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# Hereditary Motor and Sensory Neuropathies (HMSNs) With Conduction Block

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The objectives of this activity are to: Recognize clinical and electrodiagnostic features of HMSNs with non-uniform slowing. Learn the pathophysiology underlying conduction block and temporal dispersion. The AANEM is accredited by the American Council for Continuing Medical Education (ACCME) to provide continuing education for physicians. AANEM designates this Journal-based CME activity for a maximum of *1.0 AMA PRA Category 1 Credit*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Keywords:** CMT | conduction block | hereditary motor and sensory neuropathy | HMSN | temporal dispersion

## ABSTRACT

Dysmyelinating forms of hereditary motor and sensory neuropathy (HMSN) typically exhibit uniform conduction slowing on electrophysiological studies. However, this has been challenged in the past few decades with the discovery of novel gene mutations that induce nonuniform conduction slowing resembling acquired demyelinating neuropathies. Conduction block (CB) and/or excessive temporal dispersion (TD) are characteristic of segmental changes. Nevertheless, there is no consistent definition for CB and TD in inherited neuropathies. Pathological changes at paranodal regions or segmental demyelination might be explanatory in some patients.

## 1 | Introduction

Hereditary motor and sensory neuropathies (HMSN) or Charcot Marie Tooth (CMT) are the most common forms of inherited neuropathies with variable prevalence rates in different countries ranging from 9.7 to 82.3/100,000 [1]. HMSN is characterized by symmetrical distal muscle weakness and atrophy, sensory loss, and absent tendon reflexes. The first modern electrophysiologic classification of HMSN was proposed by Dyck and Lambert in 1968 [2]. Traditionally, it has been classified on the basis of histopathology and nerve conduction studies (NCS) into demyelinating (or dysmyelinating, type 1) and axonal (type 2) subtypes [2, 3]. Electrophysiological studies of patients with HMSN type 1 typically demonstrate uniformly slow conduction velocities [4–6]. The term "uniform conduction slowing" refers to disorders in which the physiological changes suggest that all myelinated nerve fibers are affected along the entire length of the nerve [7].

The concept of uniform conduction slowing was generalized to all inherited dysmyelinating neuropathies [8]. Nevertheless, it has become evident that the electrophysiologic aspects of these diseases are more complex than previously recognized. Novel pathogenic variants have been discovered causing non-uniform slowing of conduction velocities (CV) similar to acquired demyelinating neuropathies. Indeed, electrodiagnostic features of

**Abbreviations:** AAV, Adeno-associated virus; CB, Conduction block; CMAP, compound motor action potential; CMT, Charcot Marie Tooth; CV, conduction velocity; Cx32, connexin 32; GJB1, gap junction protein beta-1; HMSN, Hereditary motor and sensory neuropathy; HNPP, Hereditary neuropathy with liability to pressure palsies; LITAF, lipopolysaccharide-induced tumor necrosis factor-a factor; MPZ, myelin protein zero; SIMPLE, small integral membrane protein of the lysosome/late endosome; TD, temporal dispersion; TLI, terminal latency index.

non-uniform slowing such as abnormal conduction block (CB) and/or excessive temporal dispersion (TD) have been observed in some patients with dysmyelinating HMSN and other types of inherited neuropathies (Table 1) [5, 17–27]. Nevertheless, there are no definite criteria for CB and TD in inherited neuropathies. Pathologically, paranodal alterations or segmental demyelination might well explain non-uniform slowing in most of these disorders [20, 22, 28–39]. Hence, these patients might be diagnosed initially as inflammatory demyelinating neuropathy and might receive unnecessary immunotherapies [27, 40, 41]. To date, there is no FDA curative treatment for these neuropathies.

This monograph reviews clinical presentations of HMSNs that are characterized by non-uniform slowing, as well as their electrophysiological and pathological features.

## 2 | HMSNs With CB

Figure 1 outlines the suggested approach to patients with HMSNs and CB.

