Journal of Neurology (2025) 272:41
https://doi.org/10.1007/s00415-024-12839-7

REVIEW

Literature review of clinical analysis of hereditary neuropathy with liability to pressure palsies

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Received: 24 October 2024 / Revised: 23 November 2024 / Accepted: 26 November 2024 / Published online: 12 December 2024

Abstract

This review summarizes the clinical and electromyography (EMG) characteristics and peripheral myelin protein 22 (*PMP22*) gene-related diseases of hereditary neuropathy with liability to pressure palsies (HNPP). Clinical, EMG, and laboratory data of patients diagnosed with HNPP at our institution from 2022 to 2023 were retrospectively reviewed. Relevant literature from January 2003 to June 2024 was retrieved from PubMed using the keywords "hereditary neuropathy with liability to pressure palsies" and "HNPP." Clinical manifestations, EMG characteristics, and gene detection results of HNPP were summarized. All patients exhibited transient neurological symptoms and tested positive for the *PMP22* deletion. EMG revealed multiple peripheral nerve abnormalities. Sixty-eight studies meeting the inclusion and exclusion criteria were included, comprising 124 HNPP cases (including six from our study), with 67 males and 57 females. The mean age of onset and diagnosis for the 124 cases were 26.5 ± 18 years and 32.7 ± 18.9 years, respectively, with a maximum onset-to-diagnosis interval of 40 years. Typical weakness and numbness in vulnerable areas were observed in 63.7% of cases, with 62% experiencing recurrent episodes. Atypical symptoms were present in 29.8%, while 6.5% were asymptomatic. Patients exhibited pain and muscular dystrophy (17.7%), pes cavus (12.1%), and a family history of HNPP (64.5%). Among symptomatic patients, triggers were traction or compression (57.8%), temperature changes (3.4%), or unclear (38.8%). Heterozygous *PMP22* deletions and other *PMP22* gene mutations were found in 77.4% and 22.6% of cases, respectively.

Keywords PMP22 · EMG · HNPP · CMT1

Introduction

Hereditary neuropathy with liability to pressure palsies (HNPP) is a rare form of autosomal dominant hereditary peripheral neuropathy. The prevalence of HNPP is approximately 16/100,000 [1]. However, because of its similarity to other types of peripheral neuropathy, the prevalence of this disease may be underestimated. Genetic screening of asymptomatic newborns predicts that the prevalence of HNPP may be as high as 58.9/100,000 [2]. It is characterized by episodic mononeuropathies at typical sites of nerve compression or minor trauma, most frequently affecting the peroneal nerve at the fibular head, ulnar nerve at the elbow, brachial plexus, radial nerve at the spiral groove, and median nerve at the wrist [3]. However, electromyography (EMG) findings are often more extensive and severe than clinical symptoms and are often underdiagnosed or misdiagnosed owing to heterogeneity in clinical and electrophysiological presentations. Most patients with HNPP have a heterozygous deletion on chromosome 17p11.2, the region that encompasses the gene for peripheral myelin protein 22 (*PMP22*) [4]. In our study, we collected data on three probands and their families diagnosed with HNPP in our department from 2022 to 2023 and combined it with the PubMed database to summarize the symptoms, signs, EMG characteristics, and genetic detection of these patients. This review aims to assist clinicians in making accurate and timely diagnoses to shorten the interval from onset to diagnosis.

