

REVIEW

Conduction slowing, conduction block and temporal dispersion in demyelinating, dysmyelinating and axonal neuropathies: Electrophysiology meets pathology

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Abstract

Nerve conduction studies are usually the first diagnostic step in peripheral nerve disorders and their results are the basis for planning further investigations. However, there are some commonplaces in the interpretation of electrodiagnostic findings in peripheral neuropathies that, although useful in the everyday practice, may be misleading: (1) conduction block and abnormal temporal dispersion are distinctive features of acquired demyelinating disorders; (2) hereditary neuropathies are characterized by uniform slowing of conduction velocity; (3) axonal neuropathies are simply diagnosed by reduced amplitude of motor and sensory nerve action potentials with normal or slightly slow conduction velocity. In this review, we reappraise the occurrence of uniform and non-uniform conduction velocity slowing, conduction block and temporal dispersion in demyelinating, dysmyelinating and axonal neuropathies attempting, with a translational approach, a correlation between electrophysiological and pathological features as derived from sensory nerve biopsy in patients and animal models. Additionally, we provide some hints to navigate in this complex field.

KEYWORDS

conduction block, conduction slowing, neuropathies, pathology, temporal dispersion

1 | INTRODUCTION

Nerve conduction studies are, after clinical examination, the first diagnostic approach in peripheral nerve disorders and their results are the basis for planning further investigations. However, in the interpretation of electrodiagnostic findings, there are some clichés that, although of some utility in the everyday practice, may be misleading: (1) conduction block (CB) and abnormal temporal dispersion (TD) of compound muscle action potential (CMAP) are distinctive features of acquired demyelinating disorders; (2) hereditary neuropathies are characterized by uniform slowing of conduction velocity (CV); (3) axonal neuropathies are simply diagnosed by reduced CMAP and sensory nerve action potential amplitudes (SNAP) with normal or slightly slow CVs. Nerve pathology, a useful diagnostic tool in the past decades, is

currently reserved to selected cases but remains of paramount importance in understanding the pathophysiology of peripheral nerve diseases. By bridging electrophysiology to pathology, in this review we will reappraise the occurrence of CV slowing, CB and abnormal TD in demyelinating, dysmyelinating and axonal neuropathies attempting a correlation with pathological features as derived from sensory nerve biopsy in patients and animal models. In addition, we will provide some hints to navigate in the complexity of this area.

1.1 | Basics on nerve conduction

Reminding a few concepts on nerve conduction can be useful to understand the electrophysiological and pathological correlates in

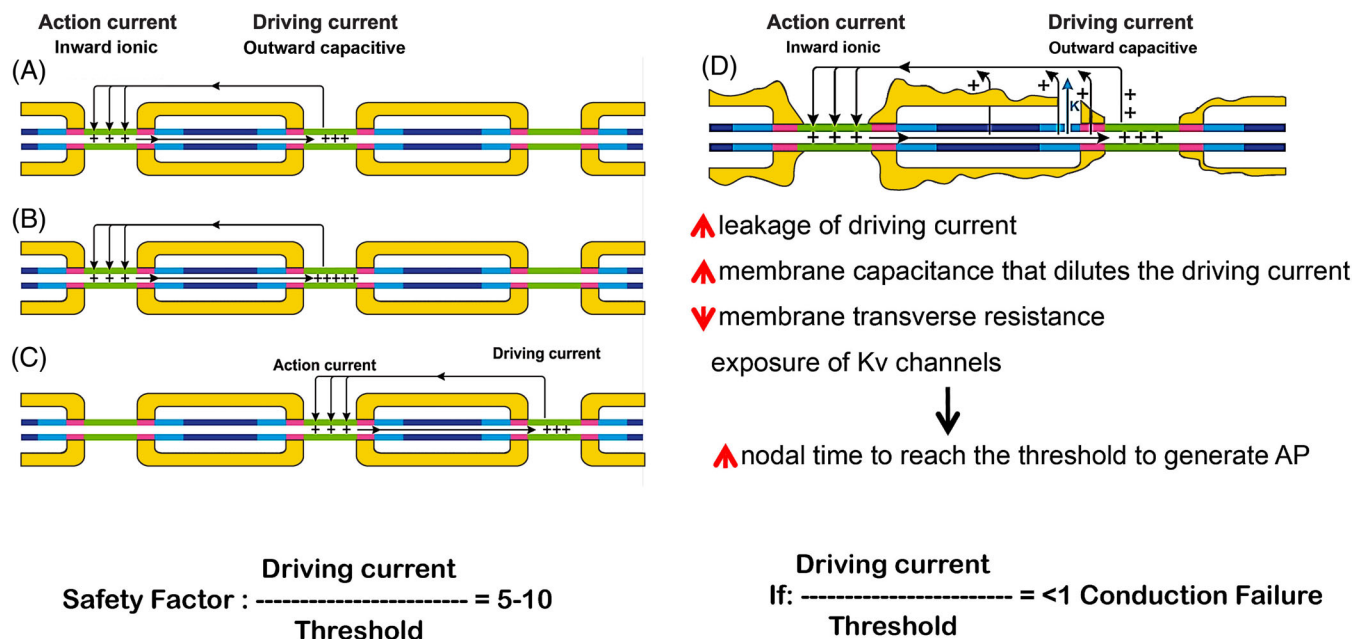


FIGURE 1 Saltatory conduction in normally myelinated and demyelinated fibers. Green: node, violet: paranode, light blue juxtaparanode, dark blue: internode. Plus sign (+) represents positive charges. AP: action potential, Kv: K^+ voltage gated potassium channels. (A) At the active node (left), voltage gated Na channels (Nav) are open, inducing an inward ionic action current that generates the AP. (B) This causes a current circuit that leads to an internal longitudinal current inside the axon and an outward capacitive driving current with positive charges that accumulate inside the node to be activated and are withdrawn outside depolarizing the nodal membrane. (C) As soon as the membrane is depolarized to the threshold, Na^+ voltage gated channels open, Na^+ enters into the axon and induces further depolarization converting the driving current into an action current generating an AP. (D) Damage of the myelin sheath induces biophysical alteration leading to block of the saltatory conduction (conduction failure). Modified with permission from Uncini and Kuwabara.¹

neuropathies. The action potential (AP) is generated at the axon initial segment and in myelinated fibers regenerates at the node of Ranvier (NR) where voltage gated Na^+ channels (Nav) are highly concentrated and, by opening, induce an inward ionic action current that triggers the AP (Figure 1A). This causes a current circuit with an internal longitudinal current inside the axon and an outward capacitive driving current that depolarizes the successive node (saltatory conduction) (Figure 1B,C). The safety factor for saltatory conduction is the ratio between the capacitive driving current to the threshold current required to depolarize the membrane till to the opening of Nav channels. The safety factor it is quite high (5–10) and is furtherly increased longitudinally because the inward current activates, at once, 3–4 successive NRs.² It should be underlined that the conduction time between successive NRs is mainly due to the time spent at the node to reach the threshold to generate the AP (about 25 μ s), being the internodal conduction virtually instantaneous.³ The CV of myelinated fibers depends on the nerve fiber diameter, myelin thickness, and internodal length. CV is proportional to the fiber diameter according to a multiplying factor of 5.7 in humans and, in a motor nerve with myelinated fibers' diameter of 6–12 μ m, the range of CV is 35–68 m/s.⁴ In computer simulations CV increased with myelin thickness being maximal when the ratio of axonal diameter to the total fiber diameter (g-ratio) was between 0.6 and 0.7.⁵ Impulse propagation failed when the ratio was greater than 0.95 and the lowest calculated CV, before conduction failure, was about 22% of that of a normal fiber. Another

study showed that impulse propagation continued past a single demyelinated internode until myelin thickness was 2.7% of normal or 4% at two adjacent internodes.⁶ These findings indicate that a severe reduction of CV can result with nothing altered but the myelin thickness and that demyelination must be extreme before conduction failure occurs. In the human sural nerve the range of internode lengths is between 0.2 mm, in the smallest, to 2.0 mm in the largest diameter fibers and the optimal ratio between internodal length to fiber diameter is 100.⁷ This means that a 10 μ m diameter fiber should have internodal lengths of about 1 mm to ensure maximal impulse transmission. Huxley and Stämpfli in 1949 predicted that CV in myelinated nerve fibers should reach a maximum at a particular internode length beyond which CV should not furtherly increase (flat maximum), and computer simulations showed that CV are substantially reduced for changes of internodal lengths in the shorter but not in the longer ranges.^{8,9} If the myelin sheath is damaged the driving current leaks and it is diluted over a larger area in the nodal region (Figure 1D). Additionally there is a decrease of membrane transverse resistance and the exposure and activation of juxtaparanodal K^+ voltage gated channels that shift the membrane potential toward more negative values. All these biophysical alterations increase the time to reach the threshold for generating an AP (up to 600 μ s in an experimental model) till the safety factor drops below 1 and conduction failure occurs.³ Restored conduction after demyelination may be initially continuous by increased expression of Nav channels on the demyelinated

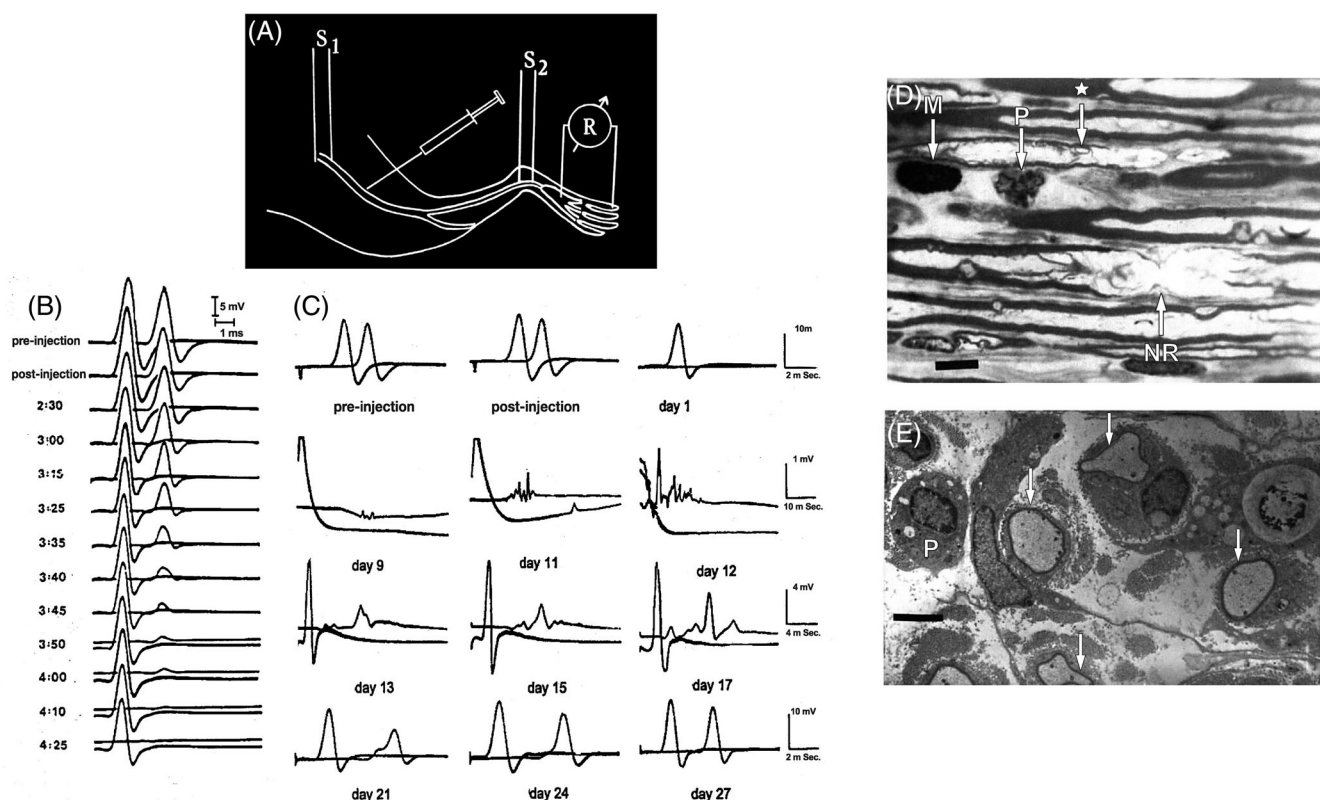


FIGURE 2 Electrophysiologic and pathologic correlates in a model of acute segmental demyelination. (A) Tellurium was injected in the rat tibial nerve and CMAPs were recorded from intrinsic foot muscles (R) following stimulation at the sciatic notch (S1) and ankle (S2). (B) Serial recordings of CMAPs from distal and proximal stimulation in the first hours following the injection. Note the progressive decline of CMAP amplitude after proximal stimulation beginning 3 h after the injection and progressing to complete CB by 4 h and 25 min. The latency of the proximal CMAP changed very little (0.1 ms) and only when the amplitude had fallen below 30% of the pre-injection value with a slowing of CV from 43.8 m/s before injection to 38.9 m/s just before complete CB occurs. (C) Serial recordings of CMAPs from pre-injection to 27 days after injection. Note that the sweep and gain are different for each row. By day 1, complete CB was established; at day 9, a low-amplitude, dispersed, long-latency (27 ms) CMAP from proximal stimulation was recorded with a CV of 4.3 m/s. In the following days, larger amplitude, shorter latency CMAPs were observed. By day 27 the proximal and distal CMAP amplitude had returned to pre-injection values; however, the proximal CMAP still had a prolonged latency. (D) Light microscopy, longitudinal section of the tibial nerve, 6 h after tellurium injection, showing splitting (star) and myelin disruption adjacent to a node of Ranvier (NR). A phagocyte (P) containing myelin debris and a mast cell (M) are present. Toluidine blue stain, bar = 10 μ m. (E) Electron microscopy, cross section of the posterior tibial nerve 9 days after injection axons showing nerve fiber with thin myelin indicative of initial remyelination (arrows), P is a phagocyte, bar = 2 μ m. Reproduced with permission from Uncini et al.¹¹

segment, then microsaltatory with formation of new Nav channel clusters and eventually saltatory, although slow, because remyelinating internodes are short. In nerve conduction studies, CV measures the velocity of fastest conducting fiber and in neuropathies CV depends on the diameter of residual functioning fibers. In an axonal neuropathy with a random loss of fibers the CMAP amplitude (the summation of individual muscle fiber APs) decreases while motor CV is normal or slightly slow if at least some large diameter, fast conducting fibers, are spared. On the other side, if only a few slowly conducting fibers remain, the CMAP amplitude is severely reduced and CV is decreased but not less than 35 m/s because the myelinated fibers originating from an α -motor neuron have a diameter not inferior than 6 μ m and, according to the multiplying factor, should not conduct slower. Motor CVs slower than 70% of lower limit of normal (approximately 35 m/s in the arms and 30 m/s in the legs) are usually thought to be indicative of a de-remyelinating or dysmyelinating

process. Motor CB is due to the arrest of the AP in demyelinated but still viable axons and is characterized by an amplitude/area reduction of CMAP from a proximal nerve stimulation site compared with CMAP from a distal stimulation site. Temporal dispersion (TD) is due to the desynchronization of CVs among nerve fibers that causes increased CMAP duration and reduction of amplitude and area because of phase cancelation between positive and negative phases of single motor unit potentials. Different cut-offs have been employed to define abnormal TD and CB. A 30% increased duration of CMAP from proximal stimulation is usually considered indicative of excessive TD. As simulations showed that abnormal TD, by itself, can reduce the area of proximal CMAP up to 50%, at least 50% reduction of proximal CMAP amplitude or area (that incorporates also the measure of CMAP duration) is required for definite CB.¹⁰ The electrophysiologic and pathologic correlates of acute demyelination and remyelination have been studied in an experimental model by intraneural injection of tellurium that induces