### 2.1 | Hereditary Neuropathy With Liability to Pressure Palsies (HNPP)

#### 2.1.1 | Phenotype

HNPP is a rare autosomal-dominant disorder caused in most patients by the deletion of chromosome 17p11.2 containing the *PMP22* gene resulting in a reduced expression of the PMP22 protein in the myelin sheath [42–46]. HNPP may be frequently

**TABLE 1** | Other inherited conditions associated with non-uniform slowing of peripheral nerve conduction velocity.

| Conditions | Inheritance | Gene | Phenotype |
|---|---|---|---|
| Adrenomyeloneuropathy [7, 9] | XL | *ABCD1* | Progressive spastic paraparesis + mixed axonal and demyelinating S, M and autonomic PN. |
| Pelizeus–Merzbacher disease [10] | XL | *PLP* null mutation | CNS demyelination ± demyelinating PN. |
| Refsum's disease [7] | AR | *PHYH* | Cerebellar ataxia, demyelinating S & M PN, retinitis pigmentosa, deafness, cardiac arrhythmias and CM. |
| MNGIE [11–13] | AR | *TYMP* | GI dysmotility, weight loss, ophthalmoparesis, ptosis, myopathy, asymptomatic CNS white matter abnormalities, and S & M PN (mostly axonal) |
| hATTR [14–16] | AD | *TTR* | Heart involvement and rapid progressive disabling S, M and autonomic PN (typically axonal) |

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CM, cardiomyopathy; CNS, central nervous system; GI, gastrointestinal; hATTR, hereditary transthyretin amyloidosis; M, motor; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; PN, peripheral neuropathy; S, sensory; TYMP, thymidine phosphorylase; XL, X linked.

