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REVIEW ARTICLE

# Clinical and Electrophysiological Aspects of Charcot-Marie-Tooth Disease

***D. Pareyson,*[*,1] V. Scaioli,[2] and M. Laurà[1]***

*[1]Division of Biochemistry and Genetics, and [2]Division of Clinical Neurophysiology, Carlo Besta National Neurological Institute, via Celoria, 11, 20133, Milan, Italy*

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## Abstract

Charcot-Marie-Tooth disease (CMT) is a genetically heterogeneous group of disorders sharing the same clinical phenotype, characterized by distal limb muscle wasting and weakness, usually with skeletal deformities, distal sensory loss, and abnormalities of deep tendon reflexes. Mutations of genes involved in different functions eventually lead to a length-dependent axonal degeneration, which is the likely basis of the distal predominance of the CMT phenotype. Nerve conduction studies are important for classification, diagnosis, and understanding of pathophysiology. The subdivision into demyelinating CMT1 and axonal CMT2 types was a milestone and is still valid for the majority of patients. However, exceptions to this partition are increasing. Intermediate conduction velocities are often found in males with X-linked CMT (CMTX), and different intermediate CMT types have been identified. Moreover, for some genes, different mutations may result either in demyelinating CMT with slow conduction, or in axonal CMT. Nerve conduction slowing is uniform and diffuse in the most common CMT1A associated with the 17p12 duplication, whereas it is often asymmetric and nonhomogeneous in CMTX, sometimes rendering difficult the differential diagnosis with acquired inflammatory neuropathies. The demyelinating recessive forms, termed CMT4, usually have early onset and run a more severe course than the dominant types. Pure motor CMT types are now classified as distal hereditary motor neuronopathy. The diagnostic approach to the identification of the CMT subtype is complex and cannot be based on the clinical phenotype alone, as different forms are often clinically indistinguishable. However, there are features that may be of help in addressing molecular investigation in a single patient. Late onset, prominent or peculiar sensory manifestations, autonomic nervous system dysfunction, cranial nerve involvement, upper limb predominance, subclinical central nervous system abnormalities, severe scoliosis, early-onset glaucoma, neutropenia are findings helpful for diagnosis.

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*Author to whom all correspondence and reprint requests should be addressed. E-mail: dpareys@istituto-besta.it

## Historical Notes, Eponyms, and Acronyms

Almost 120 yr have elapsed since the first contemporary description of the same familial neurological syndrome, "peroneal muscular atrophy," by Charcot and Marie in Paris, and Tooth in England in 1886 (Charcot and Marie, 1886; Tooth, 1886). Their reports of the syndrome, which was later named after them, already described the main clinical features (Charcot and Marie, 1886; Tooth, 1886), including inheritance, skeletal deformities, progressive distal muscle wasting and weakness, and attribution to a peripheral nerve disorder (Tooth, 1886). Some years later, Déjèrine and Sottas (1893) described in two siblings a more severe neuropathy, with early onset and nerve hypertrophy.

Gilliat and Thomas (1957) and Dyck and Lambert (1968a) first observed that electrophysiological studies revealed a marked nerve conduction slowing in some families with hereditary neuropathy, whereas conduction was preserved in others. Dyck and Lambert (1968a,1968b), and Thomas and Harding (Thomas et al., 1974; Harding and Thomas, 1980a, 1980b) greatly contributed to a rational classification of the complex of peroneal muscular atrophies according to inheritance pattern, clinical, electrophysiological, and pathological features. They introduced the term hereditary motor and sensory neuropathy (HMSN) and labeled HMSN type I the autosomal-dominant "hypertrophic" form with low conduction velocities, in which segmental demyelination and remyelination of peripheral nerves were observed. They labeled HMSN type II the autosomal-dominant form with preserved or mildly slowed nerve conduction velocities, in which nerve pathology showed axonal degeneration and regeneration. HMSN type III is the disease described by Déjèrine and Sottas as a severe "hypertrophic" demyelinating neuropathy with early onset. HMSN type IV is the autosomal-recessive hypertrophic neuropathy found in Refsum's disease. HMSN type V is characterized by peroneal muscular atrophy and spastic paraplegia. HMSN types VI and VII are the peroneal muscular atrophy syndrome complicated by optic atrophy and pigmentary retinopathy, respectively (Dyck et al., 1993). A familial disorder with hypertrophic neuropathy and tremor (Roussy–Lévy syndrome) had long been considered a separate entity (Roussy and Lévy, 1926).

Harding and Thomas (1980a) observed that in HMSNs the motor nerve conduction velocities (NCV) showed a bimodal distribution, and set at 38 m/s in the median nerve an arbitrary but rational limit between demyelinating HMSN type I (motor NCV <38 m/s) and the axonal HMSN II (motor NCV >38 m/s). They also studied a large series of patients with a pure motor form of peroneal muscular atrophy, that has been labeled "spinal Charcot-Marie-Tooth (CMT) disease," distal spinal muscular atrophy, or distal hereditary motor neuronopathy (dHMN) (Harding and Thomas, 1980b).

With the advent of the molecular era, the HMSN acronym was often substituted in the literature by the original eponym of CMT disease. Therefore, the demyelinating variety CMT1 corresponds to HMSN type I; the axonal form CMT2 stands for HMSN type II; HMSN type III has been replaced by Déjèrine–Sottas neuropathy (DSN) (and not by CMT3, which never entered into use). Distal hereditary motor neuro(no)pathy is the current term indicating the pure motor forms. Incredible advances have occurred during the last 15 yr, increasing our knowledge on pathogenic mechanisms and making genotype–phenotype correlation possible. At the same time, however, the classification and the diagnostic approach have become more complicated.

## The Typical CMT Clinical Phenotype

CMT disease is the most common inherited neuromuscular disorder, with its estimated prevalence being 17–40 : 100,000 (Martyn and Hughes, 1997). Although it is genetically a highly heterogeneous disorder, the clinical phenotype is relatively homogeneous. This is characterized by wasting and weakness of distal limb muscles, involving especially the peroneal compartment (hence the old term of peroneal muscular atrophy), usually associated with distal sensory loss, skeletal deformities, and decrease or absence of deep tendon reflexes (Shy et al., 2005) (Fig. 1).