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Patients

Three families exhibiting HNPP phenotypes were clinically evaluated through EMG and genetic testing. The EMG findings of these patients are summarized in Table 1, revealing that all individuals presented with a heterozygous deletion of the PMP22 gene. Proband 1 was an 11-year-old boy who presented with a mobility disorder affecting the right foot, which had persisted for seven days. This condition developed following a minor sprain of the right ankle and was characterized by weakness in dorsiflexion of the foot. The neurological examination utilized the Medical Research Council (MRC) Scale for grading muscle strength, revealing that the patient scored 1/5 for the distal right lower limb. There was an absence of both dorsiflexion of the right foot and an Achilles tendon reflex. The patient's father reported a history of transient numbness in the upper limbs, which improved spontaneously after oral administration of B vitamins, without undergoing systematic diagnosis or treatment. Nutritional support, including B group vitamins and rehabilitation training, was provided to Proband 1, resulting in a significant improvement in his symptoms. Proband 2 is a 7-year-old girl who was admitted with right lower limb claudication and foot numbness. Five days prior to admission, the patient experienced numbness in her right foot and could only walk after mobilizing the ankle joint; however, she also exhibited symptoms of claudication. Approximately ten days before the onset of these symptoms, the patient had fallen and

Table 1 Electromyography results of patients in our study

	Proband 1(11y)		Father of the proband 1 (39y)		Proband 2(7y)		Mother of the proband 2(33y)		Proband 3(16y)		Father of the proband 3 (41y)	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
MNCV(m/s)												
Median (elbow-wrist)	55.6	53.9	54.3	64.9	62.1	**35.8**	60.3	46.4	NE	**42.9**	**44.4**	**47**
Ulnar (elbow-wrist)	60.8	55.3	70.1	56.4	66.5	62.1	54.5	47.9	NE	49.4	56.7	55.3
Tibial (popliteal fossa-ankle)	46.0	46.6	NE	NE	41.3	40.9	**32.4**	**35**	NE	NE	NE	NE
Peroneal (below fibular head-ankle)	42.4	40.7	NE	NE	41.5	49.8	**NR**	**NR**	NE	NE	NE	NE
DML(ms)												
Median (wrist)	**3.66**	**3.75**	**3.42**	**3.12**	**4.62**	3.57	**6.48**	**6.84**	NE	**3.84**	**4.89**	**4.92**
Ulnar (wrist)	2.6	2.5	2.38	2.2	3.0	2.38	3	3.08	NE	2.68	2.58	**3.32**
Tibial (ankle)	3.87	3.75	NE	NE	3.51	3.36	**5.61**	**5.82**	3.42	3.52	NE	NE
Peroneal (ankle)	**5.04**	**5.34**	NE	NE	3.6	**5.34**	**5.7**	**5.64**	**7.48**	**6.62**	NE	NE
CAMP(mv)												
Median (wrist)	8.46	7.22	11.46	15.11	**7.03**	**5.98**	6.4	7.26	NE	7.83	6.06	8.72
Median (elbow)	7.84	6.73	**2.09**	13.51	6.66	4.08	5.81	6.13	NE	5.16	4.87	8.1
Ulnar (wrist)	12.27	12.55	14.71	15.13	11.97	12.02	14.71	15.6	NE	9.81	11.48	9.85
Ulnar (elbow)	11.70	11.28	14.47	15.16	8.8	10.15	14.27	16.37	NE	6.72	9.29	7.39
Tibial (ankle)	13.29	15.14	NE	NE	**14.66**	**15.27**	**16.4**	**18.8**	18.3	19.04	NE	NE
Tibial (popliteal fossa)	8.31	10.08	NE	NE	**2.37**	**3.63**	**3.2**	**8.2**	NE	NE	NE	NE
Peroneal (ankle)	2.76	2.70	NE	NE	3.87	3.13	1.51	1.32	**1.58**	3.4	NE	NE
Peroneal (below fibular head)	2.13	**1.47**	NE	NE	2.44	3.25	**NR**	**NR**	NE	NE	NE	NE
SNCV (m/s)												
Median (third finge-wrist)	48.5	44.2	50.4	51.2	43.2	**37.6**	**38.2**	**32.6**	NE	**41.4**	**NR**	**NR**
Ulnar (fifth finger-wrist)	41.7	45.1	75.0	56.1	47.6	46.4	42.7	42	NE	**42.5**	**NR**	**NR**
Posterior Tibial (ankle-big toe)	56.3	51.8	NE	NE	**NR**	**NR**	**25.9**	**27.4**	**NR**	**NR**	NE	NE
Sural (midcalf to lateral malleolus)	43.5	42.9	NE	NE	54.1	51.4	41	41.7	43.00	48.5	NE	NE
SNAP(μv)												
Median (wrist)	14.1	14.1	23.3	24.8	14.9	18.9	9.6	11.2	NE	6.1	**NR**	**NR**
Ulnar (wrist)	13.4	17.6	40.6	17.5	16.4	25.1	12.6	12.3	NE	10.3	**NR**	**NR**
Posterior Tibial (ankle)	3.5	3.8	NE	NE	**NR**	**NR**	2.2	2.2	**NR**	**NR**	NE	NE
Sural (midcalf)	26	14.2	NE	NE	35.3	6.3	14.9	26	20.00	18.4	NE	NE

