction block is observed (Fig. 1b). As mentioned above, partial conduction block can be detected in motor nerves only, since SNAP are subject to phase cancellation. When abnormal temporal dispersion or partial conduction block occur, latencies and conduction velocity may remain normal as long as some fast-conducting axons are functional.

Motor conduction block and abnormal temporal dispersion

Brown and Feasby (1984) were the first authors to show that conduction block is the main cause of weakness and sensory deficit in GBS. They subsequently demonstrated that demyelination is the pathological basis of conduction block in demyeli-

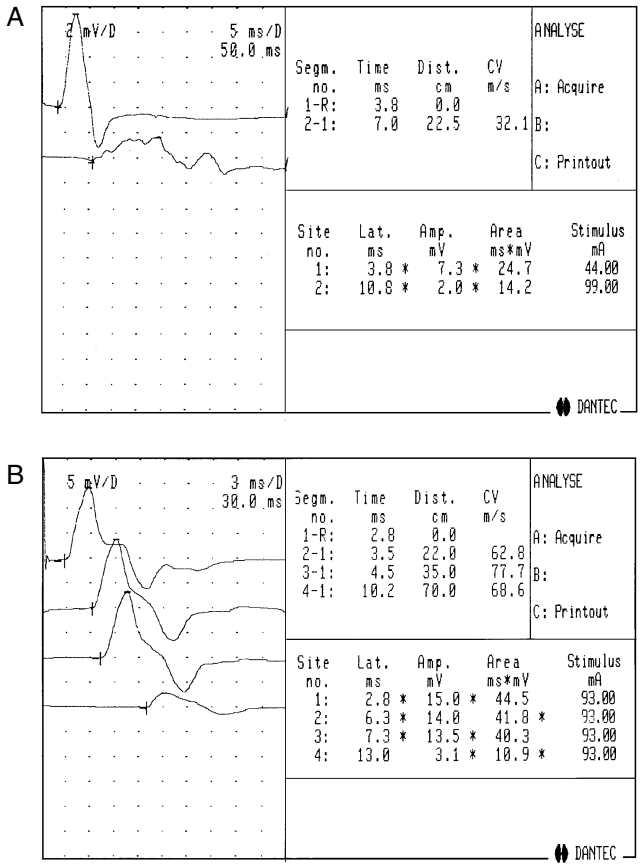

FIG. 1. — (A) Example of abnormal temporal dispersion of the proximal CMAP in the median nerve of a patient with CIDP. Negative peak CMAP amplitude and area reduction of 73 and 43%, respectively, is noted. Negative peak CMAP duration is increased by approximately 400%. (B) Example of partial motor conduction block in the ulnar nerve between Erb's point and the above elbow nerve segment in a patient with CIDP. Negative peak CMAP amplitude and area reduction of 77 and 73%, respectively, without change of duration is evident.

nating neuropathies (Feasby *et al.*, 1985). These authors found that, in normal control subjects, reduction of CMAP peak-to-peak amplitude or negative peak area never exceeded 20% and that increase in negative peak duration was less than 15% ; they considered a > 20% reduction in amplitude or area together with < 15% increase in duration evidence of definite motor conduction block (MCB). Probable MCB was defined as a > 30% reduction in amplitude or area when duration increase exceeded 15%. Other studies, however, have shown that these limits of normal values to define MCB may be too liberal and that differences exist between different nerves and between different age groups (Taylor, 1993 ; Oh *et al.*, 1994). For instance, Oh *et al.* (1994) found negative peak CMAP amplitude and area reductions of up to 41 and 25%, respectively, in the tibial nerve ; negative peak duration increased up to 30% in this nerve. The definition of MCB and abnormal temporal dispersion (ATD) is generally empirically based on the size reduction of the CMAP in various clinical populations and on the assumption that phase cancellation in motor nerves is insignificant (Kimura *et al.*, 1986). However, the findings of Kimura *et al.* (1986) relate to healthy subjects. It is conceivable, therefore, that differential slowing of conduction in demyelinating neuropathies or increased polyphasia of and a reduced number of motor unit action potentials in axonal neuropathies may result in significant phase cancellation. Rhee *et al.* (1990) have used a computer model of CMAP generation in rats to simulate MCB and ATD. They found that 1) the observed reduction in negative peak CMAP amplitude and area is related more to motor unit action potential size than number, i.e. the same result is obtained by blocking a small number of large, fast-conducting axons as a large number of small, slow-conducting axons, and 2) area reduction and amplitude reductions of up to 50 and 85%, respectively, were accounted for entirely by interphase cancellation of dispersed CMAPs. The authors concluded that the observed reduction in negative peak amplitude and area of the CMAP may under- or overestimate the degree of true MCB and that > 50% negative peak area reduction indicates at least some degree of MCB. Consensus criteria for MCB have been proposed by the American Association of Electrodiagnostic Medicine (Table 3, Guidelines in Electrodiagnostic medicine, 1999).