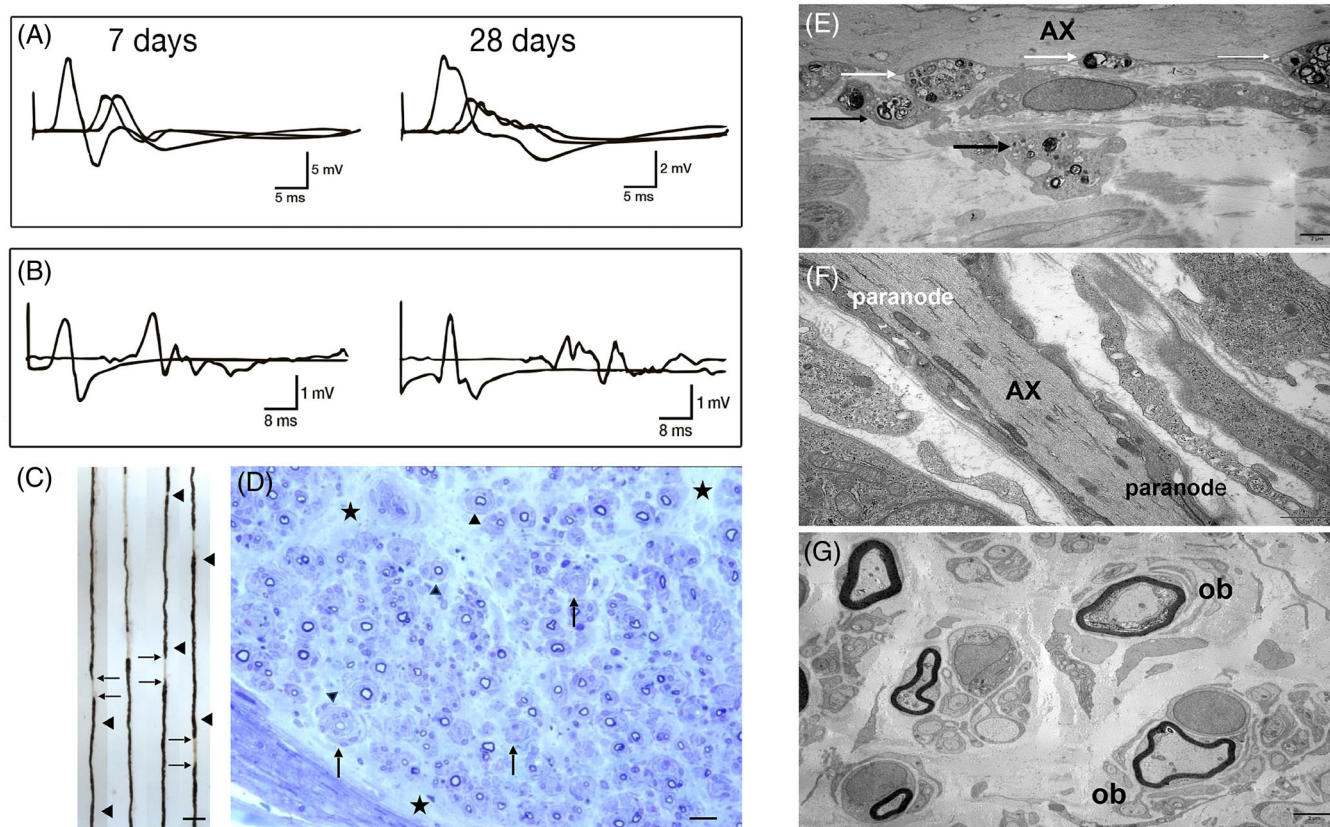


FIGURE 3 Electrophysiologic and pathologic correlates in acute and chronic demyelinating polyneuropathy (AIDP, CIDP). (A) AIDP patient. Ulnar nerve, superimposed tracings from stimulations at wrist, below elbow and elbow. Seven days after onset, DML is borderline (3.4 ms), CV in the below elbow-wrist segment is slightly slowed (45 m/s), CMAP amplitude from below-elbow stimulation is 50% reduced; 28 days after onset, DML is slightly prolonged (3.7 ms), CV is definitely slow (30 m/s), CMAP amplitude from below-elbow stimulation is 45% reduced and CMAP duration is 200% increased indicating that slow conduction and abnormal temporal dispersion are characteristic of the remyelinating phase. (B) CIDP patient. Superimposed tracings of peroneal (left) and tibial (right) nerves showing normal DMLs (peroneal: 4.6 ms; tibial: 5.7 ms) but very slow CVs (peroneal: 16.6 m/s; tibial: 14.7 m/s), and excessive TD of proximal CMAP (360% increased CMAP duration in the peroneal nerve and 420% in the tibial nerve) indicating non-uniform conduction slowing among nerve segments and nerve fibers. Reproduced with permission from Uncini et al.¹² (C–G) Sural nerve biopsies of CIDP patients. (C) Teased fibers showing segmental demyelination (between arrows) within fibers with adequate myelin sheath and regular internodal length (between arrowheads), bar = 100 μ m. (D) Semithin section showing demyelinated fibers (arrows), OB (arrowheads) and endoneurial edema (stars), bar = 25 μ m. Electron microscopy of longitudinal (E and F) and transverse sections (G). (E) Macrophages loaded with myelin debris are located in close contact to a large completely demyelinated axon (AX) under the basal lamina (white arrows) and in the interstitial tissue (black arrows), bar = 2 μ m. (F) Segmental demyelination encompassing two adjacent paranodes, the axon is completely devoid of myelin, bar = 1 μ m. (G) Onion bulbs (ob) surrounding axons with thin myelin sheaths suggesting a chronic demyelinating-remyelinating process, bar = 2 μ m.

segmental demyelination with little or no axonal degeneration (Figure 2A).¹¹ This study showed that CB with only slightly reduced CV, as long as a CMAP from stimulation proximal to the injection site was recordable, could be induced in few hours after the injection (Figure 2B). The pathological correlate, at this stage, was only myelin splitting and destruction restricted to the paranode (Figure 2D). Complete CB persisted few days while segmental demyelination developed. Then, small amplitudes, dispersed, long latency CMAPs reappeared in parallel with the beginning of remyelination (Figure 2C,E). These findings indicate that CB is the correlate of acute demyelination, with the paranode being the crucial site to ensure saltatory conduction, while slow CV and abnormal TD are the correlates of remyelination and are due to short internodes with variable lengths among nerve fibers.

2 | AUTOIMMUNE DEMYELINATING NEUROPATHIES AND PARANODOPATHIES

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are the prototypes of acquired demyelinating disorders. They are electrophysiologically characterized by a variable combination, in the individual nerves, of prolonged distal motor latency (DML), slow CV, CB and abnormal TD thus configuring a non-uniform conduction slowing pattern (Figure 3A,B). According to conservative criteria, electrophysiological demyelinating features are: prolonged DML (>130% of upper limit of normal), slow CV (<70% of lower limit of normal), motor CB (>50% of proximal CMAP amplitude/area decrement), and excessive

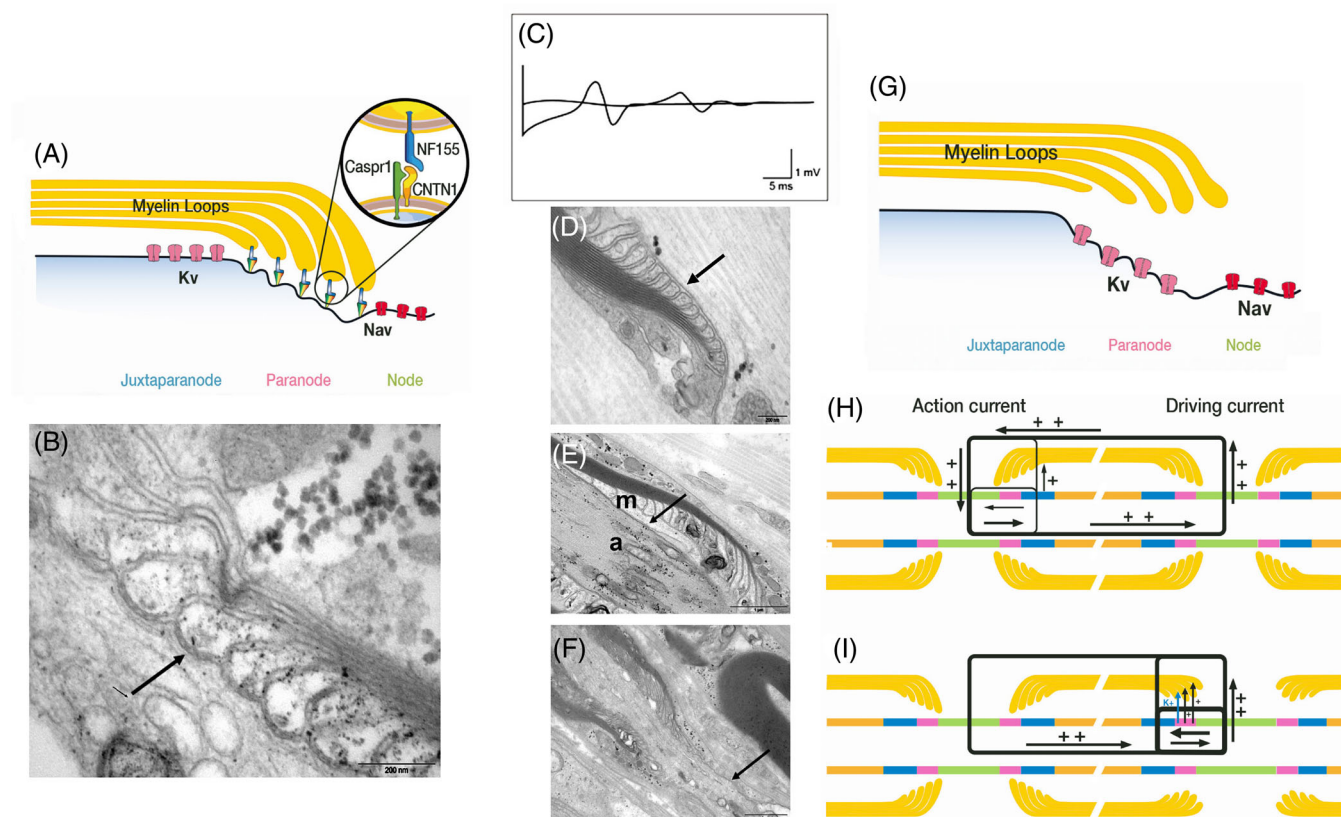


FIGURE 4 Electrophysiological and pathological correlates in autoimmune paranodopathies. (A) Normal paranodal junction showing neurofascin NF155, contactin-1 (CNTN1), contactin-associated protein-1 (Caspr1). (B) Normal paranode in a control showing myelin terminal loops closely attached to the axolemma by transverse bands (arrow), bar = 200 nm. (C–F) 67-year-old man with IgG4 anti-NF-155 antibodies. (C) Median nerve, superimposed recordings from wrist and antecubital fossa stimulation showing reduced distal CMAP amplitude (1 mV), prolonged DML (8.1 ms), slow CV (23.4 m/s) and 52% reduction of CMAP area from antecubital fossa stimulation configuring a partial CB. (D–F) Sural nerve biopsy, longitudinal ultrathin sections of the nodal region. (D) Lack of transverse bands and enlargement of the space between the axon and the paranodal loops (arrow), bar = 200 nm. (E) Cellular processes (arrow) are interposed between the paranodal myelin loops (m) and the axon (a), bar = 1 μ m. (F) A widened node (arrow), bar = 1 μ m. (G) Binding of anti-NF155 antibodies induces terminal myelin loops detachment, nodal lengthening, increased periaxonal space and dislocation of Kv channels at paranode. (H) Saltatory conduction in a normal nerve fiber. At the active node (left), Nav channels are open, inducing an inward ionic action current and a driving capacitive current flowing at the following node (right). A small amount of current flows across the axonal membrane at the internode and completes the circuit by flowing radially through the myelin sheath or flows back through the paranodal junction. (I) Terminal myelin loops detachment and nodal lengthening cause dilution and leakage of the driving current (node on the right, black arrows), radial shunting and backflow of current to the paranode and internode, note the relative thickness of the lines and arrow compared with (H), instead of progression to the following node. Nodal depolarization is additionally impaired because the Kv channels (blue arrow), dislocated from the juxtaparanode to the paranode, shift the membrane potential toward more negative values preventing the reaching of the threshold to generate an AP. Reproduced with permission from Uncini et al.¹²

TD (>30% increased duration of proximal CMAP compared with distal CMAP). Although the antigenic targets still remain elusive, AIDP and CIDP share some pathological features such as antibody and macrophage mediated segmental demyelination involving the paranode and or the internode followed by remyelination (Figure 3C,E,F).^{13–15} In CIDP, the chronicity of the process, leads to onion bulb (OB) formations that are concentrically layered proliferations of Schwann cell (SC) processes resulting from repetitive demyelination followed by abortive attempts at remyelination (Figure 3D,G).¹⁶ In AIDP and CIDP segmental de-remyelination is the correlate of non-uniform conduction slowing, CB and excessive TD. However, in autoimmune neuropathies non-uniform conduction slowing is not always

associated to segmental demyelination. Since 2013 some patients diagnosed as CIDP, were discovered to have mainly IgG4 antibodies (not activating complement but blocking the function of the target antigen) against three proteins of paranodal junction (PNJ): contactin 1 and contactin-associated protein 1 on the axonal side, and neurofascin 155 on the terminal myelin loops.^{17–19} PNJs, through the transverse bands, are responsible of the adhesion of the terminal myelin loops to the axolemma and act as an electrical and molecular barrier to the diffusion of ions and ion channels (Figure 4A,B). Patients with antibodies to PNJ components show prolonged DML, slow CV, CB, and TD fulfilling the electrodiagnostic criteria for definite CIDP (Figure 4C).^{20,21} Reduced CMAP amplitudes and denervation at EMG,

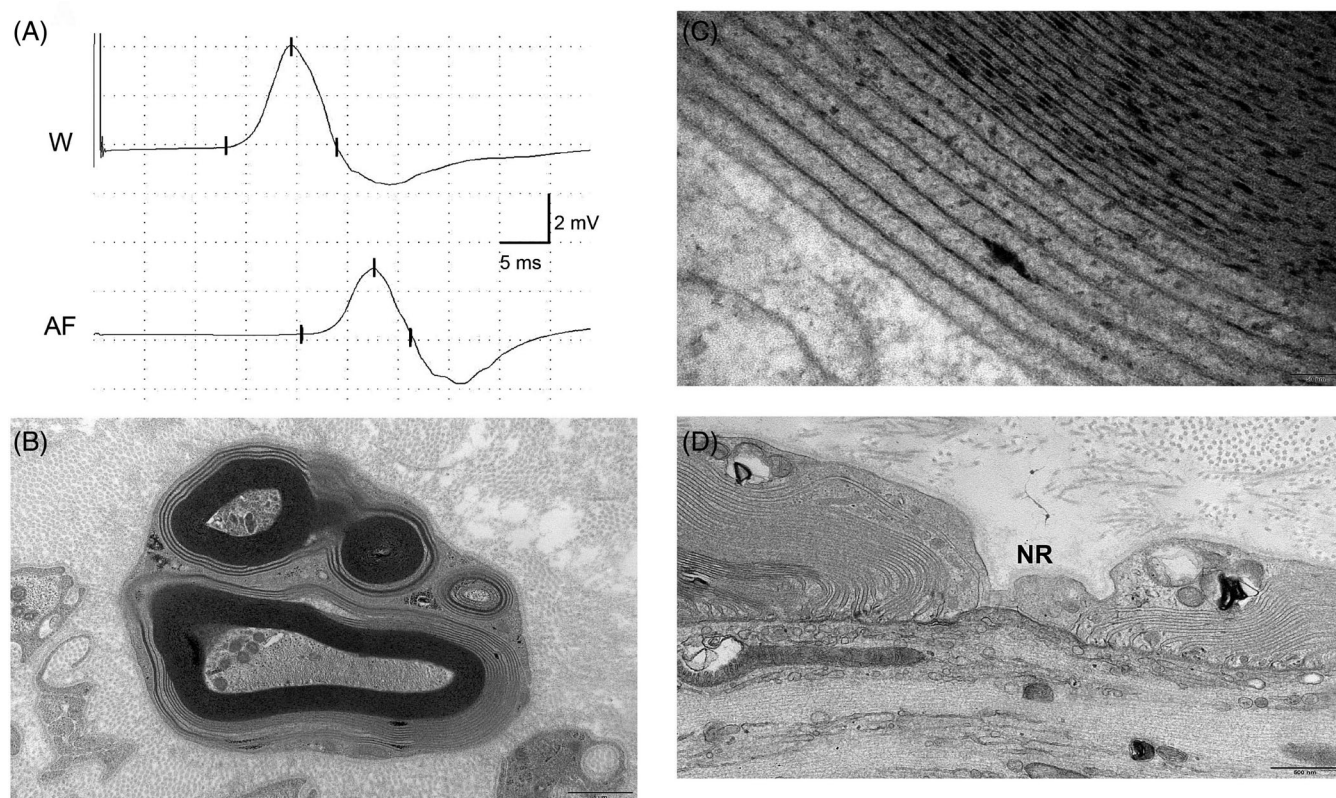


FIGURE 5 Electrophysiological and pathological correlates in anti-MAG neuropathy. (A) median nerve motor conduction study. DML is 13.1 ms and CV in the antecubital fossa (AF)-wrist (W) segment is 37.3 m/s. The terminal latency index is 0.21 (normal >0.35). (B) Electron microscopy, transverse section: widenings of the outer myelin lamellae, bar = 1 μ m. (C) At higher magnification in the widened lamellae the leaflets of the intraperiodic line are spaced out, bar = 50 nm. (D) Electron microscopy, longitudinal section showing widenings of myelin lamellae of the paranodes adjacent to the node of Ranvier (NR), bar = 500 nm.

as evidence of axonal loss, are frequently prominent. Optic microscopy of sural nerve biopsies revealed axonal degeneration and severe axonal loss with regenerating fibers without inflammatory infiltration or OBs.^{22,23} In patients with IgG4 anti-neurofascin 155 a teased fibers study showed no difference in de-remyelination compared with normal controls whereas another study showed some segmental demyelination and paranodal myelin thickening in 50% of patients.²⁴ Ultrastructural studies demonstrated detachment of terminal myelin loops due to loss of transverse bands, irregular widening of the periaxonal space with digitiform processes of SC cytoplasm interposed between the myelin loops and the axon and lengthened NRs, (Figure 4D,E,F).^{22,23} The removal of any of the three components of paranodal junction in knockout mice induced the same pathological alterations along with a decrease of CV.²⁵ A contradiction is evident in these neuropathies currently classified as autoimmune paranodopathies: the electrophysiology clearly points toward demyelination whereas pathology shows axonal degeneration and only paranodal dismantling without or little or no evidence of segmental de-remyelination.^{25,26} This incongruity can be resolved by considering that dismantling of the paranodal architecture produces biophysical changes comparable with segmental demyelination involving the paranode (Figures 1D and 4G-I).²⁵

Monoclonal IgM antibodies reacting with myelin associated glycoprotein (MAG) are associated with a chronic, slowly progressive, large-fiber sensory-motor polyneuropathy affecting initially the lower limbs. MAG, an adhesion protein localized in the uncompacted paranodal myelin and Schmidt-Lanterman incisures, maintains the normal separation of myelin layers. The electrophysiological characteristic of anti-MAG neuropathy is a marked prolongation of DMLs out of proportion with CV slowing in more proximal nerve segments and better demonstrable by the terminal latency index calculated as: distal distance/DMLX CV in the proximal nerve segment (Figure 5A).^{27,28} No CBs, employing the >50% decrease of proximal CMAP amplitude/area criterion, are usually seen.^{27,28} Pathological studies showed loss of myelinated fibers, and ultrastructural examination revealed an increase in the spacing between the dense lines of the myelin sheath due to separation of the intraperiod line by IgM antibodies, usually at the outermost myelin lamellae, that is considered a characteristic finding in the anti-MAG neuropathy (Figure 5B,C).^{29,30} In addition, at teased studies, segmental de-remyelination and tomaculous-like formations were reported to be increased compared to controls.²⁹ It has been suggested that myelin widening and loosening starts at the terminal myelin loops of paranode slowly extending to the internode being the primary cause of axonal atrophy and subsequent axonal

damage (Figure 5D).^{30,31} In anti-MAG neuropathy the disproportionate distal CV slowing has been hypothesized to be due a length dependent neuropathic process, possibly due to a disturbance of myelin-axon interaction, with a centripetal evolution over time.^{27,28} As a practical hint, a terminal latency index <0.25 in two motor nerves, although not pathognomonic because can be found also in a few CIDP patients, should prompt to search for anti-MAG antibodies.²⁸ Overall, non-uniform conduction slowing, CB and abnormal TD are characteristic features, although, as we will see in the following sections, not exclusive of acquired demyelinating peripheral neuropathies. These abnormalities are correlated with segmental de-remyelination in AIDP and CIDP, dismantling of paranodal architecture in neuropathies with IgG4 antibodies to PNJ components, and possibly with a length dependent disturbance of myelin-axon interaction in anti-MAG neuropathy.