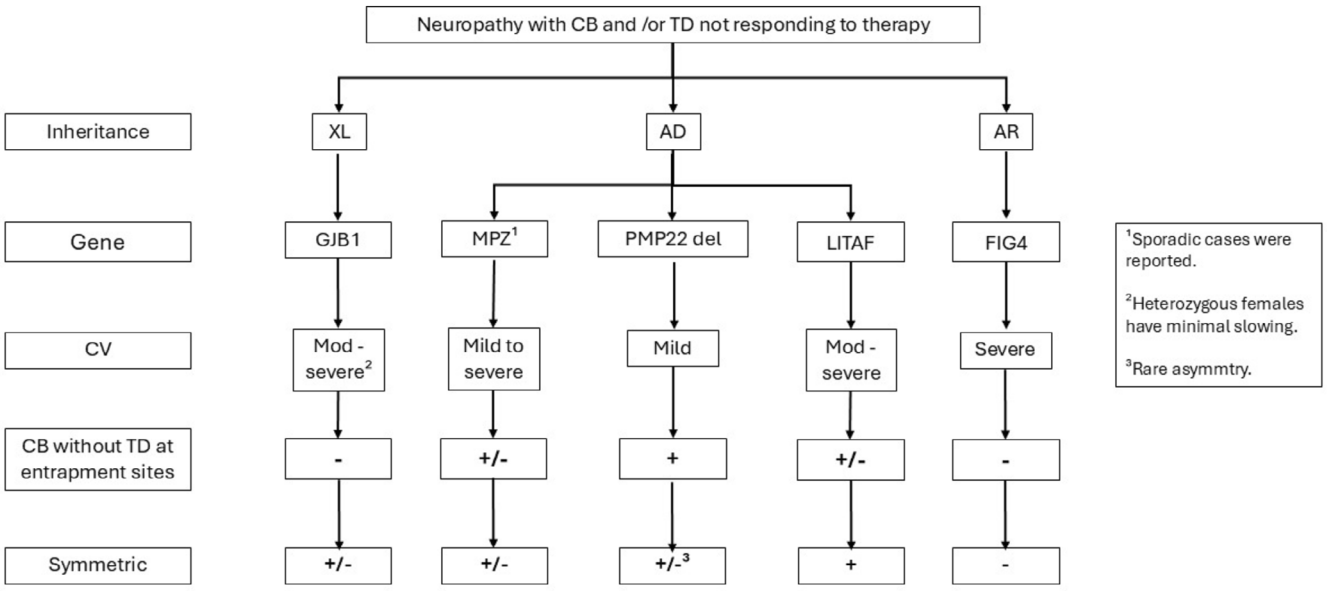


**FIGURE 1** | Proposed algorithm for the diagnosis of HMSNs with CB. AD, autosomal dominant; AR, autosomal recessive, CB, Conduction block; CV, conduction velocity; del, deletion; GJB1, gap junction protein beta-1; HMSN, Hereditary motor and sensory neuropathy; HNPP, Hereditary neuropathy with liability to pressure palsies; LITAF, lipopolysaccharide-induced tumor necrosis factor-a factor; MPZ, myelin protein zero; TD, temporal dispersion; XL, x-linked.

underdiagnosed or misdiagnosed because of the heterogeneity of clinical and electrophysiological features [47]. It typically manifests with acute, recurrent, painless nerve palsies associated with nerve stretching or compression; however, some patients present with a chronic sensory or CMT-like polyneuropathy [43, 44, 46, 48]. Isolated muscle cramping and toe walking are atypical presentations in childhood [49].

#### 2.1.2 | Electrophysiology

CB at compression sites is the electrophysiologic hallmark of HNPP. CB occurs in nerves at compression sites, most often the ulnar nerve at the elbow, median nerve at the wrist, and peroneal nerve at the fibular head [36, 46, 48–52]. CB in HNPP is usually not accompanied by abnormal TD, and it may be persistent, even for years, and regress rapidly after neurolysis or nerve transposition [36, 48, 52]. NCSs are characterized by focal motor CV slowing at nerve compression sites. CVs outside compression sites are only slightly affected. Polyneuropathy independent of superimposed compressive neuropathy is frequently observed. Diffuse sensory nerve CV slowing and prolongation of distal motor latencies might be observed [36, 46, 48–52].

Sonographic studies have demonstrated nerve enlargements at compression sites, but no abnormalities at distal nerve segments where compression is uncommon despite the fact that the distal motor latencies were increased [53]. This would suggest that factors other than mechanical compression might be responsible for the distal slowing [53].

### 2.2 | CMT1X—*GJB1*

#### 2.2.1 | Phenotype

CMT1X is the second most common form of CMT1 [54–58]. The reports of X-linked CMT date back to 1888 [59]. CMT1X is caused by mutations in the gap junction protein beta-1 (*GJB1*) gene on chromosome Xq13.1 that encodes connexin 32 (Cx32) gap junction proteins [58, 60]. Both loss-of-function and gain-of-function mutations have been reported for *GJB1*; to date, over 400 different *GJB1* mutations associated with CMT1X disease have been identified [25, 56, 58, 61–71].

Disease onset is in childhood, adolescence, or adulthood, with gait unsteadiness and frequent falls or sprained ankles [65, 66, 72, 73]. Males have earlier and more severe manifestations than females, with age-dependent progression of clinical signs [20, 40, 65, 73, 74]. Progression is typically slow [65]. Older male patients display symmetric or asymmetric weakness and atrophy of the intrinsic hand muscles (particularly in thenar muscles), leg muscle atrophy (gastrocnemius and soleus muscles), foot drop, pes cavus, areflexia of the lower limbs, and distal sensory loss; Romberg sign is positive and gait is wide-based [20, 65, 75].

Heterozygous females are asymptomatic or minimally symptomatic later in life; neurological examination may reveal symmetric or asymmetric motor deficits, sensory involvement, decreased ability to walk on their heels, pes cavus, and absent reflexes [20, 40, 65, 66, 75]. Severe forms of neuropathy with an early or late onset may occur in some affected women; [40, 67, 68, 76–78] this could be explained by either random X-chromosome inactivation, [79] or due to unusual gain-of-function mechanisms of certain mutants [77]. In a recent study, Barbat et al. observed that women who had a missense variant in the lipid bilayer domain might present with a more severe clinical presentation and earlier onset of disease compared to those with variants located in the intra- and extracellular domains [40].