BOLD: positive results

landed on both knees. Neurological examination revealed an MRC grade of 4/5 in the right lower limb, inability to dorsiflex the right foot, and a lack of response in the right Achilles tendon reflex. Sensation below the right ankle was diminished. Notably, this proband's mother, aunt, and grandfather all presented with pes cavus. Her mother exhibits no symptoms, but the EMG results revealed extensive alterations. After one month of follow-up, significant improvement was observed in the weakness of Proband 2's right lower limb, as well as a marked enhancement in dorsiflexion strength of her foot. Proband 3 is a 16-year-old girl presenting with weakness and numbness in the right foot. Six days prior to admission, the patient experienced weakness characterized by impaired dorsiflexion and an inability to perform toe flexion without apparent provocation. This was accompanied by numbness in the dorsal aspect of the foot. MRC grade of 0/5 in the distal right lower limb, along with hypersensitivity below the ankle joints on both sides. This proband's father and grandmother had a history of limb weakness and numbness following local compression, from which they were able to recover spontaneously. After one month of follow-up, there was significant improvement in the Proband 3's symptoms.

Literature review

Using "hereditary neuropathy with liability to pressure palsies" and "HNPP" as keywords, the relevant literature in the PubMed database from January 2003 to June 2024 was retrieved. The inclusion criteria were studies with basic patient information, primary symptoms, family history, specific triggers, EMG (text description or detailed table), and genetic testing. The exclusion criteria were literature not published in English, and studies involving patients with other underlying diseases that may affect EMG, such as cerebral hemorrhage, amyotrophic lateral sclerosis, schwannoma, diabetes, and hypothyroidism. A total of 68 studies meeting the inclusion and exclusion criteria were retrieved [1, 3–68]. There were 124 cases of HNPP (including six cases in our study), comprising 67 males and 57 females. The mean age of onset was 26.5 ± 18 years (age range: 2–78 years old), excluding eight asymptomatic cases, three unclear cases, two cases "in teens," and one case "in youth." There were 18 cases under 10 years old (16.1%), 34 cases between 10 and 20 years old (30.4%), 26 cases between 21 and 30 years old (23.2%), 21 cases between 31 and 50 years old (18.8%), and 13 cases (11.6%) aged 51–80 years (Fig. 1). The mean age of diagnosis was 32.7 ± 18.9 years (age range: 10–83 years, excluding seven unclear cases), and the longest interval from onset to diagnosis was 40 years. Seventy-nine cases (63.7%) showed typical symptoms of weakness and numbness in the innervation of the vulnerable area; of these, 49 (62%) experienced at least one recurrent episode. Thirty-seven cases (29.8%) exhibited atypical symptoms and eight (6.5%) were asymptomatic (Fig. 2). Pain and muscular dystrophy were found in 17.7% of the cases. Fifteen patients (12.1%) had pes cavus, and 80 (64.5%) had a family history of HNPP. Among 116 cases with positive symptoms, 67 (57.8%) of the specific triggers were traction or compression, four (3.4%) were related to temperature changes, and 45 (38.8%) were