Electrodiagnostic criteria for primary demyelination

There are 4 basic electrodiagnostic parameters of demyelination : 1) reduced motor conduction velocity (MCV), 2) MCB or ATD in nerve segments not prone to compression, 3) prolonged motor distal latency (MDL), and 4) prolonged minimal F-wave latency or absent F-waves. Over the last 15 years, various sets of criteria have been proposed for GBS (Albers *et al.*, 1985 ; Albers and Kelly, 1989 ; Cornblath, 1990 ; Ho *et al.*, 1995 ; Meulstee *et al.*, 1995 ; Italian Guillain-Barré Study Group, 1996 ; Hadden *et al.*, 1998) and CIDP (Albers and Kelly, 1989 ; Barohn *et al.*, 1989 ; Ad Hoc Subcommittee of the American Academy of Neurology, 1991). These sets of criteria are very similar because they are based on the same 4 basic parameters, but they differ quantitatively 1) in the percentage of change from normal values and 2) the number of abnormal parameters that are required (Table 4).

Using their own sets of criteria, various authors (Albers *et al.* 1985 ; Meulstee *et al.* 1995 ; Italian Guillain-Barré Study Group, 1996 ; Hadden *et al.*, 1998) have reported sensitivity levels (% of patients fulfilling criteria) of 56-71% in personal GBS patient series (Fig. 2). When Alam *et al.* (1998) applied these criteria sets as well as those reported by others (Albers and Kelly, 1989 ; Cornblath, 1990 ; Ho *et al.*, 1995) to a series of 43

Table 3

Consensus criteria for Motor Conduction Block (MCB) (Guidelines in Electrodiagnostic Medicine, 1999)

10 cm nerve segments :		
Definite MCB :	↓ negative peak CMAP amplitude	> 50% (Median and Ulnar nerves)
		> 60% (Peroneal and Tibial nerves)
	↓ negative peak CMAP area	> 40% (Median and Ulnar nerves)
		> 50% (Peroneal and Tibial nerves)
	↑ negative peak CMAP duration	< 30%
Probable MCB :	↑ negative peak CMAP duration	31-60%
Up to 3 cm nerve segments :		
Definite MCB :	↓ negative peak CMAP amplitude/area	≥ 20%
	↑ negative peak CMAP duration	≤ 10%
Probable MCB :	↓ negative peak CMAP amplitude/area	≥10%
	↑ negative peak CMAP duration	0%

GBS patients, they found sensitivity levels of 21-72% (Fig. 2). In a series of 53 GBS patients, admitted to our Department between 1993 and 1999, we obtained 25-85% sensitivity (Fig. 2). When applying the criteria sets to a series of 41 patients with definite ALS, we found that all sets were 100% specific at least as far as ALS is concerned (Fig. 3).