The clinical phenotype is similar for CMT disease caused by mutations in many different genes involved in very diverse functions, coding for structural myelin proteins, gap-junction forming proteins, cytoskeleton elements, enzymes, transcription factors, and so on. Dysfunction of all these proteins, even when primarily affecting myelin, eventually leads to an axonal degeneration that is length-dependent (Scherer, 1999; Krajewski et al., 2000, Kamholz et al.,

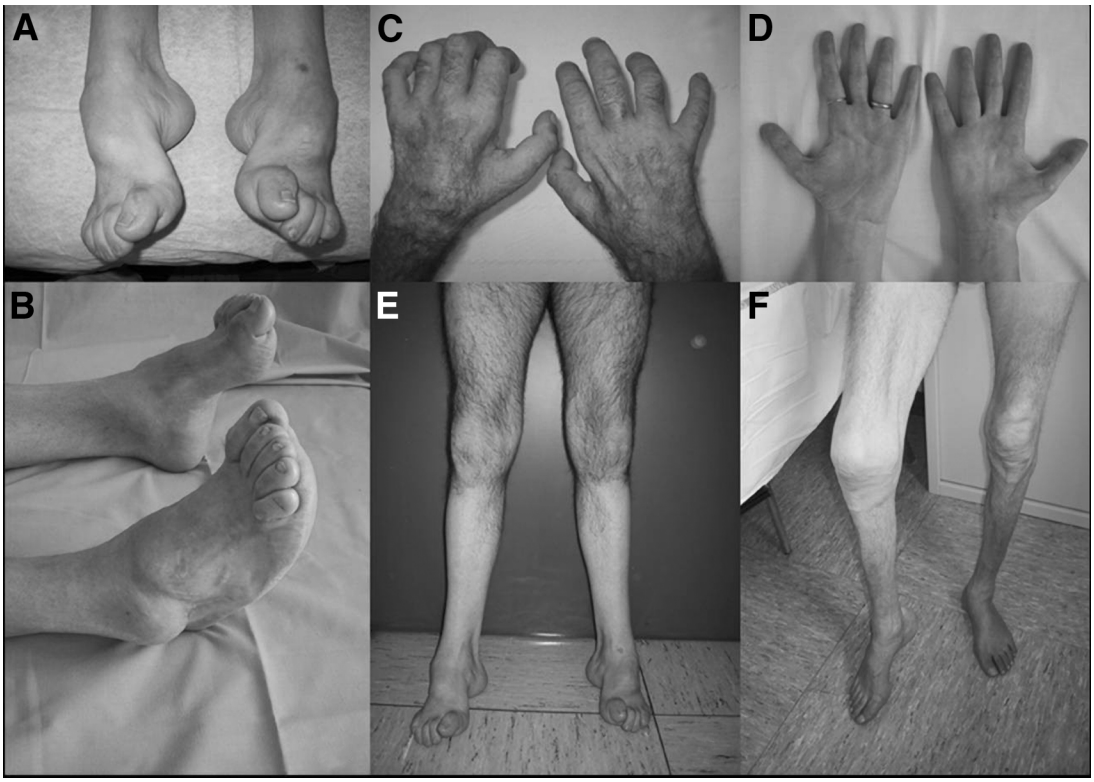


Fig. 1. Clinical features of Charcot-Marie-Tooth (CMT) disease. **(A,B)** Moderate to severe foot deformities in CMT1A and note the pes cavus, hammer toes, and callosities. **(C)** Severe wasting of intrinsic hand muscles in a male patient with CMT. **(D)** Wasting of hand muscles in a female patient with CMTX. Note that muscles of the thenar eminence are more severely involved than hypothenar muscles, suggesting that the median nerve is more severely affected than the ulnar nerve. **(E)** Patient with CMT1A and note the pes cavus, moderate wasting of leg muscles and of the lower third of the thigh. **(F)** Patient with late-onset CMT2 associated with an *MPZ* gene mutation. Foot drop, severe wasting of lower limb muscles, no evidence of foot deformities. Differential diagnosis with acquired axonal polyneuropathy is extremely difficult in the absence of family history of neuropathy.

2001). Therefore, longer fibers are affected first and more severely, thus producing distal impairment of limb functions, which progressively involves feet and legs and later hands and distal thighs, and results in the typical inverted champagne bottle appearance of the legs. At the same time, sensory loss involves first the feet and then spreads to the legs and later to the hands, and deep tendon reflexes are usually lost also with a length-dependent pattern. Exceptions to this general rule in CMT are rare and may point to specific underlying gene mutations. This is also the reason why the different forms of CMT are usually clinically indistinguishable in a single patient, and the precise CMT subtype diagnosis requires a complex approach, based also on inheritance pattern and electrophysiological examination (Ad hoc working group, 1999; Pareyson, 2003).

Disease severity is highly variable, even within the same kinship. Some individuals may show minimal signs and are unaware of being affected, whereas others may be significantly disabled. However severe impairment and loss of autonomy is infrequent in CMT. Marked difference in disease severity has been reported in identical twins with CMT1A (Garcia et al., 1995). The reasons for such variability of disease expression for CMT caused by the same mutation are unknown and the search for modifier factors is ongoing.

Disease onset usually occurs during the first decades of life and the course is very slowly

progressive over decades. Rarely, CMT arises in early infancy with hypotonia, or delay in motor milestones; onset may occur in infancy with toe walking (Thomas et al., 1997; Pareyson, 2004b). On the other extreme, there are patients and families in which CMT has a late onset (Harding and Thomas, 1980a; Shy et al., 2004). However, the most common heralding symptoms are walking difficulties with steppage gait in a child or adolescent with pes cavus (Shy et al., 2005).

Skeletal deformities are typically found in CMT, being present in more than 66% of all patients, and in 70–95% of CMT1 patients, and they are mainly characterized by pes cavus with hammer toes (Fig. 1A,B), whereas scoliosis is less common (Harding and Thomas, 1980a; Sghirlanzoni et al., 1990; Hoogendjik et al., 1994; Shy et al., 2005). Foot deformity mechanisms are still unclear, being attributed to imbalance of intrinsic foot and leg muscles especially when starting early in life. Sometimes pes planus is the first foot deformity early in infancy, with subsequent evolution into pes cavus (Feasby et al., 1992; Garcia et al., 1998). Foot deformities are absent when CMT has later onset and this may make diagnosis difficult (Fig. 1F).

Motor impairment with atrophy and weakness starts in intrinsic foot muscles (Berciano et al., 2003) and slowly ascends to leg muscles, then to the lower third of the thigh and hand muscles and later to the forearms, following the length-dependent axonal degeneration of fibers (Fig. 1C–F). Steppage gait and foot drop are the most common and first signs; weakness of foot plantar flexors usually occurs later and is less severe. Claw hand, or "main en griffe," is the typical hand deformity that may develop in the course of the disease (Fig. 1C). Weakness of proximal muscles is rare in CMT and occurs only in the most severe patients. Gait may be variably affected but is usually autonomous with the exception of the most severe patients (Harding and Thomas, 1980; Shy et al., 2005).