Connexin 32 is also expressed in the central nervous system (CNS), and some patients had mild hearing loss, tremors, and extensor plantar response [54, 65, 66, 80]. Three women with the stroke- like syndrome were reported with recurrent short-lasting (10–60 min) symptoms of hemiparesis with or without dysarthria for 20 min and flaccid tetraparesis. Brain MRI findings in some patients with CMT1X showed diffuse white matter hyperintensity [40, 65].

In a patient with CMT1X and non-uniform conduction slowing, the cerebrospinal fluid (CSF) was acellular, with a raised protein of 78 mg/dL, which led to the initial diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), but the patient did not respond to treatment [27].

#### 2.2.2 | Electrophysiology

CMT1X manifests a wide range of CV changes in the demyelinating, intermediate, or axonal range. Typically, the majority of CMT1X males have intermediate slowing of CV (between 25 and 45 m/s) [65, 66, 72–74, 81–87]. However, heterogeneity has been noted in the electrophysiological studies of CMT1X; in the same individual there is a wide range of CVs between nerves, and the degree of CV slowing varies by age and with disease severity [20, 25, 75]. Slower CV (as slow as 13 m/s) was observed in some male patients [20, 25, 75]. Heterozygous females might exhibit a normal or a lesser degree of conduction slowing than males [20, 25, 40, 66, 73, 75, 80, 83–85, 88]. Some studies have reported nonuniform conduction slowing with CB and excessive TD that led to an initial diagnosis of CIDP [5, 20, 27, 33, 40, 75].

In CMT1X there is also electrophysiologic evidence of length-dependent sensorimotor axonal loss that progresses with age [65, 66, 73, 74, 83, 85, 87]. In a study, most women (42/65, 64.6%) were found to have axonal neuropathy [40]. This might explain why some female patients classified as CMT-2 may have CMT1X.

Brainstem auditory evoked potentials have demonstrated prolonged central conduction times in males with CMT1X. Wave 1 was normal, but all central latencies were significantly slow. Females also showed statistically significant central latency prolongation but not as severely or as consistently as did males [54, 66, 80].

## 2.3 | CMT1B—*MPZ*

### 2.3.1 | Phenotype

The myelin protein zero gene (*MPZ*), located on chromosome 1q22–q23, encodes P0, the major myelin structure protein in the peripheral nervous system [89]. Mutations in *MPZ* account for a wide phenotypic spectrum of inherited peripheral neuropathies. Most *MPZ* mutations lead to the dominantly inherited HMSN1B phenotype, with some reports of Dejerine-Sottas, congenital hypomyelination [24, 25, 70, 89–100]. *MPZ* mutations have also been found in patients with axonal HMSN type 2 [100, 101].

Onset is in childhood or adulthood with possible age-dependent variability of clinical features [25, 26, 34, 35, 100, 102, 103]. Early onset with delayed walking and subsequent toe walking was described [24]. Patients present with mild–moderate neuropathy, symmetric or asymmetric [25, 26, 35]. Examination shows bilateral distal weakness and muscle atrophy of the upper and lower limbs, areflexia, and sensory loss in the feet to pain, vibration, position, and light touch [24–26, 100, 102]. Distal weakness may be disabling and may require an ankle foot orthosis [25, 102]. Mild to moderate weakness of the quadriceps muscles was also noted [25]. Pes cavus, pupillary abnormalities, nystagmus, scoliosis, and impaired hearing may be present [24, 26, 100, 103]. Marchini et al. [103] described two sisters with p.Val102fs mutation presenting with symptoms of spinal root hypertrophy and demyelinating neuropathy with CB and abnormal TD. They noted neck pain and had only pes cavus or diminished reflexes on examination without overt peroneal muscular atrophy [103].

### 2.3.2 | Electrophysiology

Electrophysiological studies are consistent with a demyelinating sensorimotor polyneuropathy, with mild, moderate, or severe conduction slowing [24–26, 34, 35, 100, 102, 103]. CB has been reported in a few published patients, [24–26, 34, 35, 102, 103] and it may occur at compression sites [34, 35].