It should be highlighted, that there is not a universally agreed definition for segmental demyelination. An operational definition, based on teased fiber preparation and independently of the pathogenetic mechanism, has been provided by Dyck.³² In internodal demyelination no myelin should be recognized along the entire internode whereas in paranodal demyelination the nodal gap is increased. However, nodal widening, without other features of segmental de-remyelination, is found in paranodopathies with IgG4 antibodies against PNJ components, in acute neuropathies with anti-gangliosides antibodies and in some inherited peripheral myelin disorders because of developmental defects of the SC.^{25,33,34} Therefore, misinterpreting nodal widening as exclusive evidence of segmental demyelination may generate some confusion in electrophysiologic and pathologic correlations.

3 | DYSMYELINATING NEUROPATHIES

Dysmyelinating neuropathies include a large number of inherited disorders characterized by developmentally defective structure and function of the myelin sheath that, in our opinion, should be kept distinct from acquired demyelinating neuropathies where there is destruction of a previously normal myelin. Nonetheless, inherited dysmyelinating neuropathies are almost unanimously classified as demyelinating.

In 1980 Harding and Thomas showed that in patients with the peroneal muscular atrophy phenotype, median motor nerve CV was below 38 m/s for the hypertrophic form (currently Charcot-Marie-Tooth type 1: CMT1) and above 38 m/s for the axonal form (Charcot-Marie-Tooth type 2: CMT2), although with minor degrees of overlap.³⁵ Actually, in 1978, Davis and colleagues had already introduced, for patients with median nerve CV between 25 and 45 m/s, the term “intermediate” group.³⁶ More recently, forearm nerve CV has been further classified into: very slow (<15 m/s), slow (15–35 m/s), intermediate (35–45 m/s), and normal (>45 m/s) and this categorization has proven to be of some utility in selecting genetic testing for patients with inherited neuropathies.³⁷ In 1982 Lewis and Sumner highlighted that in patients with CMT1, in contrast to CIDP, the slowing of CV was uniform in different nerves and in different segments of the same nerve, without CB and abnormal TD.³⁸ These observations

TABLE 1 Dysmyelinating neuropathies with uniform and non-uniform conduction slowing.

Dysmyelinating neuropathies with uniform conduction slowing

- CMT1A
- CMT1B
- CMT3A, CMT3B, congenital hypo/amyelination
- CMT4F
- Metachromatic leukodystrophy
- Cockayne's disease
- Krabbe's disease
- Merosin deficiency

Dysmyelinating neuropathies with non-uniform conduction slowing^a

- HNPP
- Some MPZ point mutations
- CMT1X
- CMT1C
- CMT4J
- Coexisting hereditary and inflammatory neuropathies
- MNGIE

Abbreviations: CMT, Charcot-Marie-Tooth disease; HNPP; hereditary neuropathy with liability to pressure palsies; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; MPZ, myelin protein zero.

^aIncluding conduction block and/or abnormal temporal dispersion.

were extended to the neuropathies seen in metachromatic leukodystrophy, Krabbe's leukodystrophy, Cockayne's syndrome, and, in the common knowledge, the concept of uniform conduction slowing was somehow generalized to all inherited dysmyelinating neuropathies.³⁹ A reappraisal, in the molecular diagnosis era, showed that the electrophysiological aspects were more complex and possibly associated with the specific genetic mutation and pathological features.⁴⁰

It should be pointed out that the maximal CV difference among nerves to label conduction slowing as uniform has been not clearly defined.^{38,40} In this review, basing on the personal experience of one author (AU), we consider a slowing of conduction non-uniform when the CV difference in nerves of the same limb and in segments of the same nerve is more than 10 m/s and we include in the concept also CB and abnormal TD. In Table 1 is an updated view of the dysmyelinating disorders with uniform and non-uniform conduction slowing.

3.1 | Dysmyelinating neuropathies with uniform conduction slowing

3.1.1 | CMT1A with PMP22 duplication

Autosomal dominant CMT1A, caused by a 1.4 Mb duplication of chromosome 17p12 encompassing the PMP22 gene, is the most common CMT form. PMP22, a minor glycoprotein of the compact myelin, plays multiple functions in SC maturation, myelination, myelin compaction and maintenance. The duplication functions through a gene-dosage

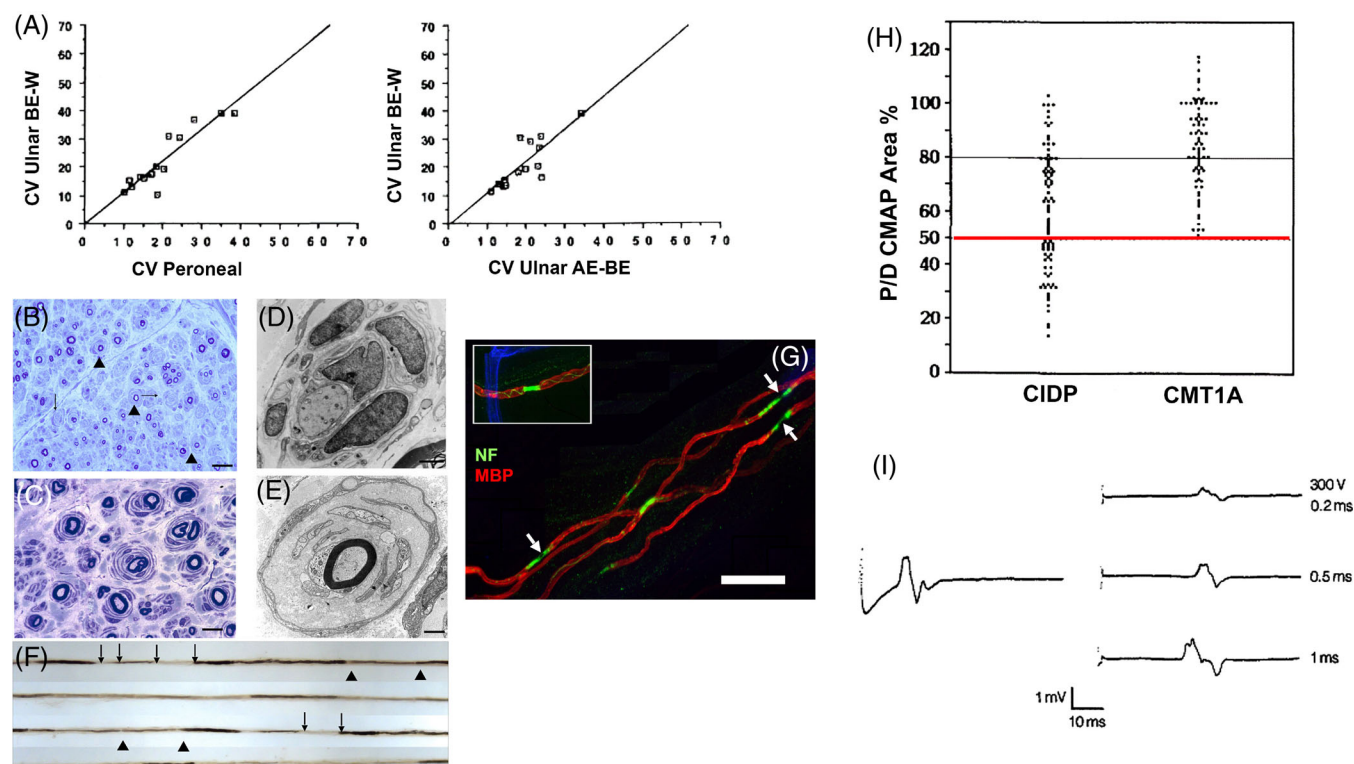


FIGURE 6 Electrophysiological and pathological correlates in CMT1A with 17p12 (PMP22) duplication. (A) Scatterplots of motor CVs of ulnar nerve segment below elbow (BE)-wrist (W) versus the peroneal nerve and of ulnar in the BE-W segment versus the above elbow (AE)-BE segment in 16 CMT1A patients. CVs are highly positively correlated in ulnar and peroneal nerves ($y = -67\,343e-2 + 11\,149x$; $R = 0.91$) and even in different segments of the ulnar nerve ($y = -10\,952 + 11\,424x$; $R = 0.81$). Reproduced with permission from Uncini et al.⁴³ (B, C, and E) Sural nerve biopsy from a 51-year-old man and (D and F) from a 27-year-old woman with CMT1A. (B) Semithin section shows a moderate reduction of myelinated fibers. The myelin sheath thickness is variable: there are some thinly myelinated and rare fibers completely devoid of myelin, so-called “naked axons” (arrows). Numerous OBs are evident (arrowheads) (bar = 25 μ m). (C) At higher magnification, the multilayering of the schwannian cytoplasmic constituents of the OBs can be appreciated, bar = 10 μ m. (D) Electron micrograph of an OB consisting of at least five SC surrounding a naked axon with densely packed axoplasm, bar = 2 μ m. (E) A properly myelinated fiber is surrounded by SC cytoplasmic processes enclosing a large amount of collagen fibrils, bar = 2 μ m. (F) Teased fibers showing some internodes completely devoid of myelin (arrows), whereas others have very thin myelin and shorter internodal lengths consisting with different stages of remyelination (arrowheads), bar = 100 μ m. (G) Confocal images from skin biopsy of a CMT1A patient showing widening of the nodes (arrows) and elongation and asymmetry of the paranodes with expansion of neurofascin clusters (NF: green) along the internode (myelin basic protein, MBP: red); in the insert nodal-paranodal staining in a control, bar = 50 μ m. (H) Scatterplot showing area changes of proximal CMAP (expressed as percentage of distal CMAP, P/D) in 89 nerves of 23 CIDP patients and 76 nerves of 28 CMT1A patients. The black line represents the 20% and the red line the 50% drop of negative phase of proximal CMAP area. Note that the reduction of proximal CMAP area was greater than 20% in 33% of CMT1A nerves but it was never greater than 50%. In comparison, 40% of CIDP nerves showed a reduction of proximal CMAP area greater than 50%. Reproduced with permission from Uncini et al.⁴⁴ (I) Peroneal nerve conduction in a 12-year-old girl with CMT1A. Left: CMAP from stimulation at ankle. Right: stimulation above the fibular head. DML is prolonged (11 ms) and CV is slow (22 m/s). Stimulating with maximal voltage (300 V) and 0.2 ms duration there was a 77% decrease of the negative peak area of CMAP from proximal stimulation suggesting partial CB. Increasing stimulus duration to 1 ms reduced the area decrement to 5%.

effect possibly associated to overexpression of PMP22.^{41,42} In CMT1A motor CV ranges between 15 and 30 m/s with occasional patients reaching 40 m/s but in a given individual conduction slowing is uniform between nerves and also between segments of the same nerve (Figure 6A).^{43,45} Distal CMAP amplitudes are reduced, reflecting axonal degeneration and related with clinical impairment consistent with a slowly progressive length-dependent neuropathy. CMT1A is the prototype of inherited dysmyelinating neuropathies but shows also de-remyelinating features. Nerve biopsies disclosed a reduction of myelinated fiber density of variable extent, depending on the

severity of the disease, and at morphometric analysis g-ratio was decreased (indicating increased myelin thickness) at younger ages and increased in adulthood whereas the amount of demyelinated internodes was higher under 15 years.^{46,47} OB formations, resulting from proliferation of the SC associated with deposition of collagen and other extracellular matrix components leading to hypertrophic palpable nerves, are frequent (Figure 6C,E). OBs occur around fibers with thin or no myelin or surround a naked axon, so-called “denervated OBs” (Figure 6B-D). In CMT1A OBs frequently surround nearly all myelinated fibers in a generalized pattern, whereas in CIDP axons

surrounded by OBs can be adjacent to axons without OB and normal myelin, in a random pattern.¹⁶ The generalized pattern in CMT1A can be explained by the fact that OB reflects defective differentiation and myelination of SC rather than the result of repetitive demyelination and remyelination as in CIDP.⁴⁸ Shortened internodes, without segmental demyelination, have been described in dermal myelinated fibers of CMT1A patients and thought to be due to a developmental defect of SC extension along the axons (Figure 6G).⁴⁹ A successive study showed that internodes were shortened and nodal gaps enlarged in all CMT genotypes, including the axonal forms, although significantly more in CMT1A.³⁴

CB and abnormal TD are not considered electrophysiological characteristics of CMT1A.⁴⁰ In large series a reduction of proximal CMAP amplitude, suggestive of partial CB, has been reported in only 19 of 360 (5.3%) nerve segments and 26 of 574 (4.5%) nerves.^{45,50} There are some possible explanations. Finding CB is dependent on the CMAP parameter (amplitude or area) and the different cut-offs (% of drop of CMAP amplitude or area) employed to define it. In a study 33% of 76 nerves of CMT1 patients showed a greater than 20%, reduction of proximal CMAP area, 8% showed a greater than 50% reduction of proximal CMAP amplitude, whereas none of nerves showed a greater than 50% reduction of proximal CMAP area (Figure 6H).⁴⁴ In comparison, 36/89 (40%) of CIDP nerves showed a reduction of proximal CMAP area greater than 50%.⁴⁴ CB in CMT1A could be due to extensive segmental demyelination and therefore it should be more frequent in infancy and childhood. A greater than 50% reduction of proximal CMAP amplitude was reported in 12.5% of CMT1A children but it was unclear, according to the authors, whether it was related to technical factors.⁵¹ Indeed, the nerves of CMT1A patients can be hypertrophic resulting in a high stimulation threshold and consequent difficulty to obtain (and tolerate for the patient) a supramaximal stimulation. This may produce a factitious drop of CMAP amplitude and area and a false CB (Figure 6I). Moreover, in presence of severe axonal loss (distal CMAP <1 mV) interphase cancellation between enlarged, increased duration, residual motor unit potentials may also result in a false CB. At last, CB could be due to superimposed focal nerve compression. In conclusion, if CB is found in a CMT1A patient, technical factors and other possible causes including nerve entrapment or a coexisting inflammatory neuropathy (see the pertinent section) should be considered. In CMT1A the uniform conduction slowing and the pathologic findings argue against active segmental demyelination being the main pathological process. Uniform conduction slowing can be better explained by a SC developmental defect of internode elongation resulting in saltatory conduction at shorter intervals.