Sensory signs are usually less prominent then motor ones, and sometimes they are subtle (Harding and Thomas, 1980; Thomas et al., 1997; Shy et al., 2005). The most frequent finding is loss of sensation to touch, pain, and vibration distally in the lower limbs. Upper limbs are less frequently and less severely affected. Impairment of position sense is less common; however, sensory ataxia may develop. Positive sensory symptoms such as spontaneous distal limb paraesthesias or pain may occur. Sensory nerves are typically spared in distal HMN. Deep tendon reflexes are reduced to absent in most patients with demyelinating CMT, whereas they are less frequently abnormal in CMT2 and dHMN (Harding and Thomas, 1980a,1980b; Sghirlanzoni et al., 1990). Muscle cramps, cold feet, acro-cyanosis are other frequent complaints.

## Inheritance Pattern

CMT is usually transmitted as an autosomal-dominant trait (CMT1, CMT2, and "intermediate" CMT). However, an X-linked form, CMTX, is associated with mutations of the gap-junction protein 1 gene *(GJB1/Cx32)*, and appears to be rather common (up to 10% of all CMT patients) (Dubourg et al., 2001a; Boerkoel et al., 2002). The autosomal-recessive demyelinating forms of CMT, grouped under the term of CMT4 (a genetical classification different from the earlier CMT/HMSN classification), almost invariably have early onset and are more severe than the dominant types (De Jonghe et al., 1997; Pareyson, 2003). Autosomal-recessive axonal forms (AR-CMT2) have been reported, although rarely (Cuesta et al., 2002; De Sandre-Giovannoli et al., 2002). Distal HMN may be inherited as a dominant or recessive trait (Harding, 1993). Overall, sporadic patients are common and may be owing to *de novo* mutations (Hoogendijk et al., 1992; Boerkoel et al., 2002). Inheritance may be difficult to assess, as expression variability is high in CMT, and oligosymptomatic patients may elude diagnosis. Therefore, clinical and often electrophysiological examination of first-degree relatives is warranted to ascertain the inheritance pattern.

## Electrophysiological Aspects

Electrophysiological studies allowed a rational classification of CMT disease and were of help, together with neuropathology, in the understanding of its pathophysiology. The subdivision into two main forms was a milestone: CMT1, characterized by a marked slowing in nerve conduction velocities (by definition <38 m/s in upper limb motor nerves) and by a primary myelinopathy, and CMT2, in which nerve conduction values are preserved or only mildly slowed (>38 m/s in upper limb motor nerves) and the axon is the primary disease target (Harding and Thomas, 1980a). This partition is still

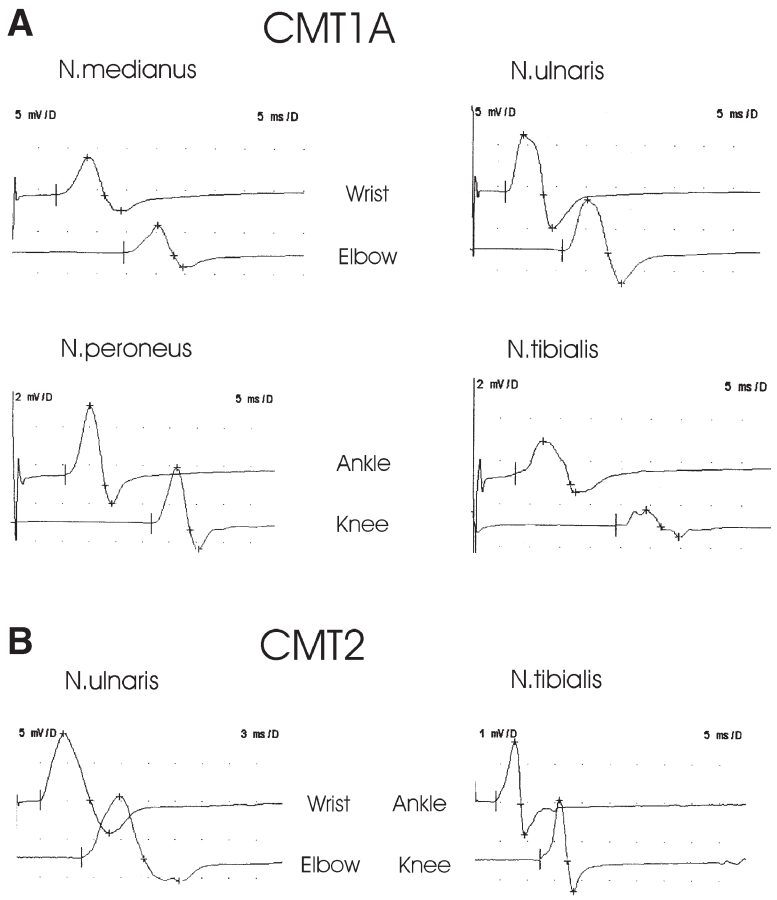


Fig. 2. Electrophysiological findings in CMT1A and CMT2. **(A)** CMT1A: Recordings obtained from a 24-yr-old female. The motor nerve conduction velocities (NCV) are markedly reduced, ranging from 18.5 to 20 m/s in all tested nerves. The distal motor latency is increased and ranges from 6.2 ms (ulnar nerve) to 10.4 ms (peroneal nerve). The compound muscle action potential (CMAP) shapes are simple, with no evidence of temporal dispersion but very mild at the tibial nerve by proximal stimulation. These findings are in keeping with a homogeneous and diffuse demyelinating involvement of the peripheral nervous system. **(B)** CMT2. Motor conduction velocity and distal motor latencies are normal; ulnar nerve CMAP is of normal amplitude (10 mV), while tibial nerve CMAP is reduced in amplitude. The CMAP shape is simple and there is no temporal dispersion. Sensory nerve action potential (SNAP) amplitude is decreased particularly in lower limb nerves (not shown). In conclusion, the findings demonstrate a length-dependent axonal sensory-motor neuropathy.

valid for the majority of patients, although exceptions to this general rule are increasing, reflecting the heterogeneity of CMT. The existence of a CMT subgroup showing NCV values "intermediate" between CMT1 and CMT2 has long been disputed (Humberston, 1972; Salisachs, 1974; Brust et al., 1978; Davis et al., 1978). Thanks to molecular genetics advances, we now know that most CMT patients and families with intermediate NCV carry mutations in the *GJB1* gene and have CMTX (Nicholson and Nash, 1993; Birouk et al., 1998); the presence of intermediate forms has been further supported by the identification of at least three forms of "dominant intermediate CMT (DI-CMT)" (Villanova et al., 1998; Verhoeven et al., 2001; Jordanova et al., 2003b; Züchner et al., 2005).

Electrophysiological examination allows evaluation of motor and sensory nerves, and of secondary muscle derangement, and is a fundamental step in the diagnostic process (*see* Figs. 2 and 3).