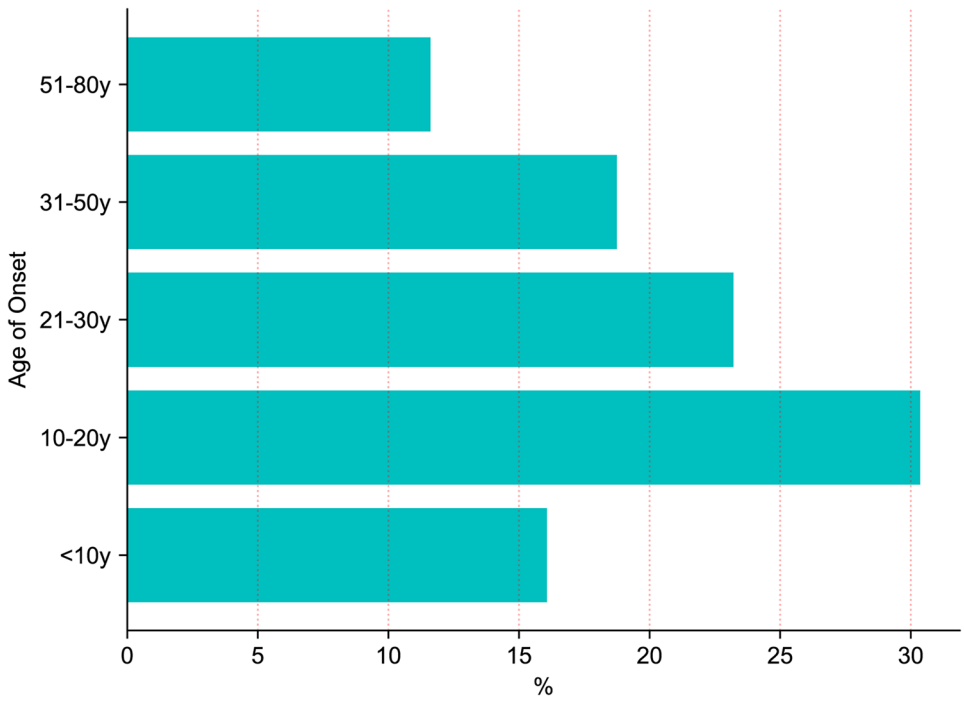

Fig. 1 Age group distribution of hereditary neuropathy with liability to pressure palsies