3.1.2 | CMT1B

CMT1B is caused by mutations in the myelin protein zero (MPZ) gene, the major structural glycoprotein of peripheral compact

myelin, that has a single transmembrane domain, an immunoglobulin-like extracellular domain and a cytoplasmic domain. MPZ acts as a homophilic adhesion protein with important functions in myelin development, compaction and maintenance. Interactions between the extracellular domain compact the myelin sheath at the intraperiod line while interactions between cytoplasmic domains contribute to the major dense line. MPZ plays also a role in the axoglial cross-talk at paranodes and NR where interacts with neurofascins 155 and 186.⁵² Autosomal dominant MPZ mutations, cause a wide range of phenotypes. The most common are: an infantile onset neuropathy with extremely slow CVs (CMT3B) and a Dejerine-Sottas syndrome (DSS) phenotype, a childhood or adult onset neuropathy with slow CVs and a CMT phenotype (CMT1B), an adult onset neuropathy with CVs in the axonal range with possible autonomic symptoms (CMT2I or CMT2J), and an electrophysiological phenotype with intermediate CVs (CMTDID).^{53,54} Phenotypical variability conceivably reflects the heterogeneity of the pathophysiological mechanisms including endoplasmic retention with activation of unfolded protein response, disruption of the intercellular adhesion properties, misglycosylation and altered radial axonal sorting during myelination.⁵³ In the classical CMT1B, CVs were reported to be uniformly slow (16–35 m/s) without CB or abnormal TD.⁵³ Two different pathological phenotypes have been described: some MPZ mutations are characterized by fibers with uncompacted myelin lamellae, other mutations are associated with tomacula-like myelin alterations or myelin outfolding.⁵⁵ MPZ-related CMTs with very slow NCV overlap with CMT3B encompassing the old chapter of DSS. CMT3B/DSS include neuropathies with neonatal or early-infantile onset associated with hypo/amyelination, without active demyelination nor remyelination, and basal lamina onion bulbs surrounding both amyelinated and hypomyelinated fibers (Figure 7A).⁵⁷ Rare missense mutations of *PMP22* may lead to similar clinical, neurophysiological and pathological neuropathies (CMT3A) due to gain-of-function mechanisms toxic for the SC (Figure 7B).⁵⁸ Congenital hypo/amyelinating neuropathies show very slow CVs (usually <10 m/s) without CB or abnormal TD or no recordable CMAPs. In these neuropathies the severe reduction of CV is mainly ascribable to the extreme and diffuse reduction of myelin thickness as predictable by computer modeling.⁵ In congenital hypo/amyelinating neuropathies the nerves are difficult to stimulate, and CMAP amplitude reduction from proximal stimulation sites may be due to the impossibility to obtain supramaximal stimulation or excessive phase cancellation among the few remaining motor unit potentials.

3.1.3 | CMT4F

Autosomal recessive CMT4F is due to mutations in the periaxin gene (*PRX*). Periaxin interacts with Dystrophin Related Protein 2 in a complex with laminin receptor Dystroglycan. The complex assembles adhesive appositions between the abaxonal surface of the myelin

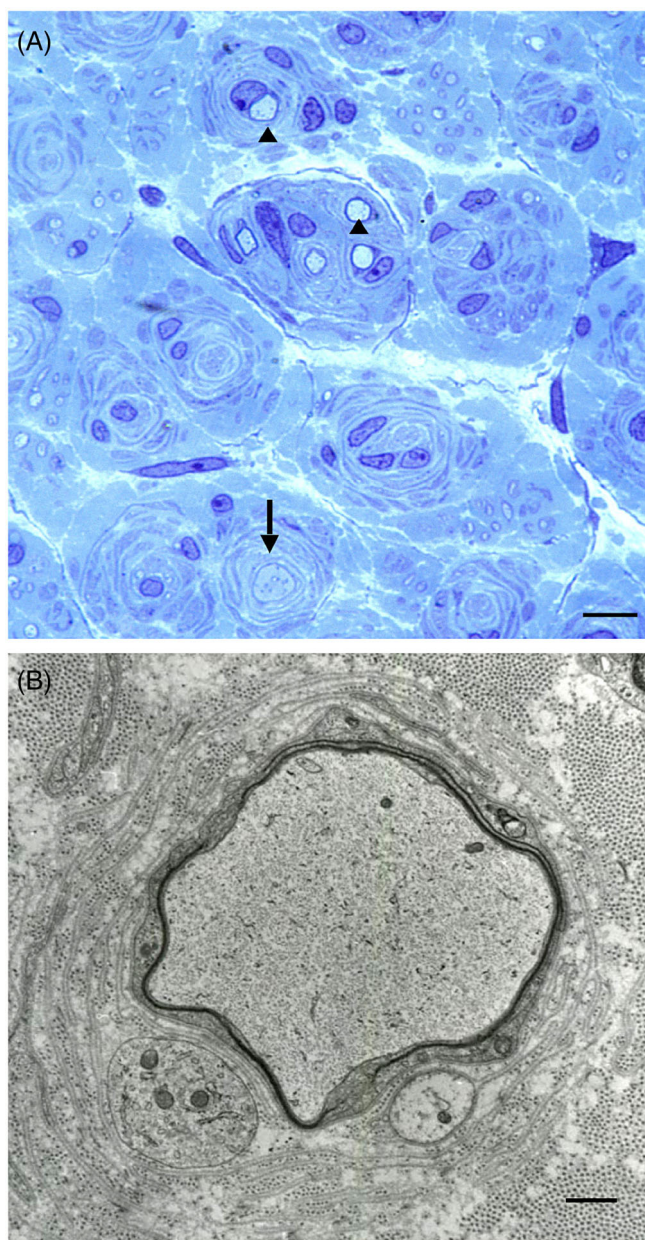


FIGURE 7 Electrophysiological and pathological correlates in hypo/amyelinating congenital neuropathies. A 22-year-old man with a heterozygous p.Gly167Arg mutation of MPZ (CMT3B). Median nerve CMAP amplitude was extremely reduced (0.06 mV), DML extremely prolonged (31.8 ms) and CV very slow (8.2 m/s). (A) Sural nerve biopsy, Semithin section showing severe loss of myelinated fibers, the residual axons are lacking of the myelin sheath (arrow) or surrounded by few myelin lamellae (arrowheads) with a g-ratio = 0.93; several OB are denervated, bar = 10 μ m. A 4-year-old child with a heterozygous p.Ser72Leu mutation of PMP22 (CMT3A). Median nerve CMAP amplitude was greatly reduced (0.2 mV), DML extremely prolonged (33 ms) and CV extremely slow 2.3 m/s. (B) Sural nerve biopsy, electron microscopy shows a fiber with few myelin uncompacted lamellae. The fiber is surrounded by multiple layers of fragmented SC basal lamina. The g-ratio is 0.92, bar = 2 μ m. Reproduced with permission from Cavallaro et al.⁵⁶

sheath and the cytoplasmic surface of the SC membrane and is crucial for the formation and stabilization of Cajal bands that are associated with proper elongation of the SC. CMT4F has an early onset, slow

progression and predominant sensory impairment. Electrophysiology shows very slow CVs (2.1–20 m/s) or undetectable CMAPs without CBs.⁵⁹ Nerve biopsies reveal severe loss of myelinated fibers with the remaining fibers being either devoid of myelin or surrounded by a few myelin lamellae, numerous OBs and some tomacula or myelin thickenings.^{59,60} In periaxin null mice, internodal SC elongation is impaired with preserved nerve fiber diameter resulting in uniformly shortened internodes and CVs reduced by more than 50% compared with the wild type.⁶¹ Very thin myelin and shortened internodes (although not verified in humans) may contribute to explain the very slow and uniform CV in CMT4F.

3.1.4 | Merosin deficiency

Merosin (laminin-2) is a heterotrimer composed of laminin- α 2, β 1, and γ 1 chains. Approximately half of the children with the classic form of congenital muscular dystrophy have a deficiency of the laminin- α 2 chain, encoded by the *LAMA2* gene on chromosome 6q22. In peripheral nerve merosin is expressed in the endoneurial basal lamina whereas its receptors (dystroglycan and α 6 β 4 integrin) are expressed in the outer membrane of the SC and myelin sheath. Besides periaxin, implicated in CMT4F, laminin- α 2, dystroglycan and utrophin are required for compartmentalization and elongation of myelin segments.⁶² A peripheral neuropathy has been reported in most patients with merosin deficiency and has been considered, on the basis of nerve conduction studies, to be “demyelinating” in nature. In a patient, CVs were uniformly slowed (31–37 m/s) with no CB nor abnormal TD.⁶³ Pathology showed a decrease number of mainly large myelinated fibers, some fibers with thickened and irregularly folded myelin sheath, but no OBs (Figure 8A). Teased-fiber examination showed internodes with irregularly thinned or thickened myelin, more than half of fibers had at least a node wider than 5 μ m, and internodal length was reduced and scarcely increased with fiber diameter with a pattern similar to newborns and small children supporting the dysmyelinating nature of the disorder and resembling murine models (Figure 8B).^{63,64}

Recapitulating, in inherited dysmyelinating neuropathies, whatever the gene involved, the uniform conduction slowing can be mainly explained by a SC developmental defect of internode elongation resulting in saltatory conduction at shorter intervals and nodal widening that dilutes the driving current and increases the nodal time to reach the threshold for generating the AP. In congenital hypo/amyelinating neuropathies and CMT4F the very thin myelin thickness may explain the severely reduced CV. However, it remains to be clarified why CV is normal, or near normal, in axonal CMT forms if they also have shortened internodes.³⁴ One study in mice expressing a mutant periaxin demonstrated, as postulated by Huxley and Stämpfli, that CV in myelinated fibers depends on internodal length until a threshold is reached beyond which conduction speed does not further increase (flat maximum).^{8,65} It can be hypothesized that in axonal CMT shortened internodes may not slow significantly CVs because the shortening remains above the internodal length threshold for flat maximum.³⁴

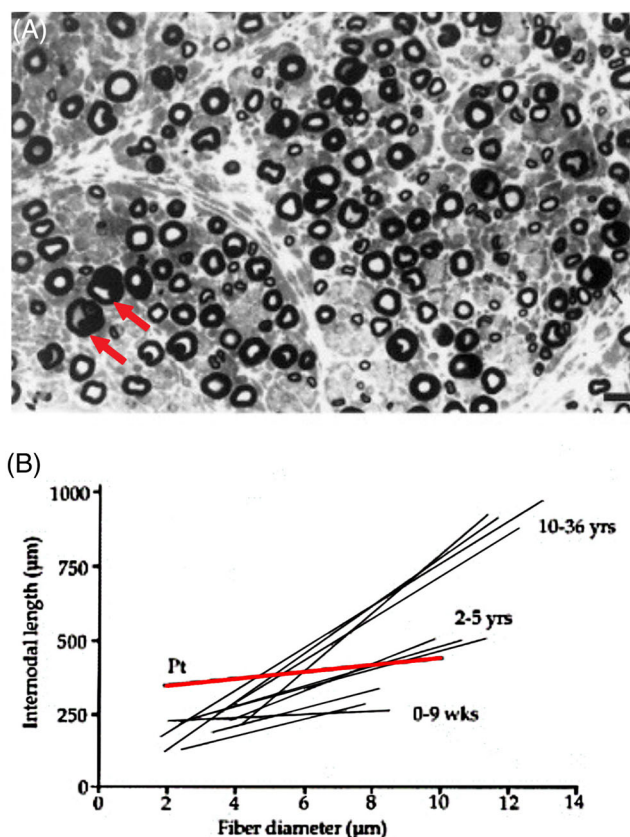


FIGURE 8 Electrophysiologic and pathologic correlates in merosin deficiency. A 20-year-old man with mild myopathy, external ophthalmoparesis, epilepsy, had partial merosin deficiency in muscle and absent merosin in the endoneurium. CVs were uniformly slowed (31–37 m/s) with no CB nor abnormal TD. Left Sural nerve biopsy. (A) Semithin sections, toluidine blue stain, bar = 10 μ m; reduction of myelinated fibers, presence of thickened and irregularly folded myelin sheath in some fibers (red arrows). (B) Linear regression of internodal length versus fiber diameter of the patient (Pt) superimposed on control regression lines from different age groups. In the patient, the internodal length scarcely increased with fiber diameter, showing a pattern similar to newborns and small children. Reproduced with permission from Di Muzio et al.⁶³

3.2 | Dysmyelinating neuropathies with non-uniform conduction slowing

3.2.1 | Hereditary neuropathy with liability to pressure palsies

Hereditary neuropathy with liability to pressure palsies (HNPP) is most commonly caused by the 1.4 Mb deletion of chromosome 17p12 containing the *PMP22* gene causing a reduction of the *PMP22* protein concentration in the myelin sheath of nerves.⁴¹ HNPP manifests typically with acute, recurrent, painless, nerve palsies associated with nerve stretching or compression but some patients present with a chronic sensory or CMT-like polyneuropathy. Conduction studies, in patients with HNPP, are characterized by focal motor CV slowing at nerve compression sites: ulnar nerve at elbow in 85.7% of patients, median nerve at

wrist in 84.4%, and peroneal nerve at fibular head in 36.7%.⁶⁶ CVs outside compression sites are only slightly affected (Figure 9A,B). CB, defined as >50% amplitude or area reduction, has been reported in 6%–22% of nerves.^{40,43} CB is usually not accompanied by abnormal TD, may be persistent, even for years, and regress rapidly after neurolysis or nerve transposition.^{43,68} The electrophysiological findings in HNPP with 17p12 deletion are therefore in striking contrast to the uniform conduction slowing seen in CMT1A, with 17p12 duplication.

Nerve biopsies show sausage-like focal thickenings (tomacula) of the myelin sheath more frequently located at the paranodes that may be associated with a constricted the axon, rare de-remyelinating fibers and no or few OBs made of one or two layers of flattened SC processes (Figure 9C–E).^{69,70} The pathology of the in 10-week-old *PMP22*^{+/-} mice is remarkably similar to HNPP patients with almost every myelinating SC forming internodal and/or paranodal tomacula.⁷¹ Tomacula are not unique of HNPP and have been found in other disorders such as anti-MAG neuropathy, CMT1B, some recessive dysmyelinating neuropathy and CIDP.

It is conceivable that the prevalence of tomacula, the characteristics of myelin foldings and their localization may play a role in pathophysiology of specific disorders. In HNPP it has been hypothesized that nerve palsies associated with CB are due to paranodal tomacula that, in combination with nerve stretching or compression, induce more easily a mechanical deformation of the paranodes, as in compressive neuropathy models, resulting in CB.^{43,72} Other mechanisms have been proposed. In the *PMP22*^{+/-} mice, focal constrictions were observed in the axonal segments enclosed by tomacula and when the tomacula flanked the NR the narrowed segments extended far beyond the paranodal regions as normally occurs in the wild type mice (Figure 9F,G).⁶⁷ It was hypothesized that the reduced axonal diameter, raising the axial resistance to the AP propagation, predisposes to CB when the nerve is compressed. The same group showed that the *PMP22*^{+/-} mice present abnormal formation and maintenance of tight/adherence junctions (but not of PNJs) causing excessively permeable myelin that would shunt current out of nerve fibers reducing the safety factor for AP propagation.⁷³ Whatever the hypothesized mechanism, or the combination of mechanisms, the function of paranode is affected in HNPP resulting in non-uniform electrophysiological demyelinating features without segmental demyelination.

3.2.2 | Some MPZ mutations

In 2004 three familial and one sporadic patients with a MPZ p.Val102/fs null mutation were reported.⁷⁴ The 65-year-old proband had a sensory motor polyneuropathy with partial motor CB and complete sensory CB in the median nerve (Figure 10A,B) in addition to 14–15 m/s difference of CV in the across-elbow segment with respect to the elbow-wrist segment in the ulnar nerves. Two sons of the proband, her nephew and the sporadic case had normal or slightly slowed motor conduction velocities, prolonged DML in at least two nerves and 13 to 25 m/s difference of CV of the ulnar nerve in the across elbow segment compared with the below elbow-wrist segment indicating a non-uniform conduction slowing