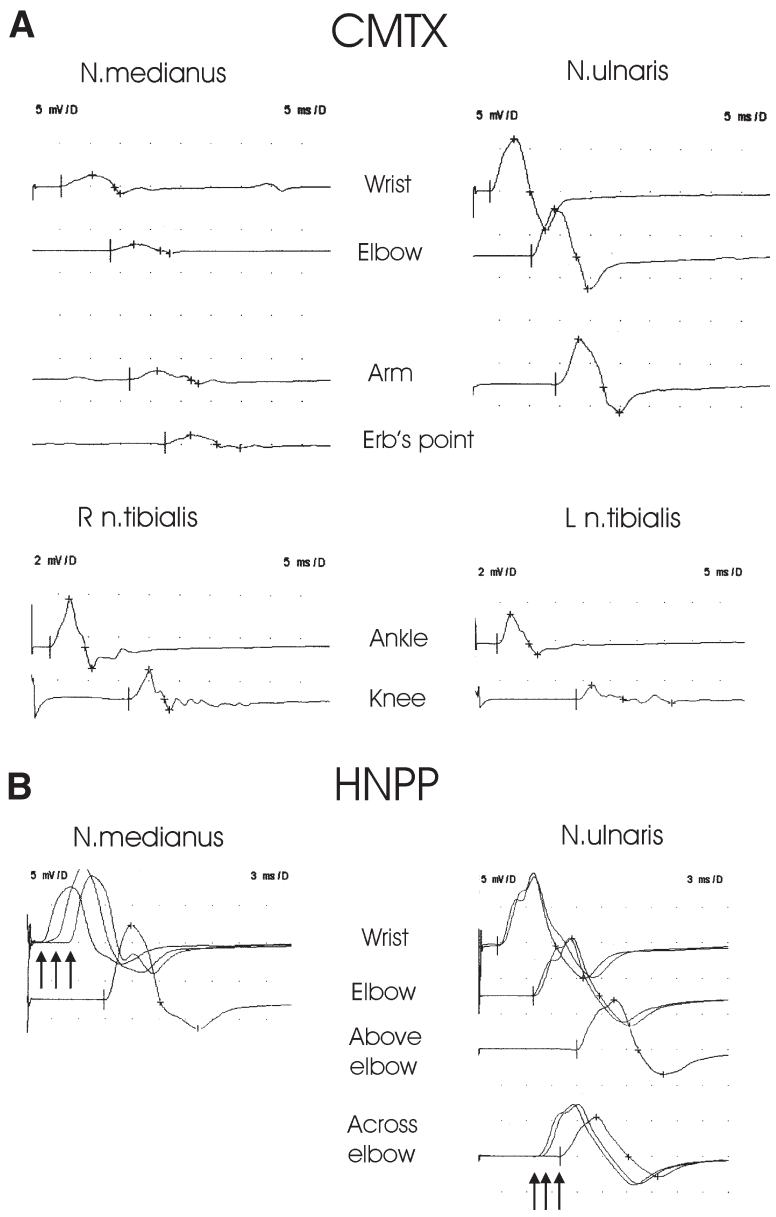


Fig. 3. Electrophysiological findings in CMTX and in hereditary neuropathy with liability to pressure pulsies (HNPP). **(A)** CMTX: median, ulnar and tibial nerve recordings from a 31-yr-old male. In lower limbs, motor conduction velocity is clearly reduced (27.6 m/s), distal motor latency is within the norm, and the distal compound muscle action potential (CMAP) is reduced in amplitude and slightly dispersed. CMAP obtained by proximal stimulation (popliteal region) is further reduced in amplitude and shows an increased temporal dispersion. In the upper limbs, the median motor conduction velocity is reduced (29 m/s), with an increased distal latency, and a severe reduction of CMAP amplitude. On the other hand, the ulnar nerve motor conduction velocity is in the intermediate range (35 m/s), the CMAP is normal, and there is no increased temporal dispersion. Conduction velocity in the intermediate range in the upper limbs, more severe involvement of the median nerve as compared to the ulnar nerve, and evidence of increased temporal dispersion represent electrophysiological features strongly suggestive of CMTX. **(B)** HNPP: the disease is characterized by focal slowing at common sites of entrapment. Median

NCV studies are performed to evaluate the presence, degree, and pattern of conduction slowing along motor and sensory nerves, and in proximal as well as in distal segments. Conduction slowing provides indirect evidence of myelin dysfunction and is usually considered a sign of demyelination or hypomyelination. However, NCV reduction may be also owing to other mechanisms, including abnormalities of ion channels, of nodes and paranodes, and of Schwann cell–axon interactions (Capasso et al., 2004). The degree of axonal damage and loss of fibers are reflected in a reduction in amplitude of compound muscle action potential (CMAP) for motor nerves, and of sensory nerve action potential (SNAP) for sensory nerves. Both axonal and demyelinating CMT eventually result in loss of axons and in reduction of CMAP and SNAP amplitudes (Lewis et al., 2000).

In a seminal article in 1982, Lewis and Sumner (1982) remarked that in hereditary hypertrophic neuropathies, such as CMT1 and Déjèrine-Sottas syndrome, the NCV slowing is uniform and diffuse, whereas in the acquired inflammatory neuropathies it is nonhomogeneous, asymmetrical, and characterized by partial conduction blocks. This seems logical, as in CMT1 and DSN there is a generalized dysfunction of myelin and Schwann cells, whereas myelin derangement and inflammation are randomly scattered and focal in inflammatory neuropathies. This criterion has long been useful for differential diagnosis, because acquired inflammatory neuropathies may be misdiagnosed as CMT and DSN, and vice-versa. It has become clear, however, that there are important exceptions. It is true that CMT1A, associated with peripheral myelin protein 22 gene *(PMP22)* duplication, is indeed characterized by a homogeneous and diffuse nerve conduction slowing, that is similar in different nerves, in upper and lower limbs, in proximal and distal segments, without conduction blocks (Kaku et al., 1993; Uncini et al., 1995; Lewis et al., 2000). On the other hand, there is increasing evidence that in CMTX, conduction abnormalities are often nonuniform among different nerve trunks and also along the same nerve, and excessive temporal dispersion and even conduction blocks may be found (Tabaraud et al., 1999; Gutierrez et al., 2000; Lewis et al., 2000; Capasso et al., 2004); patients with CMTX have been misdiagnosed as being affected by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Rarely, conduction blocks have been reported also in CMT associated with myelin protein zero (*MPZ*) gene mutations (Street et al., 2002; De Angelis et al., 2004). Moreover, hereditary neuropathy with liability to pressure palsies (HNPP) by definition is a generalized neuropathy characterized by focal conduction slowing at entrapment sites (Pareyson et al., 1996; Andersson et al., 2000; Stögbauer et al., 2000). CMTX has other peculiarities. It is an X-linked disorder, and males are more severely affected than females on clinical and electrophysiological grounds. Although NCV values may widely vary (between 18 and 60 m/s), males have lower conduction velocities, usually in the so-called intermediate range (25–45 m/s in upper limb nerves), whereas females usually have normal or mildly slowed NCV, in the lower range of CMT2 (Nicholson and Nash, 1993; Birouk et al., 1998; Hahn et al., 1999; Lewis et al., 2000; Dubourg et al., 2001b). Despite the conduction slowing observed in CMTX patients, particularly in males, nerve biopsy often shows predominance of chronic axonal changes (Birouk et al., 1998; Hahn et al., 1999; Hattori et al., 2003). It is therefore disputed whether CMTX is a primary myelinopathy or an axonopathy (Birouk et al., 1998; Scherer and Fischbeck, 1999). *GJB1* codes for connexin-32, which forms gap-junctions in noncompact myelin at the paranodal region and at the Schmidt-Lantermann incisures. It is likely that gap-junction dysfunction causes electrophysiological