The presence of CB does not correlate with severity. In a family reported by Donaghy et al. [102] the proband who had CB of 56% in the median nerve presented with progressive disabling weakness, positive sensory symptoms, areflexia, raised CFS protein (72 mg/dL) without pleocytosis. He was diagnosed with CIDP and initially responded to steroid treatment, but then he deteriorated. Other family members had uniform borderline to moderate conduction slowing without CB and they had symptoms varying from disabling weakness to occasional positive sensory symptoms. A milder phenotype characterized by recurrent mononeuropathies at compression sites (with CB mimicking HNPP) in association with a p.Tyr145 stop mutation has been reported [35].

## 2.4 | CMT1C—*LITAF* (Simple)

### 2.4.1 | Phenotype

The *SIMPLE* gene encodes a small integral membrane protein of the lysosome/late endosome (SIMPLE), which was identified in 2003 [104]. The protein was first referred to as lipopolysaccharide-induced tumor necrosis factor-α factor (LITAF), and then re-defined as the SIMPLE protein encoded by *SIMPLE* located in chromosome 16p12–13.3 [105, 106]. Mutations in *LITAF*/*SIMPLE* were reported to cause CMT1C with an autosomal dominant inheritance pattern [31, 56, 107, 108].

CMT1C clinically resembles a mild form of CMT1A [109]. The age of onset is highly variable (childhood to late adulthood) [31, 41, 107, 108]. It usually presents with toe walking, foot pain and paresthesias, and slowly progressive gait ataxia [31, 107, 109]. Neurological examination shows foot deformities (such as pes excavates and pes cavus), normal strength, normal reflexes, decreased sensations in the lower limbs with a proximal to distal gradient, and positive Romberg's sign [31, 41, 107, 109]. Weakness and areflexia occur less frequently than in CMT1A [31, 109]. Weakness, if present, is typically distal in the hands and feet and is associated with atrophy; [31, 108, 109] however, distal and proximal weakness and atrophy of the upper and lower limbs were reported [31, 41]. The hands may not be affected [107, 108]. Cramps and pain in the legs or feet are common [109]. An atypical presentation was reported of progressive weakness and paresthesias of a single upper limb resembling acquired inflammatory neuropathy. CSF showed an elevated protein level of 54 mg/dL with no pleocytosis, and electrophysiological studies showed non-uniform conduction slowing. Significant progression of polyneuropathy within 4 years despite intensive immunotherapy, and confirmatory genetic tests finally led to the diagnosis of CMT1C [41].

### 2.4.2 | Electrophysiology

Electrophysiological studies are consistent with a demyelinating sensorimotor polyneuropathy (prolonged distal motor latencies, slow CVs, absent sural responses, and prolonged F-latencies), predominantly affecting the legs [31, 107, 109]. CVs are below 30 m/s or in the intermediate range (30–38 m/s) [56, 107–109]. Upper limb CVs are usually higher than those in the lower limbs, some even greater than 40 m/s [107, 108]. CB and TD were observed in some patients [31, 41, 104, 107, 108]. CB may occur at compression sites [107]. Tibial somatosensory evoked potentials showed increased latencies of the P40 cortical component on both sides [107].

## 2.5 | CMT4J—*FIG4*

### 2.5.1 | Phenotype

CMT4J is a very rare form of demyelinating HMSN [22, 29, 110, 111]. It was first described in 2007 when Chow et al. reported that loss-of-function mutations in the lipid phosphatase *FIG4* cause a severe recessive form of CMT4J [110].

CMT4J manifests with a variable age of onset from early childhood to the sixth decade [21, 22, 29, 110, 111]. It is characterized by progressive asymmetrical distal and proximal upper and lower limb weakness and atrophy, absent reflexes, and mild or absent sensations; patients have severe disability that may result in an early loss of ambulation [22, 29, 110]. Some patients may have rapid deterioration of strength in one limb [21, 22, 111]. Initial misdiagnosis as CIDP is common [21, 111]. Cranial nerve involvement affecting right eye abduction and the tongue has

been reported [111]. A motor developmental delay consistent with Dejerine–Sottas neuropathy was described [21, 110]. CNS symptoms are uncommon [22].