Comparing 3 sets of criteria for CIDP (Albers and Kelly, 1989 ; Barohn *et al.*, 1989 ; Ad Hoc Subcommittee of the American Academy of Neurology, 1991), Bromberg (1991) found a maximal sensitivity level of 66%. Two disease control goups, consisting of patients with ALS and diabetic polyneuropathy, were used to demonstrate 100% specifity of the criteria. Using the criteria sets (Albers *et al.*, 1985 ; Albers and Kelly, 1989 ; Ad Hoc Subcommittee of the American Academy of Neurology, 1991 ; Ho *et al.*, 1995 ; Meulstee *et al.*, 1995 ; Italian Guillain-Barré Study Group, 1996 ; Hadden *et al.*, 1998) in a series of 28 CIDP and 12 MMN patients, diagnosed and treated in our Department between 1993 and 1999, we found sensitivity of 39-93% and 25-100%, respectively, with 100% specificity with respect to our ALS patient series (Fig. 3).

Our results in patients with GBS, CIDP, and MMN indicate that published criteria sets are specific at least with respect to ALS. They show that the electrodiagnostic yield in general is higher for the chronic demyelinating neuropathies. Furthermore, they show that sensitivity is higher when criteria for only 1 parameter need to be fulfilled (Albers *et al.*, 1985 ; Ho *et al.*, 1995 ; Meulstee *et al.*, 1995 ; Hadden *et al.*, 1998) as compared to 2 (Italiajn Guillain-Barré Study Group, 1996) or 3 (Albers and Kelly, 1989 ; Cornblath, 1990 ; Ad Hoc Subcommittee of the American Academy of Neurology, 1991) parameters. Most sets of criteria have been designed for clinical research studies. Although highly specific, they may be too rigid for use in routine clinical practice. Further studies are therefore underway to define and select criteria for primary demyelination that are less restrictive in order to enhance diagnostic sensitivity.

Hereditary demyelinating neuropathies (CMT1)

The distinction between hereditary demyelinating and acquired chronic demyelinating neuropathies can often be made on clinical grounds, but sometimes the family history and the clinical findings remain inconclusive. In these cases, electrodiagnostic features are helpful (Lewis and Sumner, 1982 ; Kaku *et al.*, 1993). In patients with CMT1, uniform conduction slowing in all segments of one nerve and in different nerves is observed ; conduction velocities are below 60% of normal values. Moreover, MCB and ATD do not occur in these patients ; if they occur, they are localized at sites that are prone to compression. In CIDP, conduction slowing is multifocal, different nerves are unequally affected, and MCB or ATD are frequent findings. In HNPP, multifocal slowing, MCB, and ATD do occur. A background sensorimotor neuropathy with mainly sensory conduction slowing, prolonged motor distal and F-wave latencies is common ; MCB and ATD only occur at sites of compression or entrapment (Andersson *et al.*, 2000).

CMTX is an autosomal dominantly inherited neuropathy, due to numerous mutations in a gene, encoding the Schwann cell protein, connexin 32. Although a Schwann cell disorder, there is controversy as to whether CMTX is primarily demyelinating with secondary axonal degeneration or axonal. Intermediate-range nerve conduction velocities, slower in males than in females have been reported (Nicholson and Nash, 1993). CMAP amplitudes are reduced and in lower extremity nerves, they are frequently absent (Birouk *et al.*, 1998). The finding of non-uniform slowing within

Table 4

Comparison of published electrodiagnostic criteria for primary demyelination.
% = percent deviation from the upper or lower limit of normal values.

Criteria set	Nerve conduction parameters										Number of abnormal parameters required
	Conduction Velocity slowing		Distal Latency prolongation		F-wave Latency prolongation		Conduction Block		Temporal Dispersion		
	%	# of nerves	%	# of nerves	%	# of nerves	%	# of nerves	%	# of nerves	
Albers *et al.*., 1985	5	2	10	2	20	2	30	2	30	2	1
Albers and Kelly, 1989	10	2	15	2	25	1	30	1	30	1	3
Cornblath, 1990 ; AAN criteria, 1991	20	2	25	2	20	2	20	1	15	1	3
Ho *et al.*., 1995	10	2	10	2	20	2		2	30	2	1
Meulstee *et al.*., 1995	30	2	50	2	50	2	20	2	50	2	1
Italian GB Study Group, 1996	20	2	25	2	20	2	30	2	30	2	2
Hadden *et al.*., 1998	10	2	10	2	20	2	50	2		2	1