Fig. 3. *(Continued)* and ulnar nerve recordings from a 22-yr-old female. Median nerve: distal motor latency is increased (4.8 ms), although motor conduction velocity is normal (55 m/s). The CMAP is normal in amplitude and there is no temporal dispersion. The typical focal conduction slowing across the wrist is demonstrated by the inching stimulation technique (Kimura, 1979); in the panel the arrows indicate the sites of stimulation, each 1 in. apart, across the wrist. Ulnar nerve: the distal motor latency (2.6 ms), and the conduction velocity elbow-to-wrist (53 m/s) are normal. However, the stimulation above the elbow shows a significant reduction in conduction velocity (38 m/s); the site of conduction slowing is shown to be localized to the elbow by stimulation 1 in. above and below elbow (arrows).

conduction abnormalities at the paranodal level, precocious anatomical abnormalities of incisures and paranodal regions, alterations of axonal-Schwann cell interactions and eventually an axonopathy (Hahn et al., 1999; Lewis et al., 2000; Capasso et al., 2004).

CMT2 is characterized by reduction in CMAP and SNAP amplitudes, which slowly progresses over the years, reflecting axonal degeneration and progressive fiber loss. Nerve conduction is usually normal or mildly slowed, depending on the amount of large diameter fiber loss. Sometimes nerve conduction is preserved early in the course of the disease and progressively decreases over decades. This evolution has been observed with *MPZ* mutations, which usually provoke a clearly demyelinating neuropathy, but rarely are associated with intermediate CMT (Mastaglia et al., 1999) or definitely axonal CMT2 (Marrosu et al., 1998; Chapon et al., 1999; De Jonghe et al., 1999; Misu et al., 2000). Late-onset CMT2, sometimes with severe progressive course, has also been associated with *MPZ* mutations (De Jonghe et al., 1999; Misu et al., 2000; Senderek et al., 2000; Auer-Grumbach et al., 2003). How dysfunction of a compact-myelin protein such as MPZ may result in an axonal neuropathy is still unclear (Shy et al., 2004).

As our knowledge on gene mutations increases, there is growing evidence that the distinction between demyelinating and axonal CMT is somewhat artificial. The examples of mutations of the same genes that may result either in a "demyelinating" CMT with slow conduction or in an "axonal" CMT are increasing, and include now *MPZ* (associated with CMT1B, DSN, congenital hypomyelinating neuropathy, and CMT2), neurofilament light chain in CMT2F and CMT1E), ganglioside differentiating associated protein 1 (in CMT4A and AR-CMT2), and *GJB1/Cx32* (in CMTX) (Lewis et al., 2000; Mersiyanova et al., 2000; De Jonghe et al., 2001; Nelis et al., 2002; Hattori et al., 2003; Jordanova et al., 2003a; Shy et al., 2004). Moreover, the existence of at least three genetically distinct forms of dominantly inherited intermediate CMT has been established (Villanova et al., 1998; Verhoeven et al., 2001; Jordanova et al., 2003b; Züchner et al., 2005). DI-CMT families show a wide range of NCV, overlapping both CMT1 and CMT2 values and hampering classification using traditional electrophysiological criteria; median motor NCV is usually between 25 and 45 m/s, and overall NCV range from 23 m/s to normal values (Rossi et al., 1985; Kennerson et al., 2001; Speer et al., 2002; Jordanova et al., 2003b; Züchner et al., 2005). In at least one family, NCV values decreased with age and correlated with disease severity (Rossi et al., 1985). Histopathological examination of nerve biopsies from DI-CMT subjects demonstrated features of both chronic axonal degeneration and demyelination (Rossi et al., 1985; Kennerson et al., 2001).

In distal HMNs, sensory nerves are entirely spared, and NCV studies usually show decreased CMAPs with preserved conductions. Distinction between distal HMN and axonal CMT2 is also sometimes difficult, and mutations in the same genes have been reported to be associated with both diseases: glycil-tRNA synthetase (Sambuughin et al., 1998; Antonellis et al., 2003), heat-shock 27-kDa protein 1 *(HSPB1)* (Evgrafov et al., 2004) and heat-shock 22-kDa protein 8 *(HSPB8)* (Irobi et al., 2004; Tang et al., 2005). It is likely that these gene mutations selectively or predominantly affect motor neurons, but may also impair sensory neurons to a variable extent, thus causing shift of diagnosis depending on the presence and severity of sensory involvement.

In all CMT types, needle EMG examination usually shows signs of chronic denervation with muscle unit potentials of increased amplitude and duration, distal muscles being more involved than proximal ones (Sghirlanzoni et al., 1990). Signs of ongoing denervation (i.e., fibrillation potentials and positive sharp waves) are usually seen in the most severe and rapidly progressive forms.

## The Most Frequent CMT Subtype: CMT1A

The most common CMT form is CMT1A, associated with the 17p12 duplication, which accounts for 60 to 90% of CMT1 patients and for 40 to 50% of all CMT patients (Nelis et al., 1996; Dubourg et al., 2001a; Boerkoel et al., 2002). Large series of patients have been studied (Birouk et al., 1997; Thomas et al., 1997; Hattori et al., 2003). It is the prototype of the typical CMT phenotype. It is characterized by early onset but has an overall milder course than average CMT. However, disease severity is highly variable, as mentioned earlier. Nerve hypertrophy can sometimes be clinically appreciated particularly

at the greater auricular nerve behind the ear and in the arm.