#### 2.5.2 | Electrophysiology

Patients typically exhibit severe primary demyelinating sensorimotor neuropathy, that could be asymmetric, with very slow motor CVs (as slow as 2 m/s) [21, 22, 110]. One patient had a residual sural sensory nerve action potential and an intermediate median motor CV of 41 and 37 m/s [111]. In several patients, CV and amplitude were both affected, and needle EMG findings in distal and proximal muscles were consistent with active or chronic denervation [21, 22, 29, 110, 111]. Non-uniform slowing with CB and excessive TD was noted in 10 patients [21, 22].

## 3 | Electrophysiological Aspects

### 3.1 | Conduction Block and Temporal Dispersion

In most HNPP series, CB defined as amplitude and/or area reduction of > 50% was uncommon, [46, 48, 52] being reported in 6%–22% of nerves [7, 52]. In HMSN1 with non-uniform slowing (other than HNPP), a CB of ≥ 50% reduction in amplitude and/or ≥ 30% reduction in the area under the CMAP in one or more motor nerves has been observed in most patients [20–22, 24, 25, 31, 34, 40, 102, 107, 108]. A CB of 30%–50%, [31, 40] and < 30% [40, 41] were also noted in some patients with CMT1C and CMT1X.

Although CB and excessive TD are included in the electrodiagnostic criteria for CIDP, [112] they are not well characterized in inherited demyelinating neuropathies, and different criteria have been used across different reports even in the same condition [36, 52]. Abnormal TD was defined as an increase in CMAP duration of > 40%, [20] > 15% in the median and ulnar nerves or > 30% in the tibial nerve, [75] or ≥ 30% [22] between proximal and distal CMAPs. Similarly, CB was defined as a reduction of ≥ 30% in the area under the CMAP curve or a reduction of ≥ 30% in CMAP amplitude as long as there was no significant increase in the duration of the response, [24] a > 50% drop in CMAP amplitude with a < 15% prolongation of CMAP duration, [25] or a 50% reduction of CMAP amplitude evoked by proximal stimulation [22].

The lack of a consistent definition may lead to over or under-calling a non-uniform slowing. Indeed, it was observed that when a lower cutoff is applied, CB was considered more common. Magistris and Roth noted 29 focal blocks in 12 patients, 11 with amplitude reductions of over 70%, and 10 of 40%–70% [36]. Uncini et al. compared the incidence of CB in HNPP and CMT1A using two different criteria of block, one with a 20% decrease in amplitude and area and the other with a 50% decrease. Using the less stringent criterion, there was a 21% incidence of CB in the CMT1A patients and 25% in the HNPP. With the more stringent criterion of a 50% drop, none of the CMT-1A patients and only 6% of the HNPP patients had CB [52]. Likewise, in a CMT1X study, Barbat et al. found that 43.9% of females and 42.2% of males had CB ≥ 30% and/or TD and 27.3% of females and 18.8% of males had CB between 30% and 50%, while only 12.1% of females and 9.4% of males had CB ≥ 50% [40].

### 3.2 | Terminal Latency Index

Non-uniform slowing is also demonstrated by a high terminal latency index (TLI). TLI is an electrophysiological parameter that provides a relative comparison of conduction between distal and proximal segments of motor nerves [20]. It is calculated as distal nerve conduction distance (mm)/(proximal motor CV [m/s] × distal motor latency [ms]) [113, 114]. Low TLI reflects disproportionate distal conduction slowing, [114, 115] while high TLI suggests differential slowing in the proximal segment of a nerve relative to the distal segment [20]. CMT1A patients typically display a mean TLI value of 0.42 ± 0.14 in the median, ulnar, and peroneal nerves, which is similar to normal [116]. In their cohort of five individuals in a family with CMT1X, Gutierrez et al. demonstrated that the TLI in the median and ulnar nerves of the most severely affected male patient had a value similar to that seen in CMT1A (0.46 and 0.50, respectively), but the TLI of the tibial motor response (0.63) was outside the value found in other CMT1A patients. The TLI in other patients was found to reflect a wide range of values (0.36–0.79) [20].