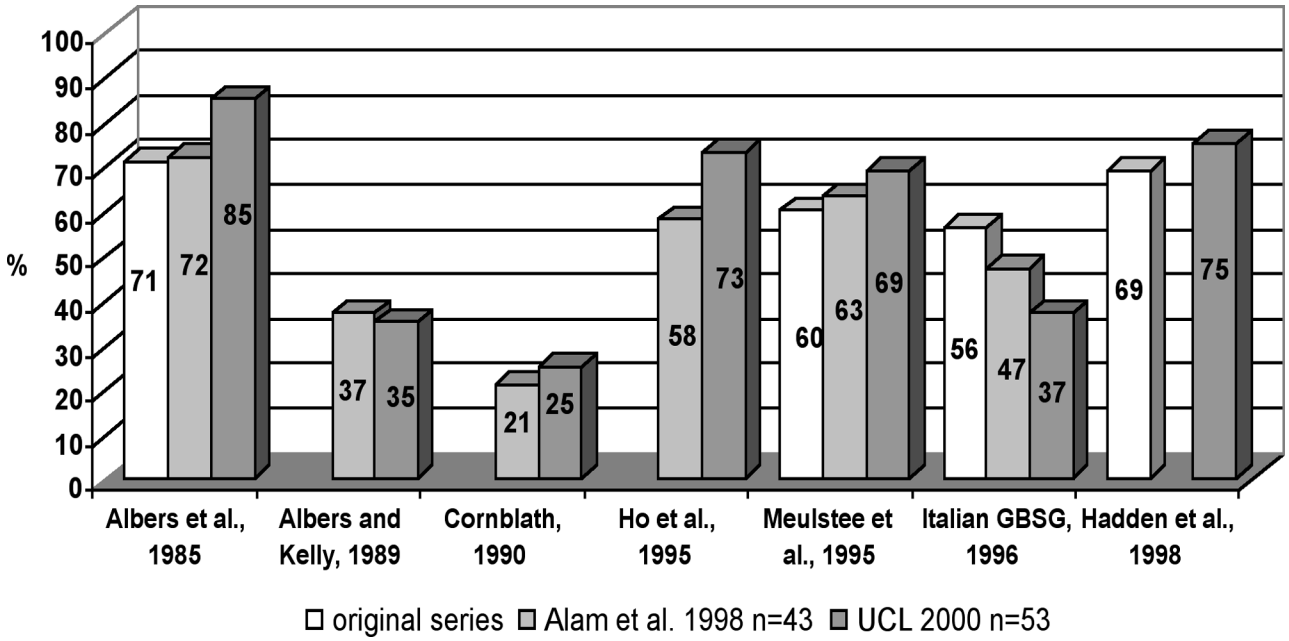

FIG. 2. — Sensitivity of published electrodiagnostic criteria sets for GBS as applied to patients recruited by the original authors, by Alam *et al.*. (1998), and in our Department of Neurology between 1993 and 1999.

and between nerves as well as ATD (Tabaraud *et al.*, 1999 ; Gutierrez *et al.*, 2000) lend support for primary demyelination. This pattern of electrodiagnostic features is unique in the hereditary demyelinating neuropathy group and raises problems for the differential diagnosis with CIDP. Interestingly, all affected males and some females have abnormal brainstem auditory evoked potentials with a I-V interpeak delay (Nicholson and Corbett, 1996 ; Nicholson *et al.*, 1998). Brainstem auditory evoked potentials, therefore, may be helpful in characterizing CMTX.