Motor and sensory NCV are typically markedly slowed in a homogeneous, uniform and diffuse way. Motor NCV values are included in the 15–30 m/s range in most patients, with exceptional patients showing upper limb motor NCV greater than 40 m/s (Nicholson, 1991; Kaku et al., 1993; Wise et al., 1993; Birouk et al., 1997; Thomas et al., 1997; Lewis et al., 2000). In our series of 78 patients in whom we performed electrophysiological studies, motor and sensory NCV were always below the limit of 32 m/s: mean upper limb motor NCV was 19.8 ± 5.2 m/s, range = 7–32 m/s. Distal motor latencies, reflecting conduction in terminal segments, and F-wave latencies, which explore also proximal nerve tracts and spinal roots, are similarly prolonged, indicating that conduction slowing is uniform at proximal as well as distal sites. Conduction slowing involves all body nerves, though clinically unaffected, including the facial and acoustic nerves, as shown by conventional NCV studies and brainstem auditory evoked potential studies, indicating a generalized Schwann cell myelin dysfunction (Scaioli et al., 1992; Kumagai-Eto et al., 2004). Conduction slowing in CMT1A does not correlate with either disease severity or duration. By contrast, severity is directly correlated with CMAP decrease and SNAP extinction. Conduction slowing is present since the early phases of myelination, it is definitely established within the age of 3–5 yr, it does not significantly change over time, independently from clinical severity and progression, and it is therefore a marker of disease even in asymptomatic or oligosymptomatic patients (Nicholson, 1991; Kaku et al., 1993; Hoogendijk et al., 1994; Killian et al., 1996; Garcia et al., 1998; Lewis et al., 2000). Disease progression appears to be determined by axonal loss rather than by demyelination *per se* (Krajewski et al., 2000).

## Special Features and Associated Findings

The diagnostic approach to the identification of the CMT subtype is complex and cannot be based on the clinical phenotype alone, as different forms are often clinically indistinguishable in a single patient. However, there are a number of clinical, laboratory, and electrophysiological features that may be of help in addressing molecular investigation. Therefore—together with definition of inheritance pattern, electrophysiological examination, and nerve biopsy for selected patients—careful clinical examination of the patient and of the family may give some further clues to diagnosis (Ad hoc working group, 1999; Pareyson, 2003).

For instance, nerve hypertrophy is present in about 25% of CMT1 patients (Shy et al., 2005), and may reveal the demyelinating nature of the CMT neuropathy before electrophysiological examination. Sometimes it is relevant enough to cause severe spinal root hypertrophy (Fig. 4), which can even cause compression myelopathy or radiculopathy (Pareyson et al., 2003).

Prominence of sensory loss and sensory ataxia may be seen in patients with periaxin *(PRX)* mutations, associated with recessive CMT4F or DSN (Boerkoel et al., 2001; Guilbot et al., 2001; Takashima et al., 2002). Prevalence of sensory symptoms over motor signs is infrequent in CMT and may be seen in rare patients of axonal CMT2 associated with *MPZ* mutations (De Jonghe et al., 1999; Auer-Grumbach et al., 2003), or of CMT2B associated with *RAB7* mutations (Verhoeven et al., 2003; Houlden et al., 2004). Indeed, CMT2B phenotype largely overlaps with that of hereditary sensory neuropathy type I, because of severe sensory loss to touch and pain resulting in painless ulcers and acromutilations. Neuropathic pain may be seen, though uncommonly, in different CMT types (Gemignani et al., 2004), but it has been consistently reported in patients with CMT2 associated with the Thr124Met *MP2* mutation. In these patients, CMT2 has late onset and is often characterized by autonomic nervous system dysfunction (pupillary anomalies, occasionally gastrointestinal and urinary disturbances), hearing loss, and sometimes dysphagia (De Jonghe et al., 1999; Misu et al., 2000; Hattori et al., 2003; Baloh et al., 2004). Autonomic nervous system involvement is fairly uncommon in CMT (Shy et al., 2005). Cranial nerve dysfunction is also rarely seen. The acoustic nerve is the most frequently involved with hearing loss being present in up to 5% of CMT1A patients (Birouk et al., 1997) (less commonly in our experience), in isolated reports of CMT associated with mutations in the *PMP22* (Kovach et al., 1999; Boerkoel et al., 2002; Sambuughin et al., 2003), *MPZ* (Misu et al., 2000; Seeman et al., 2004), and

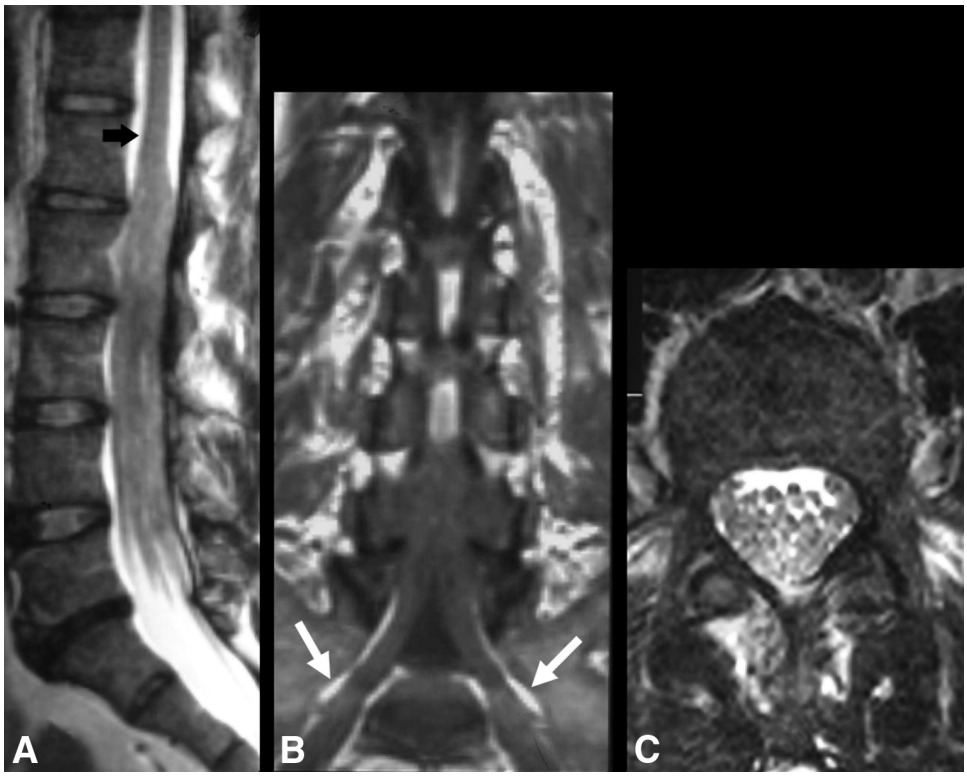


Fig. 4. Patient with CMT1A carrying the duplication in homozygosity (Pareyson et al., 2003). Midline sagittal T2-weighted **(A)**, coronal spin-echo T1-weighted **(B)**, and axial T2-weighted **(C)** images showing dramatic hypertrophy of the spinal roots, almost completely filling the spinal canal, and of the S1 ganglia (white arrows in B). Compare the normal spinal cord size (black arrow in A) with the enlargement of the cauda equina roots.