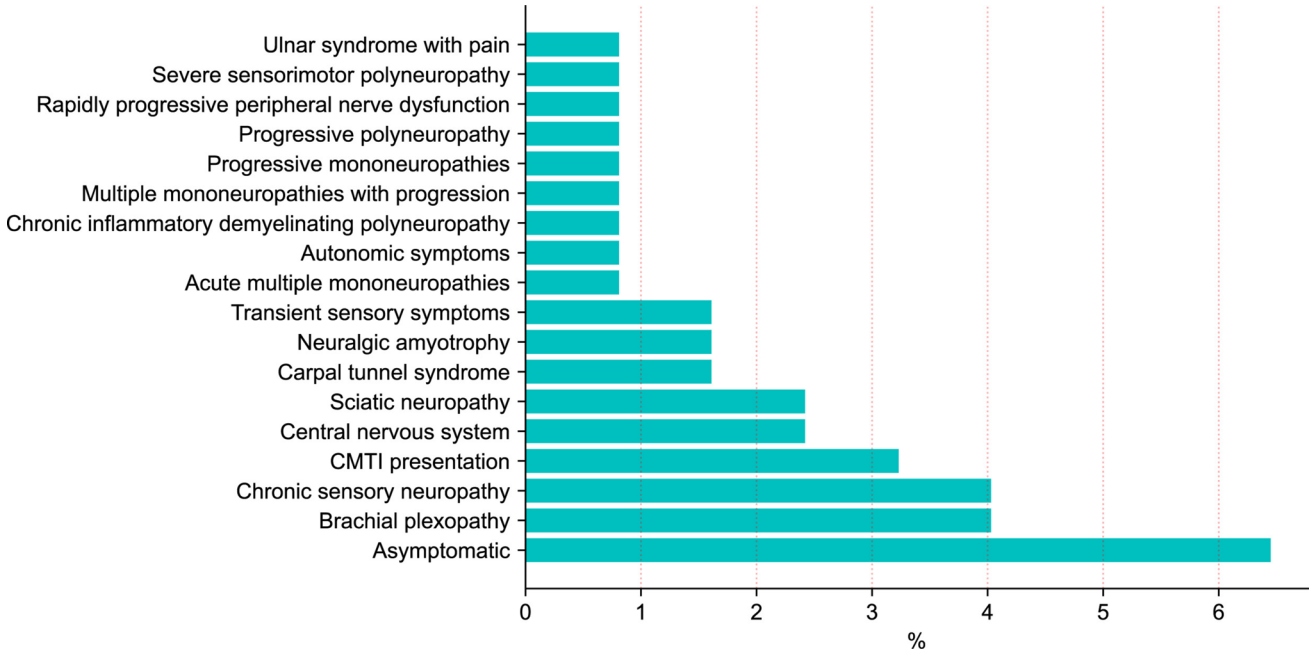

Fig. 2 Atypical symptoms and asymptomatic proportions of hereditary neuropathy with liability to pressure palsies

unclear. Heterozygous deletion of PMP22 was identified in 96 cases (77.4%), whereas point mutations in PMP22 were observed in 7.26% of the cases. Additionally, frameshift mutations in PMP22 accounted for 4.84%, and splice site mutations in PMP22 were present in 3.23% of cases. Missense mutations in PMP22 were detected in 2.42% of cases, and a small deletion involving exon 5 of PMP22 was noted in 1.61% of cases. Single-nucleotide deletions and microdeletions within *PMP22* represented 0.81% of cases each. Another subgroup comprising 0.81% exhibited heterozygous deletion and the presence of c.274 A > G (Ile92Val) in exon 3 of the LITAF; an equivalent percentage also demonstrated heterozygous deletions and T118M mutations in PMP22 (Fig. 3). Among 97 patients with detailed EMG descriptions, 82 (84.5%) had prolonged distal motor latency (DML), 50 (51.5%) had decreased compound muscle action potential (CMAP), and 76 (78.3%) had decreased motor nerve conduction velocity (MNCV). Additionally, 39 patients (40.2%) had prolonged (distal sensory latency) DSL, 65 (67%) had decreased sensory nerve action potential (SNAP), and 73 (75.3%) had reduced sensory nerve conduction velocity (SNCV) (Supplementary Table 1).

Discussion

Clinical manifestations of HNPP

The clinical manifestations of HNPP have obvious clinical heterogeneity and often involve peripheral nerves. Typical symptoms are primarily caused by tension or compression of nerves in vulnerable parts, repeated weakness, numbness, and painlessness in the affected innervation area [3]. For example, median nerve paralysis is caused by carpal tunnel compression, ulnar nerve paralysis is caused by cubital canal compression, and peroneal nerve paralysis is caused by compression of the small head of the fibula. According to our literature review, 79 cases (63.7%) showed typical symptoms of weakness and numbness in the innervation of the vulnerable area. Of these, 49 (62%) experienced at least one recurrent episode. However, 37 cases (29.8%) had atypical symptoms, and pain occurred in 17.7% of cases. Figure 3 shows the various phenotypes and their proportions. These phenotypes may influence the clinician's judgment. Luigetti et al. reported 64 patients with HNPP, 28 (44%) of whom presented with recurrent mononeuropathy. Thirty-six patients (56%) presented with general weakness and spasm, chronic ulnar neuropathy, carpal tunnel syndrome, chronic sensory neuropathy, and Guillain–Barré syndrome or Charcot–Marie–Tooth type-1A (CMT1A). Nine patients (14%) had no neurologic symptoms [69]. Our literature review revealed that 17.7% of patients had signs of muscle atrophy of varying degrees, and 12.1% of patients had characteristics of pes cavus, which must be identified with CMT1A. Other reports have also suggested that approximately 10–15% of patients with HNPP may have no obvious symptoms and are only diagnosed through family members' onset, medical treatment, and family genetic testing [70]. The mother of proband 2 is asymptomatic, representing one of eight asymptomatic cases in our literature review. However, EMG revealed multiple peripheral neuropathies,