Conclusion

In establishing the diagnosis of demyelinating neuropathies, nerve conduction studies play a key role. In experienced hands, application of electrodiagnostic criteria for primary demyelination are highly specific, but the level of sensitivity is inversely proportional to the amount of change from normative values for individual parameters of demyelination and the number of abnormal parameters of demyelination required for the diagnosis. In most instances, the pattern of nerve conduction abnormalities may provide important clues for the distinction between acquired inflammatory and hereditary demyelinating neuropathies. Based on the electrodiagnostic features and advances in molecular genetics, a definitive diagnosis can be reached in a short period of time and without nerve biopsy, an invasive and time-consuming procedure. Further studies may refine and improve the yield of the electrodiagnostic examination in demyelinating neuropathies.

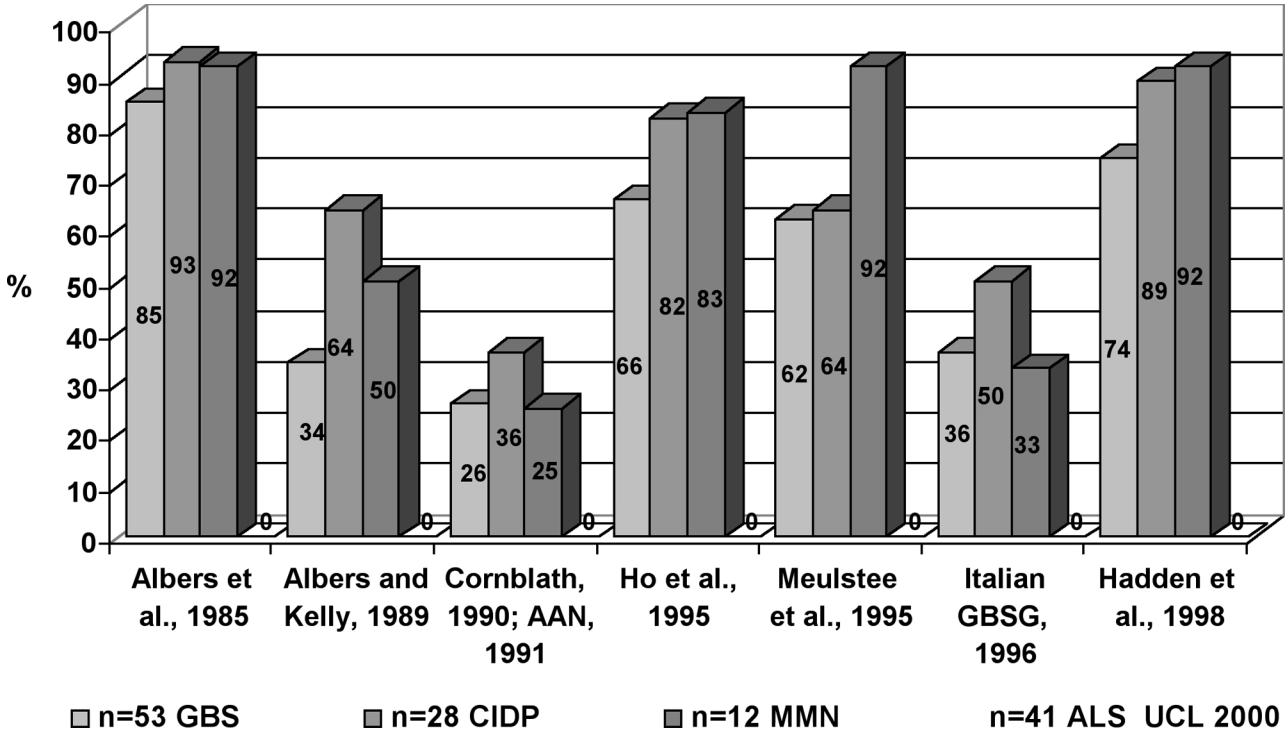

FIG. 3. — Sensitivity and specificity of published criteria sets for primary demyelination as applied to patients with GBS, CIDP, MMN, and ALS, admitted to our Department of Neurology between 1993 and 1999.

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