*GJB1/Cx32* (Stojkovic et al., 1999) genes, and in the rare HMSN-Lom type described in gypsies carrying N-myc downstream-regulated gene-1 *(NDRG1)* mutations (Kalaydjieva et al., 1998 and 2000). Familial trigeminal neuralgia has been rarely reported in association with CMT (Coffey and Fromm, 1991), and we have observed it in a CMT1B family (Testa et al., 1981).

Oculomotor nerve involvement with diplopia is exceedingly rare. It has been reported in a patient with vocal cord paresis and CMT1D owing to a mutation in the early-growth-response-2 gene (Pareyson et al., 2000). Interestingly, its murine *Krox20* orthologue is known to be involved in hindbrain development (Schneider-Maunoury et al., 1993), and cranial nerve involvement has been reported in other patients with early-growth-response-2 gene mutations (Taroni et al., 1999; Timmerman et al., 1999).

Vocal cord paresis is a rare but potentially life-threatening feature when abduction of the cords is completely impaired. It is a feature of the axonal CMT2C, linked to chromosome 12q23-24 (Klein et al., 2003), of dHMN type VII mapping to chromosome 2q14 (McEntagart et al., 2002), of the lower motor neuron disease associated with dynactin 1 *(DCTN1)* mutation (Puls et al., 2005), and of early onset AR-CMT2 or CMT4A owing to mutations in the ganglioside differentiating associated protein 1 gene (Sevilla et al., 2003). Respiratory involvement owing to intercostal muscle or diaphragm weakness may be seen in patients with vocal cord paresis or occasionally in other CMT patients (Hardie et al., 1990). Both the recurrent laryngeal nerve innervating the larynx and the phrenic nerve which drives impulses to the diaphragm are relatively long nerves and their impairment occurs in the severe CMT set; however, there must be some still unknown reason

for such a selective involvement, as vocal cord paresis sometimes precedes CMT. Moreover, other patients with very severe CMT do not display vocal cord paresis or respiratory distress.

Upper limb predominance is another uncommonly observed feature and should alert the clinician for addressing the molecular studies towards the glycil-tRNA synthetase gene, associated with CMT2D (axonal CMT with upper limb predominance) and dHMN type V (pure motor form with upper limb predominance) (Antonellis et al., 2003), and the Berardinelli-Seip congenital lipodystrophy type 2 gene *(BSCL2)*, which is associated with a wide spectrum of clinical manifestations (*see* below) (Windpassinger et al., 2004; Auer-Grumbach et al., 2005).

In CMTX, the median nerve is often more severely affected than the ulnar nerve both clinically (Fig. 1D) and electrophysiologically (Fig. 3A) (Hahn et al., 1999; Pareyson, 2003); however, this is a finding not restricted to CMTX and can be observed in other CMT types.

Subclinical involvement of the central nervous system (CNS) is also frequently seen in CMTX, especially in males. Abnormalities of evoked potentials, particularly of brainstem auditory evoked potentials, are common (Nicholson and Corbett, 1996; Bahr et al., 1999). Transient symptoms related to CNS dysfunction (ataxia, dysarthria, weakness, aphasia, disorientation) have been described in few CMTX male patients; some patients showed confluent symmetrical white matter abnormalities at MRI, which resolved over several months (Panas et al., 2001; Paulson et al., 2002; Hanemann et al., 2003; Schelhaas et al., 2003; Taylor et al., 2003). Cx32 expression in olygodendrocytes is the likely explanation of CNS involvement in CMTX (Kleopa et al., 2002).

CMT associated with spastic paraplegia or with less severe corticospinal tract involvement is rare and has been classified as HMSN type V for a long time (Dyck et al., 1993). It is likely to be genetically heterogeneous (Vucic et al., 2003). It has been recently associated with mutations in the mitofusin 2 *(MFN2)* (Zhu et al., 2005) and *BSCL2* (Auer-Grumbach et al., 2005) genes. Neurological manifestations associated with mutation in the latter gene show considerable variability of disease expression. Patients carrying the N88S *BSCL2* mutation may present different phenotypes, including CMT2, distal HMN with upper limb predominance (dHMN type V), Silver syndrome (lower limb spasticity with upper limb distal atrophy and weakness), pure spastic paraplegia, or a combination of these features (Auer-Grumbach et al., 2005). Dominant mutations of the senataxin gene *(SETX)* have been found in patients showing upper and lower motor neuron involvement; it is debated whether this is a benign form of familial amyotrophic lateral sclerosis (ALS4) or a distal HMN with pyramidal signs (De Jonghe et al., 2002; Chen et al., 2004).

CMT with optic atrophy corresponds to the old HMSN type VI, and vision impairment occurred in patients with CMT2 as a result of mutations in the *MFN2* gene, involved in fusion of mitochondria (Züchner et al., 2004; Claeys et al., 2005). This is interesting, as mitochondrial dysfunction might explain both the optic nerve and peripheral nerve derangement. The original Roussy–Lévy syndrome family was shown to carry a mutation in the *MPZ* gene (Plante-Bordeneuve et al., 1999), but postural and action tremor is a nonspecific additional feature that may be seen in different CMT types, including CMT1A, CMT1B, CMTX, and CMT2.

Among skeletal deformities, scoliosis may be seen in all CMT types, especially if onset occurs early in life, but it has been reported to be particularly severe in the recessive CMT4C associated with *KIAA1985* mutations (Senderek et al., 2003). Other exceptional findings are glaucoma and neutropenia. Early-onset glaucoma may accompany CMT4B2 owing to myotubularin-related protein-13 gene *(MTMR13)* mutations (Azzedine et al., 2003; Hirano et al., 2004), and neutropenia has been observed in two families with DI-CMT carrying mutations in the dynamin 2 gene (Züchner et al., 2005). The latter is an interesting and useful observation, as laboratory work-up is usually normal in CMT, apart from possible CK elevation (Hattori et al., 2003).

Late onset CMT2 should alert to the possibility of *MPZ* mutations (Shy et al., 2004), whereas early onset severe CMT2 has also been reported in patients carrying *MFN2* mutations (Züchner et al., 2004).