### 3.3 | Conduction Slowing

Electrodiagnostic studies in disorders with uniform conduction slowing exhibit similar velocity changes when different nerves are compared and when different segments of nerves are compared [7]. However, the maximal CV difference among nerves to label conduction slowing as uniform has not been clearly defined [4, 7]. A 10 m/s difference in conduction velocity across nerve segments was considered indicative of non-uniform slowing in two sisters with an MPZ mutation [103].

## 4 | Pathological Correlation

Tomacula formation is the pathological hallmark of HNPP. CB may be related to the localized focal thickening of the myelin sheath (tomacula) more frequently at paranodes that may be associated with a constricted axon, rare demyelinating and remyelinating fibers, and no or few onion bulbs (OBs) made of one or two layers of flattened Schwann cell processes [36–39, 48]. It can be hypothesized that paranodal tomacula in combination with nerve stretching or compression may lead to more easily induced mechanical deformation of the paranodes, as in compressive neuropathy models resulting in CB [52, 117]. Tomacula also causes focal constriction in the axon that extends beyond the paranodal regions, as observed in the *PMP22*+/mice [118]. This constriction raises the axial resistance to the action potential propagation and might cause CB when the nerve is compressed. In addition to tomacula, increased permeability of myelin in PMP22+/mice was also hypothesized to shunt current out of nerve fibers reducing the safety factor for action potential propagation and causing CB in HNPP [119].

In analogy to HNPP, segmental conduction abnormalities in some *MPZ* mutations can be explained by excessive myelin

irregularity and thickening (resembling a small tomacula) at the paranodal region in concurrence with compression at entrapment sites [34, 35]. Additionally, infolded myelin loops at paranodes in *MPZ* and *SIMPLE* mutant mice causing compression of the axon and widened nodal gaps were hypothesized to be responsible for the segmental nerve conduction abnormalities in CMT1B and CMT1C, respectively [120, 121].

In CMT1X, clustering of abnormal Schwann cells lacking Cx32 at the paranodes in some females with CMT1X causing functional alteration was suggested as the cause of abnormal CB and excessive TD; however, males with the same functional abnormality exhibit less frequently non-uniform conduction slowing features [32, 122]. Another possible explanation for non-uniform conduction in CMT1X is the increased number of thinly myelinated regenerating fibers which might lead to desynchronization of CVs [20, 30–33].

Rarely observed segmental demyelination in CMT4J and CMT1X might explain the non-uniform conduction features [22, 28–30]. An operational definition for segmental demyelination, based solely on teased fiber preparation (Figure 2), has been proposed by Dyck et al. [123]. In internodal demyelination no myelin should be recognized along the entire internode whereas in paranodal demyelination the nodal gap is increased. Nevertheless, nodal widening, without other features of segmental de-remyelination, is found in some dysmyelinating inherited neuropathies with uniform slowing such as HMSN1A because of developmental dysfunction of Schwann cells and impaired Schwann cell-axon interactions [74, 124, 125]. Moreover, in some patients with *GJB1* mutations, paranodal instability with widened nodes of Ranvier was observed in association with uniform conduction slowing [74, 125]. Therefore, misinterpreting nodal widening as evidence of segmental demyelination may be confusing.