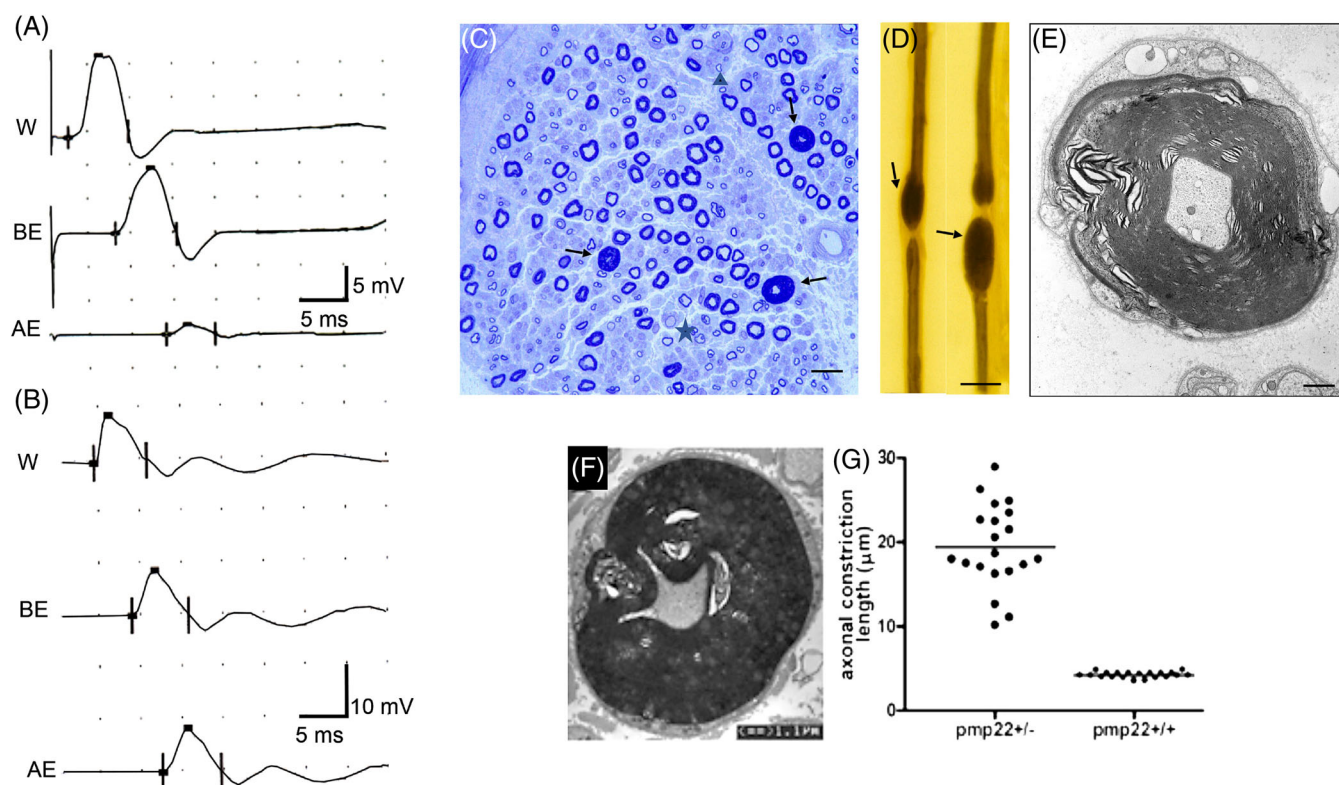


FIGURE 9 Electrophysiologic and pathologic correlates in hereditary neuropathy with HNPP and 17p12 (*PMP22*) deletion. A 45-year-old male developed acute weakness in right ulnar innervated hand muscles after 1 day of heavy manual work. (A) Right ulnar nerve: DML was normal (2.5 ms), CV in the below-elbow (BE) wrist (W) was slightly reduced (46 m/s). In the above elbow (AE)-BE segment CMAP area was 80% reduced without excessive TD and CV was very slow (19 m/s). (B) Lt ulnar: DML was prolonged 4.4 ms, CV in the BE-W segment was still normal (50 m/s) whereas CV in the AE-BE was slow (29 m/s). (C-E) Sural nerve biopsy from a 27-year-old male. (C) Semithin section showing fibers with abnormal concentric thickening of the myelin sheaths (arrows), bar = 25 μ m. Remyelinating fibers are infrequent (star) as well as OBs made by only one or two layers of SC processes (arrowhead). (D) On teased fibers tomacula (arrows) with a globular or fusiform shape and a length of 30–50 μ m are localized to paranodes, bar = 30 μ m. (E) At electron microscopy a tomaculum characterized by an abnormally large number of myelin lamellae that fold irregularly surrounding a constricted axon, bar = 2 μ m (Reproduced from Cavallaro et al.⁵⁶). (F and G) Mouse model with one of the two *PMP22* alleles deleted. (F) A constricted axon on transverse section. (G) The lengths of constricted axon segment at paranodes with tomacula in *PMP22*^{+/-} mice was 19.4 ± 4.9 μ m whereas wild type mice (*PMP22*^{+/+}) without tomacula was 4.2 ± 0.2 μ m ($p < 0.0001$). Reproduced with permission from Bai et al.⁶⁷

(Figure 10C). Nerve biopsy showed loss of large diameter fibers more severe in the oldest patient (Figure 10D,E), excessive myelin irregularity and thickenings in virtually all fibers, evidence of de-remyelination and few small OBs (Figure 10F,G). Myelin thickenings consisted of myelin foldings surrounding irregularly the axon outside the normal myelin sheath (outfoldings) or of redundant loops extending toward the axons (infoldings) deforming the nodal and paranodal region (Figure 10H,I,O). Occasionally myelin thickenings had the appearance of classic tomacula, although smaller in size (Figure 10M). Myelin uncompaction was also evident (Figure 10N). In the 4-month-old *P0*^{+/-} mice about 70% of fibers showed in the paranodal region ovoids which by electron microscopy were identified as complex and asymmetric infoldings causing compression and crescent-like deformation of the axon.⁷⁵ Furthermore, the p.-Val102fs mutation has been described in two sister with symptoms of spinal root hypertrophy showing CB and abnormal TD.⁷⁶ Three additional patients with *MPZ* mutations and a patchy neuropathy with CBs have been reported: one with p.Ser140Thr, the second with a

p.Arg98His and the third with p.Ile112Thr.⁷⁷⁻⁷⁹ Another mutation, p.-Tyr145stop, has been reported in a mild context of neuropathy presenting with mononeuropathies, even recurrent, at compression sites mimicking HNPP with the main pathological features being small size tomacula.⁸⁰

It can be hypothesized that in these patients with *MPZ* mutations, in analogy with HNPP, myelin thickenings and infoldings, when numerous and localized at the paranodal region, in concurrence with compression at entrapment sites or minor repetitive trauma may induce mechanical distortion of the paranodal region and segmental conduction abnormalities.

3.2.3 | CMT1X

CMT1X, the second most common form of CMT, is due to mutations of gap junction protein beta-1 (*GJB1*) gene on chromosome Xq13 that

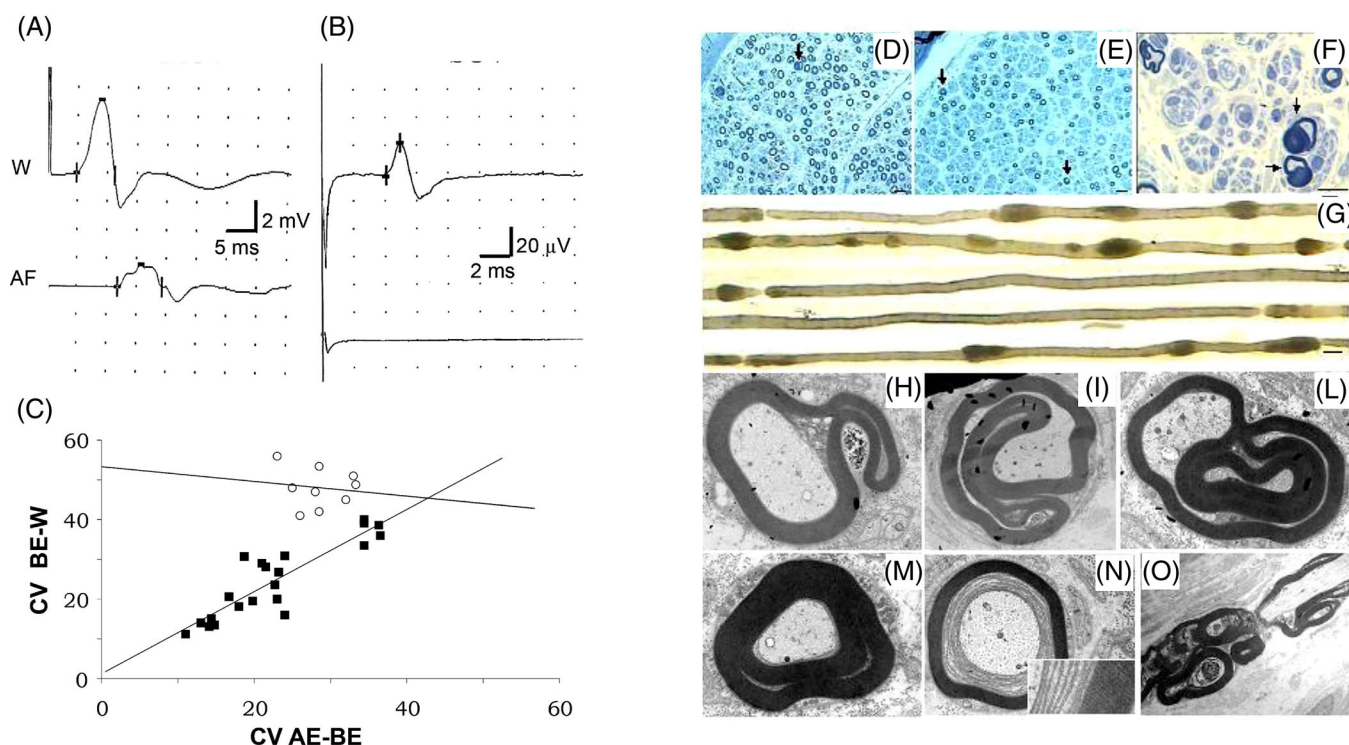


FIGURE 10 Electrophysiological and pathological correlates in patients with p.Val102/fs null mutation of MPZ gene. A 65-year-old woman referred for carpal tunnel syndrome. (A) median nerve motor conduction showing slightly prolonged DML (4.8 ms), reduced CV (34 m/s), and partial motor CB (60% reduction of CMAP area) from antecubital fossa (AF) compared with wrist (W) stimulation. (B) Antidromic median nerve sensory conduction recorded from the third finger showing complete CB from AF stimulation compared with W stimulation. (C) Scatterplot of motor CV of ulnar nerves in the segment below-elbow-wrist (BE-W) versus the above-below elbow segment (AE-BE) in 18 nerves of patients with CMT1A (black squares) in whom the CVs were highly positively correlated ($y = 1.033x + 1218$; $R = 0.89$) and in nine nerves of patients with Val102/fs MPZ mutation (empty circles) in whom there was no correlation ($y = -0.184x + 53.27$; $R = -0.13$). (D–F) Sural nerve biopsy semithin transverse sections; toluidine blue stain, bars = 20 μ m. (D) A 29-year-old patient; (E and F) a 65-year-old woman. Note marked loss of myelinated fibers, more severe in the 65-year-old patient. Many residual fibers have abnormally thickened and irregularly folded myelin sheath (arrows). (G) teased fibers of the 29-year-old patient, bar = 10 μ m. Note various degrees of myelin thickenings in nodal, paranodal, and internodal regions. (H–O) Electron microscopy of the 65-year-old patient. (H–N) Transverse sections showing myelinated fibers with an abnormally thick and redundant myelin forming an external loop (H), internal loop (I), outfoldings and infoldings (L), tomacula like concentric myelin thickening (M), a fiber with uncompacted myelin in the inner layers of the myelin sheath (N). (O) Longitudinal section of one fiber with irregular thickenings deforming the nodal and paranodal region. (H, I, and L): $\times 11\,000$, (M): $\times 5600$, (N): $\times 4000$ and $56\,000$, (O): $\times 1800$. Reproduced with permission from De Angelis et al.⁷⁴

encodes connexin 32 (Cx32) expressed by SCs and localized in the non-compact myelin at Schmidt–Lanterman incisures and paranodal loops. Cx32 forms gap-junctions that allow a radial diffusion of ions and small molecules between the adaxonal and perinuclear cytoplasm of the SC. Many Cx32 mutants fail to form functional gap-junctions or form gap-junctions with abnormal biophysical properties.⁸¹ CMT1X is clinically moderate to severe in males. In females two groups were identified after 48 years of age: 55% of women progressed as severely as men although with a later age of onset, the remaining had mild or no symptoms.⁸² In the majority of CMT1X males median CV is in the intermediate slowing range (between 25 and 45 m/s). However, a review showed that intermediate CV slowing in median nerves was found, besides X-linked CMT, in 11 types of autosomal dominant and 4 types of autosomal recessive CMT making this categorization of limited electrodiagnostic utility.⁸³ In women CVs are between 30 and 50 m/s.⁸⁴ Some women have normal CVs probably because of

predominant inactivation of the mutant X chromosome (Lyonization phenomenon) in SCs. In CMT1X there is also electrophysiologic evidence of axonal loss with reduction of distal CMAP amplitudes. In a few males and in up to 39% of females non-uniform conduction slowing, CBs and excessive TD have been reported leading, in some cases, to an initial diagnosis of CIDP (Figure 11A–D).^{82,85,87–89}

In CMT1X pathology reveals a loss of large myelinated fibers increasing with age, active degeneration in 5%–10% of fibers, clusters of regenerating fibers, few OBs and increased g-ratio (indicating decreased myelin thickness) but not in the range of values that could significantly reduce nerve CV according to computer modeling (Figure 11E–G).^{5,33,47,85} Teased fiber showed high incidence of lengthened NRs due to apparent remodeling of paranodal myelin attachments and reduced internodal length which scarcely increased according to fiber diameter.^{33,85} This remodeling of paranodal myelin, not accompanied by segmental de-remyelination, was thought to be

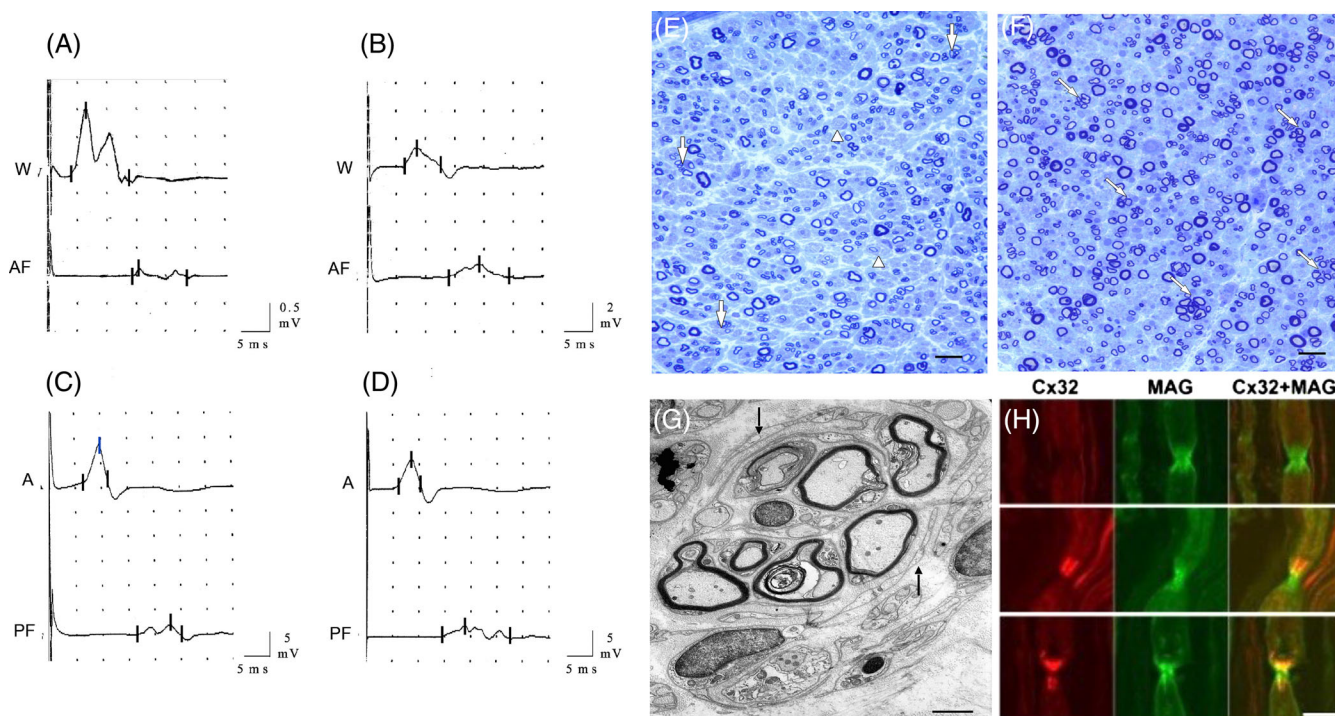


FIGURE 11 Electrophysiological and pathological correlates in CMT1X. Motor conductions in three patients of the same family harboring a p.Arg15Gln mutation of *GJB1*. (A) Patient 1, a 55-year-old man, left median nerve: distal CMAP amplitude is reduced (1.2 mV), DML is normal (4.1 ms) whereas CV is very slow (14 m/s), CMAP from proximal stimulation is 87% reduced in area and with and abnormal TD (38% increased duration), the median to ulnar CV difference was 21 m/s. (B) Patient 2, a 57-year-old man (brother of patient 1), right median nerve, distal CMAP amplitude is reduced (1.4 mV), DML is prolonged (6.2 ms) and CV is slow (31 m/s), CMAP from proximal stimulation is abnormally dispersed (73% increased duration). (C and D) Patient 3, a 32-year-old woman (daughter of patient 2), (C) right tibial nerve: distal CMAP amplitude is normal (7.6 mV), DML is slightly prolonged (6.5 ms) and CV is slightly reduced 39 m/s, CMAP from proximal stimulation is 64% reduced in area with abnormal TD (68% increased duration); (D) left tibial nerve: distal CMAP amplitude is normal (6.1 mV) as well as DML (4.7 ms), CV is slightly reduced (38 m/s) and CMAP from proximal stimulation is abnormally dispersed (220% increased duration). W: wrist, AF: antecubital fossa, A: ankle, PF: popliteal fossa. Reproduced with permission from Capasso et al.⁸⁵ (E–H) Sural nerve biopsies from a 21-year-old male with a p.Ser26stop mutation of *GJB1* (E and G) and a 17-year-old female with an p.Arg183His mutation of *GJB1* (F and H). (E and F) Semithin section showing variable loss of large myelinated fibers and several clusters of regeneration (arrows); rare mono-bilayers OBs are recognizable (arrowheads), bar = 25 μ m. The pathological picture is similar in both patients but the loss of fiber is more evident in the male (E). (G) Electron microscopy showing a regeneration cluster: multiple fibers with excessively thin myelin are enclosed by SC cytoplasmic processes (arrows), bar = 2 μ m. (H) Immunofluorescence on longitudinal sections with antibodies against Cx32 (red) and anti-MAG (green); merge is yellow. Cx32 and MAG localize to regions of non-compact paranodal myelin. Top: Cx32 is absent in both SC expressing the mutated allele, whereas MAG is regularly detected. Middle: Cx32 is expressed only by one the two opposite SCs; the finding is consistent with a mosaicism related to lyonization. Bottom: both SCs express Cx32 (bar = 10 μ m). Reproduced with permission from Boso et al.⁸⁶

specific for CMT1X and significant because of the localization of the Cx 32 protein to the paranodal region.³³ In CMT1X intermediate CV slowing can be explained, as for other dysmyelinating neuropathies, by shortened internodes and elongated nodes. In females abnormal TD and CB might be due to clustering, along nerve fibers, of SCs not expressing Cx32 at the paranodes that may induce functional alterations disturbing nerve conduction (Figure 11H).⁸⁶ However, this hypothesis does not completely explains why CMT1X males, who should express the mutation with the same functional effect in all paranodes, seem to show less frequently non-uniform conduction slowing features. Regenerating fibers, with thin myelin respect to axonal diameter, may also contribute to abnormal TD by increasing the desynchronization of CVs among nerve fibers.