The disease course of CMT is usually slowly progressive over decades. More severe forms may show faster worsening. In other patients the disease appears to stabilize. Sudden worsening or repeated relapses may rarely occur. Superimposition of an inflammatory neuropathy, such as CIDP, on the hereditary peripheral nerve disorder is the likely explanation. In some patients this diagnosis has been supported by very high levels of cerebrospinal fluid

Table 1
Clinical Phenotype and Electrophysiological Findings in Different CMT Types, With Genes Involved and Special Features

| Clinical phenotype | Inheritance | Nerve conduction studies | Disease | Involved genes/ types of CMT | Special clinical and electrophysiological features that may be associated |
|---|---|---|---|---|---|
| Typical sensory-motor CMT | AD | Uniform and diffuse motor and sensory NCV slowing <38 m/s in upper limb motor nerves. | CMT1 | *PMP22*, CMT1A<br>*MPZ*, CMT1B<br>*SIMPLE*, CMT1C<br>*EGR2*, CMT1D<br>*NEFL*, CMT1F | Possible nerve hypertrophy<br>*MPZ*: exceptionally conduction blocks<br>*EGR2*: cranial nerve involvement |
| Males more affected than females; no male-to-male inheritance | X-linked | Wide range of NCV (18–60 m/s); values often intermediate in males (30–45 m/s), in the lower range of CMT2 in females. Conduction slowing often nonuniform and asymmetrical; median nerve more affected than ulnar nerve. | CMTX | *GJB1/Cx32* | Subclinical abnormalities of central components of multimodal evoked potentials; exceptionally transient clinical signs of CNS involvement |
| Sensory-motor CMT | AD | Preserved or midly slowed NCV, >38 m/s in upper limb motor nerves. | CMT2 | *MFN2*, CMT2A<br>*RAB7*, CMT2B<br>?, CMT2C<br>*GARS*, CMT2D<br>*NEFL*, CMT2E<br>*HSPB1*, CMT2F<br>*HSPB8*, CMT2L<br>*GDAP1*,<br>*MPZ* | *MFN2*: optic atrophy<br>*RAB7*: acromutilations<br>CMT2C: vocal cord and respiratory involvement<br>*GARS*: upper limb predominance<br>*MPZ*: possible late onset, pupillary anomalies, pain, hearing loss, dysphagia |

| | | | | | |
|---|---|---|---|---|---|
| Early onset, severe CMT | AR | NCV >38 m/s in upper limb motor nerves. | AR-CMT2 | *LMNA*<br>*GDAP1* | *GDAP1*: vocal cord paresis |
| | AR | Slowed NCV, <38 m/s | CMT4 | *GDAP1*, CMT4A<br>*MTMR2*, CMT4B1<br>*MTMR13*, CMT4B2 | *MTMR13*: early-onset glaucoma |
| | | | | *KIAA1985*, CMT4C | *KIAA1985*: severe scoliosis |
| | | | | *PRX*, CMT4F | *PRX*: prominent sensory loss |
| | | | | *NDRG1*, HMSN-L | HMSN-L: gypsies, hearing loss |
| | | | | ?, HMSN-R | HMSN-R: gypsies |
| Sensory-motor CMT | AD | Intermediate NCV | DI-CMT | *DNM2*, other loci | *DNM2*: neutropenia |
| Pure motor CMT | AD-(may be AR) | Preserved or mildy slowed NCV, >38 m/s in upper limb motor nerves; reduced CMAP amplitude with normal SNAPs | dHMN | *HSPB1*<br>*HSPB8*, dHMN II<br>*GARS*, dHMN V<br>*BSCL2*, dHMNV<br>(*SETX*, ALS4) | *GARS* and *BSCL2*: upper limb predominance<br>*BSCL2*: pyramidal involvement, spastic paraplegia<br>*SETX*: pyramidal involvement |

*Note:* Other loci have also been associated with CMT and distal HMN subtypes, but the genes involved have not yet been identified.

(CSF) proteins, temporal dispersion and conduction blocks at electrophysiological examination, and inflammatory infiltrates at nerve biopsy, all findings suggestive of CIDP diagnosis, and by favorable response to steroid or immunomodulatory treatment (Dyck et al., 1982; Donaghy et al., 2000; Ginsberg et al., 2004; Pareyson, 2004a).

Ethnic background is sometimes important for diagnosis. For instance, HMSN-Lom associated with *NDRG1* gene mutations (Kalaydjieva et al., 1998, 2000; Merlini et al., 1998) and HMSN-Russe (Thomas et al., 2001) are two recessive demyelinating neuropathy described in gypsy communities from different countries. Where consanguineous marriages are traditionally frequent, autosomal recessive forms of CMT are much more common (Vallat et al., 2005). Studies of CMT in families from North-Africa have allowed the identification of several recessive forms (Baxter et al., 2002; De Sandre-Giovannoli et al., 2002; Azzedine et al., 2003).

In conclusion, the great advances in molecular genetics are leading to the reinterpretation of the clinical phenotype–genotype correlation, and are shedding light on the pathophysiology of CMT (Table 1). A correct approach to clinical and electrophysiological investigations is fundamental for properly addressing molecular studies.

## Abbreviations

| | |
|---|---|
| Inheritance | |
| AD | autosomal dominant |
| AR | autosomal recessive |
| Electrophysiology | |
| CMAP | compound muscle action potential |
| NCV | nerve conduction velocities |
| SNAP | sensory nerve action potential |
| Diseases | |
| ALS 4 | amyotrophic lateral sclerosis 4 |
| CMT | Charcot-Marie-Tooth disease |
| DI-CMT | dominant intermediate CMT |
| dHMN | Distal Hereditary Motor Neuronopathy |
| HMSN-L | Hereditary Motor and Sensory Neuropathy – Lom |
| HMSN-R | Hereditary Motor and Sensory Neuropathy – Russe |
| Genes | |
| *BSCL2* | Berardinelli-Seip congenital lipodystrophy type 2 |
| *DNM2* | dynamin 2 |
| *EGR2* | early-growth-response-2 |
| *GARS* | glycil-tRNA synthetase |
| *GDAP1* | ganglioside-induced differentiation-associated protein-1 |
| *GJB1/Cx32* | gap-junction B1 / connexin 32 |
| *HSPB8* (or *HSP22*) | heat-shock 22-kDa protein 8 |
| *HSPB1* (or *HSP27*) | heat-shock 27-kDa protein 1 |
| *SIMPLE* (or *LITAF/SIMPLE*) | lipopolysaccharide-induced tumor necrosis factor-α factor; Small Integral Membrane Protein of Lysosome/Late Endosome |
| *LMNA* | lamin A/C nuclear envelope protein |
| *MFN2* | mitofusin 2 |
| *MPZ* | myelin protein zero |
| *MTMR2* | myotubularin-related protein-2 |
| *MTMR13* (or *SBF2*) | myotubularin-related protein-13 (or SET binding factor 2) |
| *NDRG1* | N-myc downstream-regulated gene-1 |
| *NEFL* | neurofilament light chain |
| *PMP22* | peripheral myelin protein-22 |
| *PRX* | periaxin |
| *RAB7* | small GTP-ase late endosomal protein RAB7 |
| *SETX* | senataxin |

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