## 5 | Summary and Recommendations

HMSNs with CB are very rare inherited neuropathies which usually pose a diagnostic challenge, especially in the absence of a family history. Recognizing the pattern of symptoms and how they progress over time should improve diagnostic accuracy and

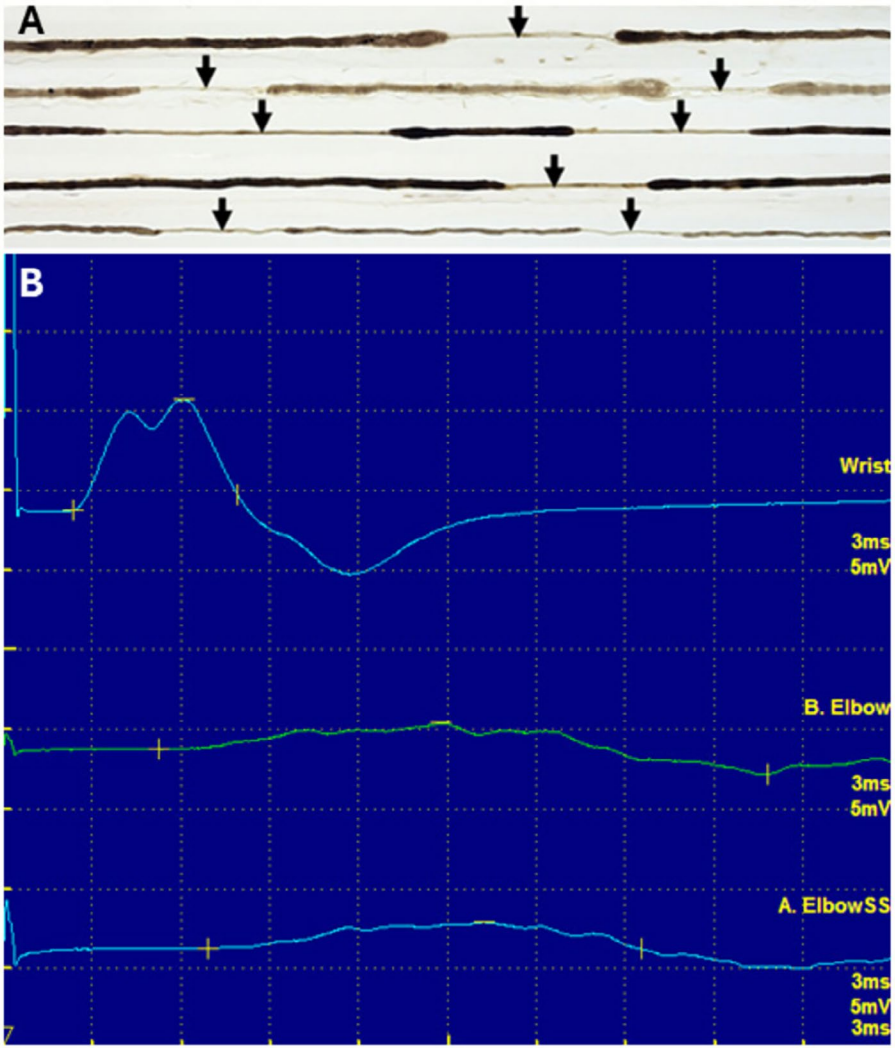


**FIGURE 2** | Segmental demyelination and conduction block in two unrelated patients. (A) Closely aligned teased nerve fibers stained with osmium tetroxide showing segmental demyelination (arrows). (B) CB and TD in the ulnar nerve between wrist (top blue line) and below elbow segments (green line). A. elbow, above elbow; B. elbow, below elbow; CB, conduction block; TD, temporal dispersion.

prevent the utilization of unnecessary, sometimes harmful immunotherapies. A lack of response to immunotherapy should prompt reconsideration of the diagnosis. Establishing definite criteria for CB and TD in inherited neuropathies is mandatory to avoid over or under-calling a non-uniform slowing. Although paranodal alterations and segmental demyelination might well explain non-uniform slowing in some patients, other pathophysiological mechanisms should be further elucidated. With recent advances in gene therapy and drug development, identifying these neuropathies becomes pivotal.

### Author Contributions

**Hebatallah R. Rashed:** Conceptualization, data curation, formal analysis, investigation, methodology, validation, writing, review and editing.

### Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

### Conflicts of Interest

The author declares no conflicts of interest.

### Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Peer Review

This paper underwent peer review by the AANEM Clinical Publications Review Committee and review by the *Muscle and Nerve* editor.

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