3.2.4 | CMT1C

Charcot-Marie-Tooth disease type 1C (CMT1C) is a rare, dominantly inherited neuropathy caused by mutations in the lipopolysaccharide-induced tumor necrosis factor (*LITAF*) gene, also known as small integral membrane protein of the lysosome/late endosome (*SIMPLE*). CMT1C is clinically indistinguishable from a mild presentation of CMT1A.⁹⁰ Patients with CMT1C have usually CVs in the CMT1 range; however, some patients presenting with partial CB and or abnormal TD have been described.^{91–95} In CMT1C nerve biopsy showed a severe reduction in the number of the myelinated fibers, some of the remaining had a very thin myelin sheath compared to axonal diameter and some were surrounded by SC proliferations.⁹⁴ Teased fiber did

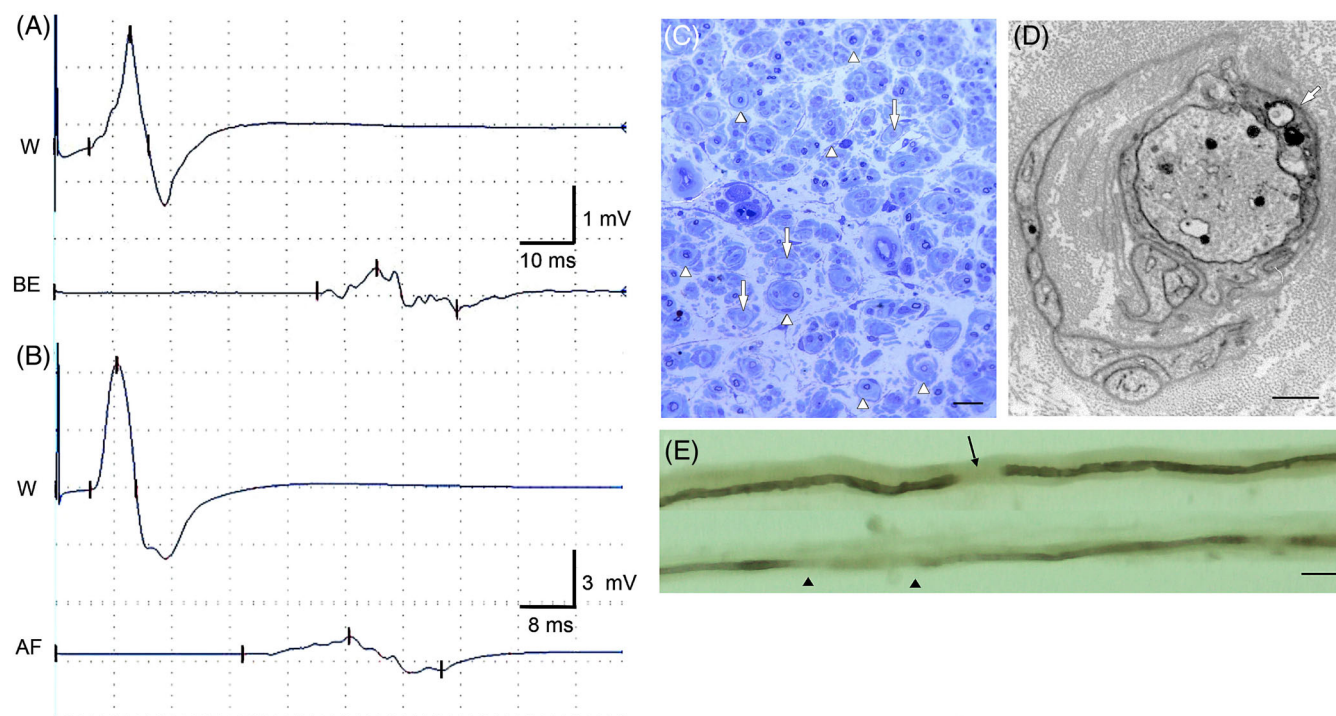


FIGURE 12 Electrophysiological and pathological correlates in CMT4J. (A) Motor nerve conduction studies in a 29-year-old male harboring a heterozygous compound mutation of *FIG4* (p.Ile41Thr; p.Pro605GlufsTer43). (A) Ulnar nerve, distal CMAP amplitude is 2 mV, DML is prolonged (5.9 ms), CV in the below-elbow (BE) wrist (W) segment is severely reduced (6.1 m/s), CMAP amplitude from BE stimulation is 75% reduced and CMAP duration 217% increased compared with CMAP from W stimulation. (B) Median nerve, distal CMAP amplitude is 6.5 mV, DML is slightly prolonged (4.6 ms), CV in the antecubital fossa (AE)-W segment is 11.8 m/s, CMAP amplitude from AF stimulation is 77% reduced and CMAP duration 459% increased compared with CMAP from distal stimulation. (C–E) Sural nerve biopsy. (C) Semithin section showing a diffuse and severe loss of myelinated fibers; remaining fibers shows thin myelin or absent myelin sheath (arrows); OBs are frequent (arrowheads), (bar = 25 μ m). (D) electron microscopy demonstrates a fiber in a very early stage of remyelination; intracytoplasmic products of myelin breakdown in the SC are evident (arrow), (bar = 3 μ m). (E) Teased fibers showing randomly distributed paranodal (arrow) and internodal (arrowheads) demyelination interposed with normally myelinated internodes, (bar = 40 μ m). Reproduced with permission from Cavallaro et al.⁵⁶

not show segmental demyelination. *SIMPLE* mutant mice show decreased motor and sensory nerve CVs and reduced CMAP amplitudes; pathology documented focally infolded myelin loops at paranodal regions that protrude into the axons, often linked to constricted axons and widened nodal gaps.⁹⁶ The limited pathologic observations in humans do not allow up to draw a conclusion although, on the basis of the animal model, it is hypothesizable that paranodal myelin infoldings and widened nodal gaps may be responsible of segmental nerve conduction abnormalities in CMT1C.

3.2.5 | CMT4J

CMT4J is a very rare recessive disorder caused by loss-of-function mutations in the phosphoinositide phosphatase (*FIG4*) gene. *FIG4* dephosphorylates PI(3,5)P₂ a phosphoinositide localized on the cytoplasmic surface of vesicles of the endosome/lysosome pathway membrane trafficking that is important for myelination. CMT4J manifests a high variable onset, from early childhood to adulthood, and severity affecting asymmetrically both proximal and distal upper and lower limbs with prevalent motor involvement. Some patients present rapid

deterioration of strength in a single limb.^{97,98} Neurophysiology revealed non-uniform slowing of CVs with CB and TD (Figure 12A,B).^{98,99} Pathology displayed a severe reduction of myelinated fibers with the residual fibers showing too thin or absent myelin with OBs and at teased fibers segmental demyelination (Figure 12C–E). In *Fig4*^{−/−} mice teased nerve fiber examination revealed segmental demyelination and decreased internodal length.⁹⁸ In CMT4J segmental demyelination can well explain the non-uniform conduction features.

3.2.6 | Coexisting hereditary and inflammatory neuropathies

In pre-molecular diagnosis era several patients with hereditary sensory and motor neuropathy who responded to prednisone were reported.^{100,101} In 2004 Ginsberg and colleagues described seven genetically proven CMT1A presenting with an acute or subacute deterioration.¹⁰² Six patients had neuropathic pain or prominent sensory symptoms and three showed partial motor CB that, in one case, was reversed by immunomodulation. Nerve biopsy demonstrated, besides

the classical CMT changes, excess of lymphocytic infiltration (>100 CD4⁺ per section) in all patients, active or recent demyelination in four and extensive supepineurial edema in one. Four patients were treated with steroids and/or intravenous immunoglobulin, with variable positive response. In 2016 a review on genetically confirmed hereditary neuropathy patients with a possible coexisting inflammatory neuropathy totaled 62 cases.¹⁰¹ Taking a definite therapeutic response as a major supportive criterion for a coexisting inflammatory neuropathy a beneficial effect was described in 16/28 (57%) CMT1A cases and in 9/23 (41%) there was evidence of non-uniform conduction slowing including CB and TD, although variably defined.¹⁰¹ Regarding the possible association of MPZ mutations with and inflammatory neuropathy, immunomodulatory or immunosuppressant treatments were variably reported from being ineffective to a good and even repeated response after relapses.^{103–107} Interestingly, the heterozygous MPZ knockout mice develop an age-dependent neuropathy with asymmetric slowing of CV with TD and CB and, at pathology, multifocal demyelination and inflammatory infiltrates, suggesting that an immune-mediated mechanisms may contribute to the pathogenesis.¹⁰⁸ However, it should be reminded that some MPZ mutations may be associated with non-uniform conduction slowing without any evidence of a coexisting inflammatory process.^{74,77–79} In CMT1X no convincing response to immunomodulatory therapy was reported in the majority of patients whereas non-uniform slowing, including partial CB, was present in 82% of cases.¹⁰¹ This observation suggests that non-uniform conduction slowing resulted from the *GJB1* gene mutation by itself rather than an associated inflammatory process.

In conclusion, although at present a chance association cannot be excluded, a possible link between inherited neuropathies and an inflammatory process should be kept in mind suggesting an individual additional genetic susceptibility to develop an immune-mediated disorder. Alternatively disturbance of myelin maintenance and myelin

destruction, may expose normally sequestered myelin antigens breaking self-tolerance and inducing a secondary autoimmune process.

3.2.7 | Mitochondrial neurogastrointestinal encephalomyopathy

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal-recessive disorder caused by mutation in the gene encoding thymidine phosphorylase (*TYMP*) and characterized by gastrointestinal dysmotility, major weight loss, ophthalmoparesis, ptosis, mitochondrial myopathy, asymptomatic central nervous system white matter abnormalities, and sensory and motor neuropathy. Peripheral neuropathies in mitochondrial disorders are mostly chronic axonal and sensory more than motor.¹⁰⁹ In one of the first MNGIE reported cases CVs were slow with distal CMAP amplitudes in the normal range (Figure 13A).¹¹⁰ Abnormal TD (at least 36% increased duration) of proximal CMAPs was present with a reduction of CMAP area that however, was never more than 39% compared with the distal CMAP. Sural nerve biopsy showed a loss of myelinated axons and many of the remaining myelinated fibers had very thin myelin sheaths but no OBs were evident (Figure 13B). Teased fibers examination showed segmental demyelination and remyelination in 34% of fibers. Ten years later, Bedlack and colleagues described five patients with MNGIE in whom the electrophysiology showed conduction slowing and amplitude reduction of proximal CMAP (although not always fulfilling the most restrictive criteria for CB).¹¹¹ All patients were initially misdiagnosed with CIDP, and three treated with immunomodulatory drugs without benefit. De-remyelination was found at nerve biopsy in two cases.

To explain non-uniform conduction slowing in MNGIE it may be hypothesized that the loss of thymidine phosphorylase function

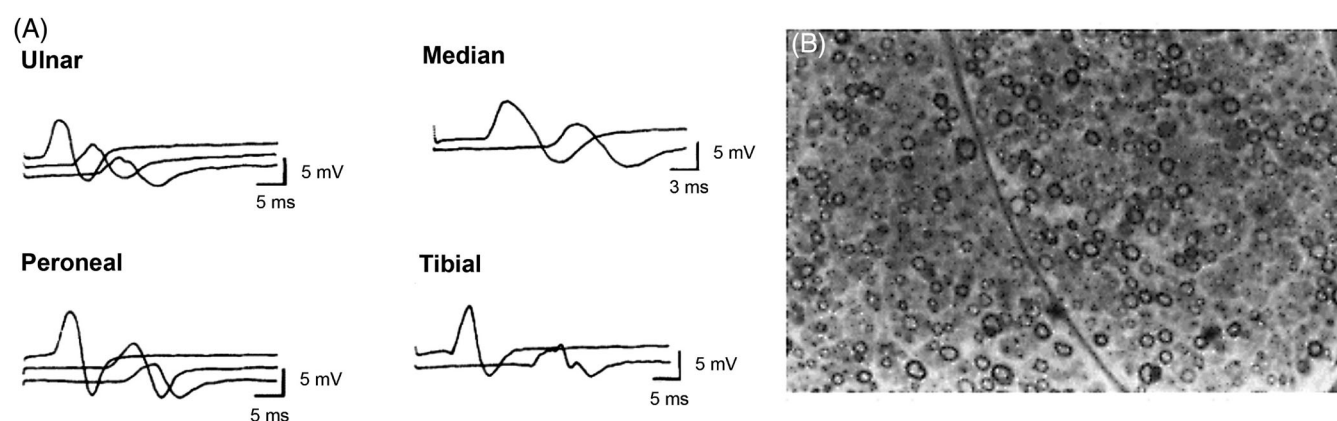


FIGURE 13 Electrophysiologic and pathologic correlates in a 37-year-old woman with mitochondrial neurogastrointestinal encephalomyopathy. (A) superimposed tracings of motor nerve conduction studies of ulnar, median, peroneal and tibial nerves. Upper tracings are the responses from distal stimulation (wrist, ankle), lower tracing are responses from proximal stimulation (elbow, knee). Ulnar nerve was also stimulated below elbow and peroneal nerve below the head of the fibula (middle tracings). CV ranged from 24 m/s in the tibial to 31.5 in the ulnar nerve with distal CMAP amplitudes in the normal range and excessive TD (at least 36% increased duration of proximal CMAP) was present in ulnar, peroneal and tibial nerves. (B) Sural nerve biopsy showing a loss of myelinated axons. Many of the remaining myelinated fibers had very thin myelin sheaths but no onion bulbs were evident. Reproduced with permission from Uncini et al.¹¹⁰

induces, because of mitochondrial heteroplasmy and in analogy to ragged-red fibers in muscle, a non-homogeneous distribution of SCs with mutated mtDNA leading to segmental demyelination and non-uniform conduction changes.

Summarizing, hereditary neuropathies with non-uniform conduction slowing are associated with and might be caused by pathological changes focused at the paranode such as: paranodal tomacula with axonal constrictions, paranodal myelin thickening with infoldings, abnormal formation and function of paranodal and tight/adherence junctions. In some conditions as CMT4J and MNGIE segmental demyelination can play a role. Because of non-uniform conduction slowing some inherited neuropathy patients, above all if sporadic, can be erroneously diagnosed as CIDP. A lack of response to treatment should prompt to reconsider the diagnosis. On the other side, a rapid clinical decline or a stepwise progression in an inherited neuropathy, along with the documentation of CB and excessive TD, should rise the suspicion of a coexisting inflammatory process and an “ex juvantibus” immunomodulation treatment with objective assessment of the response appears justified.

4 | AXONAL NEUROPATHIES

It is common opinion that axonal neuropathies are electrophysiologically characterized by just reduction of CMAP and SNAP amplitudes with normal or slightly slow CV as the correlate of axonal degeneration and loss. Following are some examples demonstrating that the pathophysiology of axonal neuropathies is more complex than commonly believed.

4.1 | Hereditary transthyretin amyloidosis neuropathy

Hereditary transthyretin amyloidosis (hATTR), also reported as ATTRv, is an adult onset disease caused by mutation of the transthyretin gene (*TTR*) and characterized by extracellular deposition of amyloid fibrils in tissues, especially heart and peripheral nerves, leading to a rapidly progressive and disabling sensory-motor neuropathy. Electrophysiology shows, at early stages of the disease, distal axonal features possibly due to a dying-back degeneration because of deposits of amyloid fibrils and damage in roots and dorsal root ganglia.¹¹² However, at later stages, prolonged DMLs, slow CVs, abnormal TD, even fulfilling the EFNS/PNS criteria for definite demyelinating polyneuropathies, have been reported in about one third of patients so that the most frequent misdiagnosis is CIDP (Figure 14A).^{20,113–115} Nerve biopsy at this stage shows besides severe axonal loss and amyloid deposits (Figure 14B,C), some thinly myelinated fibers and occasional OBs suggestive of de-remyelination (Figure 14D).^{111,113} At teased fibers study paranodal and internodal segmental demyelination, although not quantified, were reported in about 10% of patients.¹¹⁶ It is hypothesizable that over time, amyloid deposits spread along the peripheral nerve inducing progressively increases axonal loss and

myelin alterations that are usually in close contact with transthyretin deposits (Figure 14E). This may suggest a direct mechanical or toxic effect of fibrillar and prefibrillar material and possibly explain demyelinating nerve conduction changes in hATTR neuropathy.¹¹²

Regarding the electrophysiological differentiation between hATTR neuropathy and CIDP it may help to consider that in hATTR patients CV slowing is usually associated with marked reduction of distal CMAPs and SNAPs amplitudes whereas in CIDP, at least in the initial stages, CVs are slow with relatively preserved CMAPs and SNAPs. Anyway, as diverse treatments are currently available in hATTR, a *TTR* gene testing should be considered in late-onset, sporadic progressive neuropathies even when presenting some demyelinating features.

4.2 | Autoimmune axonal neuropathies

About 30 years ago, an acute motor axonal neuropathy (AMAN) associated with antecedent *Campylobacter jejuni* infection and anti-GM1 antibodies was described and considered a form of Guillain-Barré syndrome (GBS).¹¹⁷ AMAN was initially thought to be characterized simply by axonal degeneration and its electrodiagnosis was based on the lack of demyelinating features and low amplitude CMAPs.¹¹⁷ However, some patients with antibody to GM1 showed CB and conduction slowing which promptly resolved without the development of excessive TD.¹¹⁸ This feature, named reversible conduction failure (RCF), to distinguish it from demyelinating CB, mimics acute demyelination but sequential recordings do not show the development TD of CMAPs characteristic of remyelination suggesting a transient conduction impairment at the NR.^{118,119} Figure 15 summarizes the hypothesized immunopathologic cascade and the electrophysiological correlates in AMAN beginning with IgG deposition at the NR leading to conduction failure that may be transitory and even completely reversible or progress to axonal degeneration. This pathophysiological continuum explains why the recovery in AMAN patients may be either rapid and complete or delayed and poor according to the relative amount of RCF and axonal loss in the nerves of the individual patient. RCF is not rare as it was detectable in two motor nerves of 46.6% of patients with axonal GBS and is an “a posteriori” diagnosis as can be recognized only by at least two serial electrophysiological studies.¹²⁰ RCF has been also demonstrated in sensory nerves of patients with acute motor and sensory axonal neuropathy, and in other GBS variants and subtypes with anti-ganglioside antibodies such as pharyngeal-cervical-brachial weakness, acute sensory ataxic neuropathy and Miller Fisher syndrome.²⁵ GBS variants and subtypes with anti-gangliosides antibodies are classified as axonal. However, the term may be deceptive as, in the common knowledge, it is correlated to axonal degeneration and unfavorable prognosis and not to the possibility of a transient dysfunction of the nodal region with prompt recovery.

Antibodies to neurofascin 186, a molecular adhesion protein expressed in the nodal axolemma that with gliomedin has a crucial role in Nav channels clustering, have been reported in a few patients

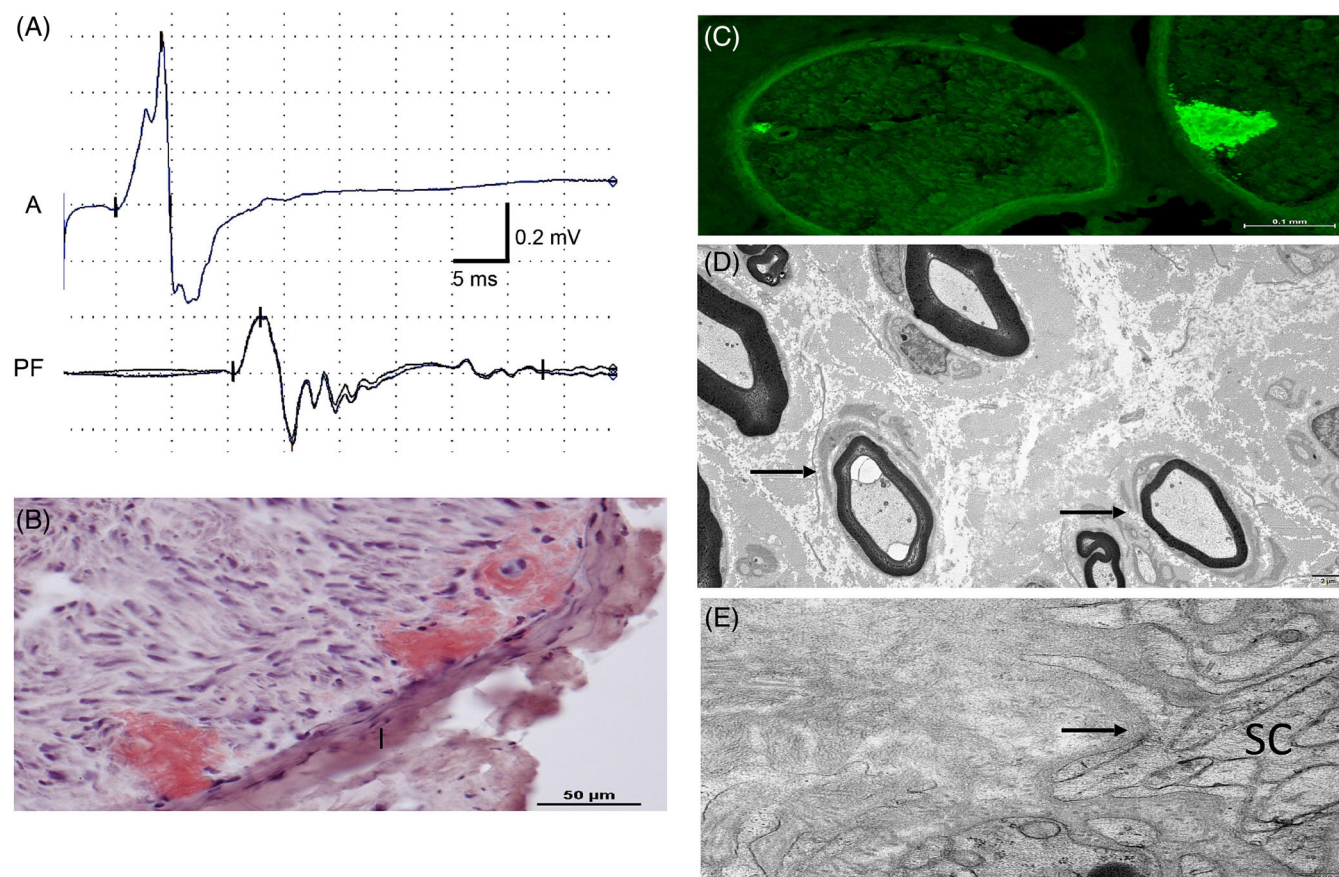


FIGURE 14 Electrophysiologic and pathologic correlates in a 66-year-old man with hATTR. (A) Tibial nerve: distal CMAP amplitude is severely reduced (0.6 mV), DML is normal (5.1 ms) but CV in the popliteal fossa (PF)-ankle (A) segment is slow (27 m/s), CMAP amplitude from PF stimulation is 70% reduced and CMAP duration is extremely prolonged (580%) compared with CMAP from A stimulation (two tracings are superimposed to show the consistency of the late components of CMAP). (B) Sural nerve biopsy of a 70-year-old man. Paraffin embedded section, congo red staining showing endoneurial amyloid deposits, bar = 50 μ m. (C) immunofluorescence of frozen sural nerve fascicles: amyloid deposits are specifically labeled by anti-TTR antibody. (D) electron microscopy identifies remyelinated axons with a too thin myelin sheath and surrounded by onion bulb formations (arrows), bar = 2 μ m. (E) The basal lamina of a Schwann cells (SC) (arrow) is disrupted by entangled amyloid fibrils, bar = 500 nm.

with conduction slowing and CB classified as CIDP.¹²¹ A patient with IgG3 against neurofascin 186 activating the complement presented with a classical GBS progressing to tetraplegia and respiratory failure that persisted 4 months.¹²² Then he began to improve quickly and recovered almost completely in 9 months. Serial electrophysiology showed long lasting partial CBs that at the nadir of the disease became complete in two nerves along with CVs 47%–50% reduced in other nerves (Figure 16A). These alterations resolved, without development of excessive TD, in parallel with clinical improvement. Antibodies stained the NR of the mice nerve and electron microscopy showed loss of SC microvilli and decreased length till to complete occlusion of the NR by extensions of SC cytoplasm but no segmental demyelination (Figure 16C–F). The same alterations along with disorganization and loss of Nav channels at NR, besides a 35% reduction of CV, have been described in mice with ablated NF186.¹²³ Saltatory conduction depends on the clustering and rapid opening of Nav channels at the NR. If a smaller amount of Nav channels is available more time is required to reach the threshold to generate an AP. This, replicated for many consecutive nodes, can result in CV slowing, even in

the demyelinating range. In keeping, inactivation in humans of the Nav channel by intravenous lidocaine reduced CVs by 20–30 m/s.¹²⁴ These considerations can explain why CV can be slow in disorders affecting the excitability of nodal axolemma without demyelination resolving the apparent contradiction between electrophysiology and immunopathology.

Overall, some autoimmune neuropathies with paranodal myelin detachment and/or nodal Nav channels disruption can present with RCF and CV slowing, even in the demyelinating range. These observations widen the spectrum of the electrophysiological features of autoimmune axonal neuropathies and should be taken into account to avoid misdiagnoses and for correct prognostication.

4.3 | Axonal neuropathies due to energy restriction

Saltatory nerve conduction is an efficient but highly energy demanding process and mitochondria are, during nerve activity, concentrated

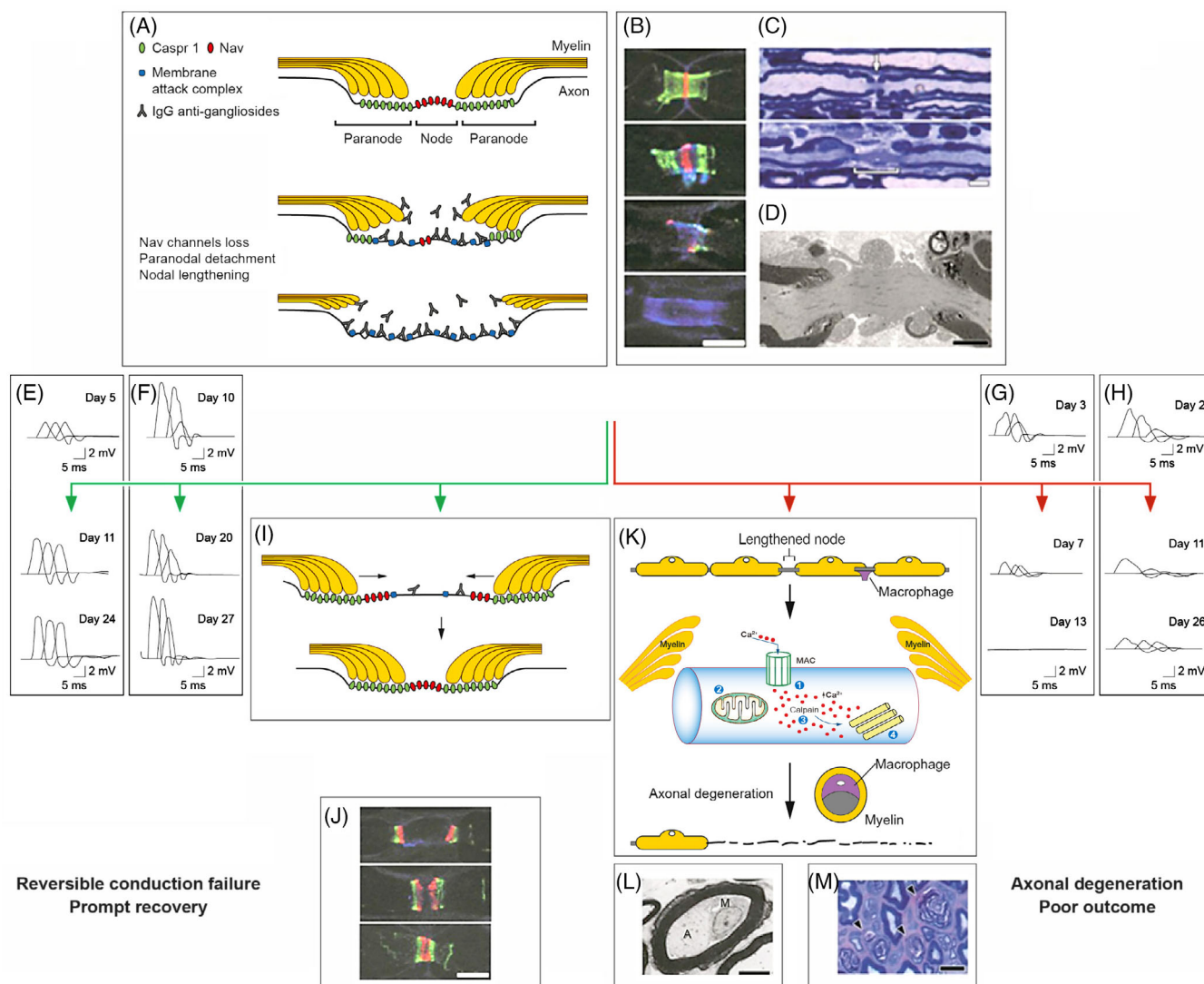


FIGURE 15 Electrophysiologic and immunopathological correlates in acute motor axonal neuropathy (AMAN). Pictures are from the AMAN rabbit model. Tracings are from patients (Ab). (A–D) Disruption of the nodal region. (A) Schematized normal node (upper). Anti-ganglioside Ab bind at the axolemma and the classical pathway of complement is activated forming the membrane attack complex (MAC) pore with sodium voltage gated (Nav) channel clusters disruption, contactin-associated protein1 (Caspr1) disappearance, myelin loops detachment and lengthening of nodes (middle and lower). At this point conduction failure occurs. (B) Immunostaining of ventral roots from a normal rabbit (upper) and AMAN rabbits with IgG anti-GM1 antibodies (lower pictures). MAC (blue) forms at node extending to paranodes. Clusters of Nav (red) and paranodal Caspr (green) fades away (bottom). (C) Toluidine blue staining. normal node (upper, arrow), elongated node (lower, bracket). (D) Electron microscopy showing a lengthened node and myelin loops detachment. In B–D bar is 10 μ m. (E–H) Superimposed compound muscle action potentials (CMAPs) after stimulation of ulnar nerves showing patterns of conduction failure. (E) All CMAP amplitudes are decreased. (F) CMAP amplitude reduction across the elbow. (G) All CMAPs amplitudes are slightly decreased. (H) CMAP amplitude reduction across the elbow. At this point, the pathophysiological cascade may follow two paths. Left (I, J), rapid recovery (green path). Clusters of Nav channels and Caspr1 are formed and fuse to form a new node, bar = 10 μ m. Serial conduction shows: in (E) increase of all CMAP amplitudes without development of TD since day 11 configuring a distal reversible conduction failure; in (F) improvement of proximal CMAP amplitude without TD configuring reversible conduction failure in intermediate nerve segment. Right (K–M) Events leading to axonal degeneration (red path). (K) (1) Ca^{2+} (red dots) enter through the MAC pores and accumulates in the axoplasm, (2) damaging the mitochondria and (3) activating Ca^{2+} -dependent calpain, (4) that causes proteolytic cleavage of neurofilaments (NF), and finally axonal degeneration. Then macrophages penetrate from the node into the periaxonal space to remove degenerating axons. (L) Electron microscopy of a ventral root fiber: a macrophage (M) is in the periaxonal space of an injured axon (A), myelin sheath is intact, bar = 5 μ m. (M) Toluidine blue staining. Arrowheads indicate degenerated nerve fibers, bar = 10 μ m. (G, H) serial conduction showing the evolution from conduction failure to axonal degeneration. (G) Progression on day 13 to unrecordable CMAPs. (H) Further reduction on day 26 of distal CMAP amplitude without amplitude reduction of proximal CMAPs suggesting advancing axonal degeneration. Reproduced with permission from Uncini.²⁵

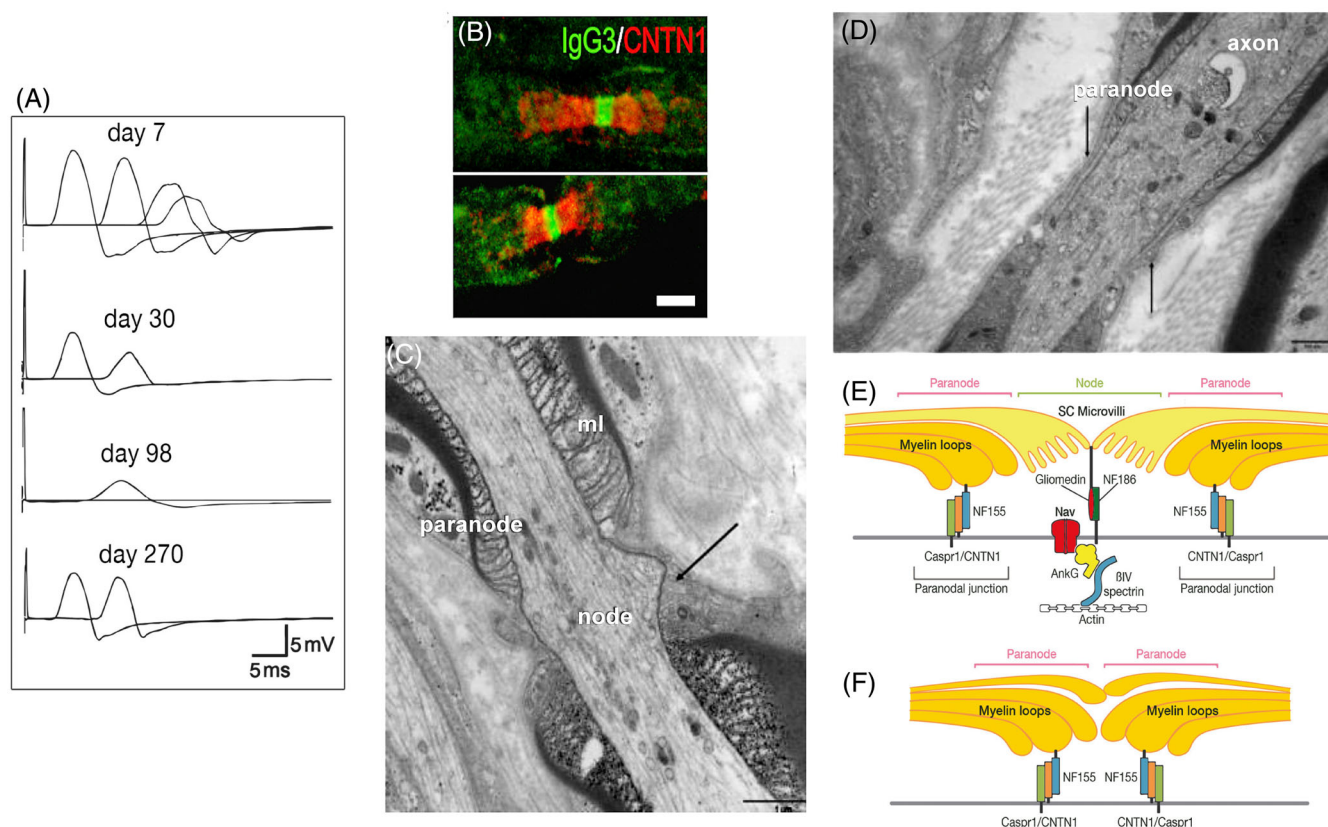


FIGURE 16 Electrophysiologic and immunopathologic correlates in neuropathy with anti-neurofascin (NF) 186 antibodies. (A) Median nerve. Superimposed compound muscle action potentials (CMAPs) recorded from abductor pollicis brevis muscle after stimulation at wrist, elbow, axilla and Erb's point showing a partial CB progressing to a complete CB at clinical nadir (day 98). On day 270, when patient had almost completely recovered, CB was not any longer present. (B) Mouse sciatic nerve fibers stained with antibodies to Contactin1 (CNTN1) (red) and patient's IgG3 anti-NF186 (green) binding specifically to the node. Bar = 5 μm. Reproduced with permission from Vallat et al.¹²¹ (C) Electron microscopy, longitudinal sections, sural nerve biopsy, normal control. At NR, presence of microvilli (arrow): myelin loops (ml) characterize the paranode. Bar = 1 μm. (D) Sural nerve of patient with anti-NF186 antibodies; longitudinal section; electron microscopy. Disappearance of microvilli; elongated extensions of Schwann cell cytoplasm occlude the nodal gap (arrows). Bar = 500 nm. (E) NF186 coordinates nodal organization by recruiting voltage-gated sodium channels (Nav) and AnkG at node NR. (F) When NF186 is deficient Schwann cell (SC) microvilli disappear, Nav and AnkG fail to assemble and paranodal junction components are dislocated into the nodal gap with decreased nodal length till to complete occlusion by extensions of Schwann cell cytoplasm. Reproduced with permission from Uncini.²⁵

at the NR.¹²⁵ Energy depletion and mitochondria are involved in number of conditions such as ischemia, trauma, inflammation and metabolic mismatch leading to axonal degeneration.¹²⁶ These disorders can be categorized as neuropathies due to energy restriction and, in some of these, a transitory, potentially reversible, conduction failure has been documented, at least in early stages.¹²⁷

Peripheral neuropathy is often encountered in patients with vasculitis and it is classified as axonal. Early nerve conduction may show an amplitude reduction of CMAP from stimulation sites proximal to the site of nerve ischemia that, at follow up, leaves the place to a reduction in amplitude or disappearance of both proximal and distal CMAPs (Figure 17A,B). Pathology shows inflammatory destruction and fibrinoid necrosis of vessel walls with restriction or occlusion of lumen (Figure 17C). The distribution of fibers loss and Wallerian degeneration may be asymmetric between fascicles or also inside the same fascicle and edema may be present (Figure 17E,F). Primary axonal degeneration, with fiber loss and/or presence of ovoids indicate

recent ischemic damage that can evolve in complete replacement of all endoneurial structure by fibrotic tissue (Figure 17D). The transient proximal CMAP amplitude reduction in vasculitic neuropathy has been called "pseudo-CB" and explained by the fact that the axons, distally to the site of ischemia, are still able to conduct for a few days till they undergo to complete Wallerian degeneration.¹²⁹ However, reversible CB has been described in vasculitic and other acute ischemic neuropathies.^{130,131} Transient CB has been also reported following experimental acute occlusion of vasa nervorum and morphological examination did not reveal segmental demyelination suggesting a "metabolic" nature of CB¹³² (Figure 17G-I). In patients and the experimental model the fast resolution of CB without development of excessive TD well fit into the concept of RCF. Ischemia impairs the ATP dependent Na^+/K^+ pump which maintains the physiological electrochemical gradients and membrane resting potential. Dysfunction of Na^+/K^+ pump leads to an excess of positive charge inside the axons, sustained membrane depolarization and depolarizing conduction

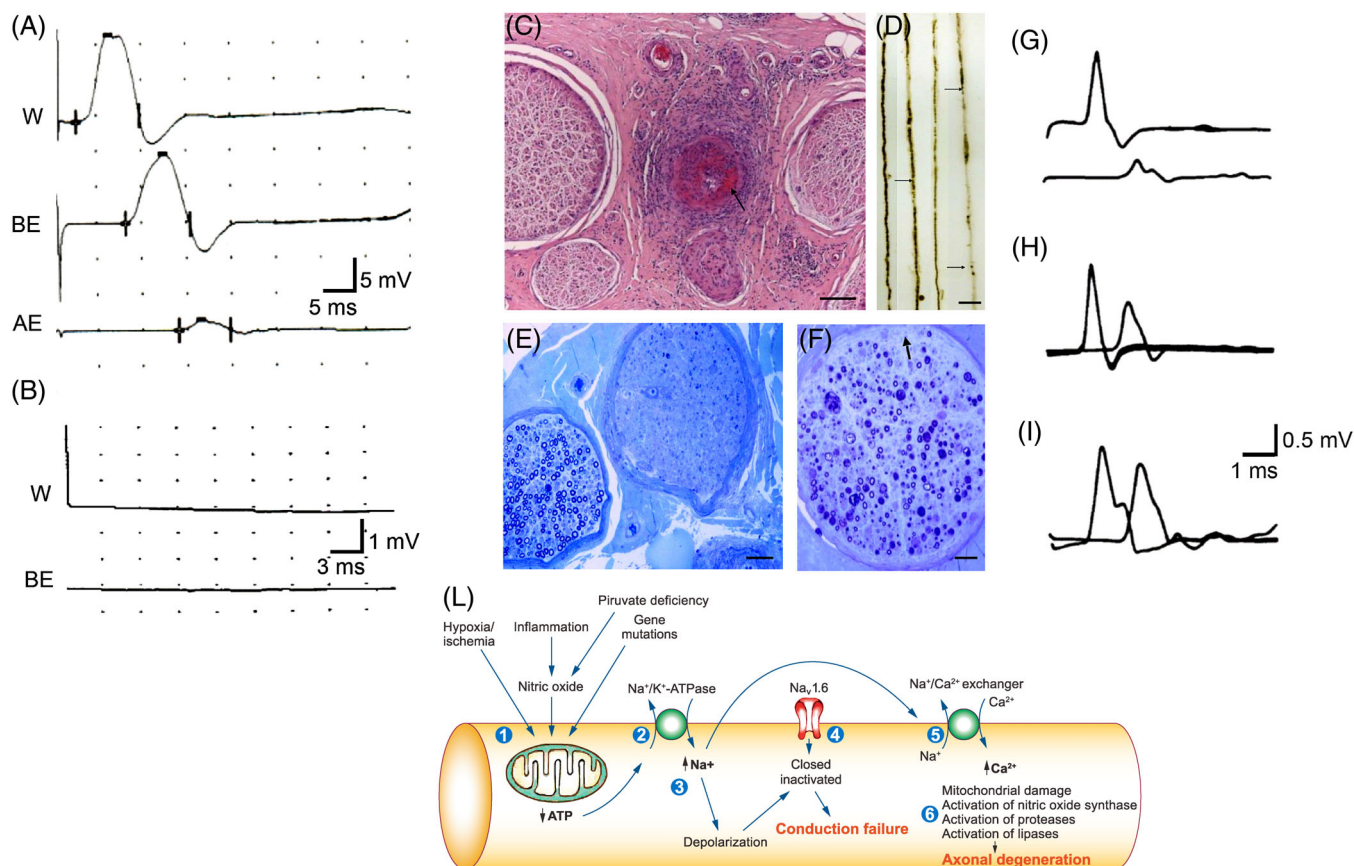


FIGURE 17 Electrophysiologic and pathologic correlates in vasculitic neuropathy. (A) Ulnar nerve of a 52-year-old woman who developed acute weakness of intrinsic hand muscles. Three days after onset there is a 62% reduction of CMAP area from above elbow (AE) compared with below elbow (BE) stimulation. (B) A control after 2 weeks showed no recordable CMAPs indicative of axonal degeneration of all nerve fibers. (C–F) Sural nerve biopsies showing elementary lesions associated with nerve vasculitis. (C) Paraffin section demonstrating the necrotizing vasculitis of an epineurial arteriole with fibrinoid degeneration (arrow) and almost complete occlusion of the vessel, extensive perivascular inflammation is also evident, (bar = 50 μ m). (D) Teased fibers showing nerve fibers at different stages of Wallerian degeneration characterized by fragmentation of the myelin sheath into typical ovoids (arrows), (bar = 100 μ m). (E) Semithin section showing asymmetric loss of nerve fibers between fascicles (interfascicle) and inside the same fascicle (intrafascicle), bar = 25 μ m. (F) Semithin section demonstrating myelinated fibers with axonal degeneration, note the endoneurial and subperineurial edema (arrow), bar = 25 μ m. (G–I) Experimental acute occlusion of rat vasa nervorum by injecting arachidonic acid into the femoral artery. Tibial motor nerve conduction studies, CMAP evoked by proximal and distal stimulation were recorded 1 (G), 3 (H) and 7 (I) days after nerve infarction. At day 1 the proximal CMAP amplitude is 77% reduced compared with distal CMAP, at day 2 is 53% and at day 7 is 24% reduced (near normal) without the development of TD. These findings indicate a reversible conduction failure. Reproduced with permission from Parry and Lynn.¹²⁸ (L) Schematic representation of the possible events leading to conduction failure and axonal degeneration in energy restriction neuropathies. A number of factors (ischemia, pyruvate deficiency, nitric oxide produced in inflammation, mutations of genes involved in mitochondrial respiratory chain), can induce depletion of ATP at the nodal region (1) with reduction of the Na^+ , K^+ -ATPase pump function (2), that cannot maintain the transmembrane Na^+ gradient and leading through leaky Na^+ channels, to an excess of Na^+ ions inside the axons (3), this induces a sustained membrane depolarization and depolarizing conduction failure due to the inactivation of Nav channels that remain in the closed inactivated state (4). The excess of intra-axonal Na^+ drives the Na^+ / Ca^{2+} exchanger to operate in a calcium-importing mode (5). Ca^{2+} increase further aggravates energy failure by damaging mitochondria, activating nitric oxide synthase, proteases and lipases, to finally induce axonal degeneration. Reproduced with permission from Uncini and Santoro.¹²⁷

failure due to the inactivation of Nav channels that remain in the closed and refractory state.¹³³ Depolarizing conduction failure may resolve with vessel recanalization,¹³⁴ but if Na^+ axoplasmic content is excessive the Na^+ / Ca^{2+} exchanger reverts its activity expelling Na^+ and increasing Ca^{2+} inside the axon that triggers axonal degeneration. Therefore, acute ischemic neuropathy has the characteristic of an axonopathy due to energy restriction. It is probably more correct to define the early reduction of proximal CMAP amplitude in ischemic

neuropathies as a conduction failure that rarely is reversible and more frequently progresses to axonal degeneration.

Another example of neuropathy due to energy restriction is beriberi neuropathy due to thiamine deficiency that, in resource-rich countries, develops in chronic alcohol abusers, recurrent vomiting, long-term total parenteral nutrition and bariatric surgery. Beriberi neuropathy is classified as axonal on pathological basis.¹³⁵ However, in three patients with Wernicke–Korsakoff, encephalopathy and

polyneuropathy distal CMAP amplitudes were reduced, and SNAPs were not recordable or reduced in amplitude without conduction slowing at first recording.¹³⁶ Thiamine infusion induced in 2–4 weeks, 214%–281% increase of CMAP amplitudes. SNAP amplitudes also increased by 350%–387% and previously not recordable sural nerves SAP normalized. Sural nerve biopsy showed only mild axonal degeneration. Thiamine has a crucial role in the tricarboxylic acid cycle and its deficiency decreases pyruvate dehydrogenase activity and ATP production that, with a cascade of events similar to ischemic neuropathy and through reduction the Na^+/K^+ pump activity, may induce membrane depolarization and conduction failure.

One more example of axonal energy restriction neuropathy may be critical illness polyneuropathy that can present with RCF possible due soluble factors released during sepsis, as nitric oxide, that inhibits the activity of the mitochondrial respiratory chain inducing malfunction of the Na^+/K^+ pump.¹²⁷

Energy restriction neuropathies, whatsoever the primary cause, can induce a depolarizing conduction failure due to dysfunction of the ATP dependent Na^+/K^+ pump that may be transient and even completely reversible or progresses to axonal degeneration through alteration of intra-axonal calcium homeostasis (Figure 17L). The occurrence in antibody mediated and energy restriction axonal neuropathies of RCF indicates a potential therapeutic temporal window (although limited) in which appropriate treatments might halt the progression to axonal degeneration.

5 | CONCLUSIONS

The aim of this review was, with a translational approach, to bridge the gap between clinical electrophysiologists and pathologists in the effort to reach a common ground to explain CV slowing, CB and abnormal TD in acquired and inherited peripheral neuropathies. Following are the main remarks.

- Non-uniform conduction slowing, CB and abnormal TD are characteristic, although not exclusive, features of autoimmune peripheral neuropathies. These features are correlated with segmental demyelination in AIDP/CIDP, dismantling of paranodal architecture in neuropathies with IgG4 antibodies to paranodal junction components, and possibly with a length dependent disturbance of myelin-axon interaction in anti-MAG neuropathy.
- In inherited dysmyelinating neuropathies, independently of the gene involved, uniform conduction slowing is mainly ascribable to a SC developmental defect of internode elongation, resulting in saltatory conduction at shorter intervals, and nodal widening that dilutes the driving current and increases the time to reach the threshold for generating the AP. In congenital hypo-amyelinating neuropathies the very thin myelin thickness may explain the severely reduced CV.
- In inherited dysmyelinating neuropathies non-uniform conduction slowing, CB and abnormal TD are associated with and possibly due to pathological changes focused at the paranode such as:

paranodal tomacula with axonal constrictions, paranodal myelin thickenings with infolding, abnormal formation and function of paranodal and tight/adherence junctions and, more rarely, segmental de-remyelination. Caveat: patients with inherited neuropathies and non-uniform electrophysiology are often initially misdiagnosed as CIDP but a lack of response to treatment should prompt to reconsider the diagnosis. On the other side, in patients showing a rapid clinical decline or a stepwise progression a coexisting inflammatory process should be suspected.

- hATTR neuropathy is considered a length-dependent axonal sensory-motor neuropathy but at late stages can present with conduction abnormalities fulfilling the electrodiagnostic criteria for demyelinating polyneuropathies and CIDP is the most frequent misdiagnosis leading to an incorrect treatment.
- Some autoimmune neuropathies classified as axonal can present with RCF and CV slowing, even in the demyelinating range, due to paranodal myelin detachment and/or nodal Nav channels disruption. These features should be taken into account to avoid misdiagnoses and for correct prognostication.
- Axonal neuropathies due to energy restriction can show, at early stages, conduction failure due to dysfunction of the ATP dependent Na^+/K^+ pump that may be transient and even completely reversible or, more frequently, progresses to axonal degeneration through alteration of intra-axonal calcium homeostasis.

AUTHOR CONTRIBUTIONS

AU conceived the review and wrote the first draft; TC, GMF, FM, and JMV contributed with electrophysiologic and pathologic observations and reviewed all the versions of the paper.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data will be available on request.

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How to cite this article: Uncini A, Cavallaro T, Fabrizi GM, Manganelli F, Vallat J-M. Conduction slowing, conduction block and temporal dispersion in demyelinating, dysmyelinating and axonal neuropathies: Electrophysiology meets pathology. *J Peripher Nerv Syst*. 2024;29(2):135-160. doi:[10.1111/jns.12625](https://doi.org/10.1111/jns.12625)