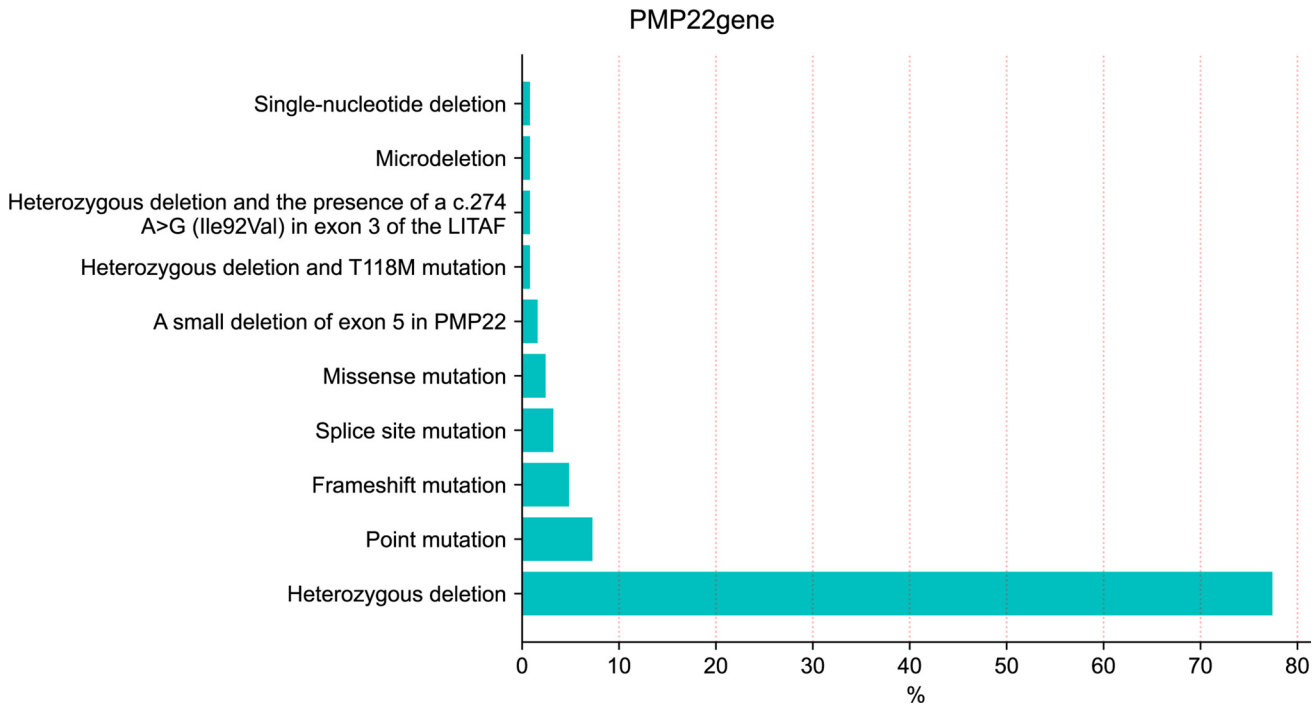

Fig. 3 The proportion of mutation types in hereditary neuropathy with liability to pressure palsies

indicating that the incidence of this disease was easily underestimated. In addition, more attention should be paid to HNPPs that involve the central nervous system [23, 35, 63]. In a prospective study exploring whether patients with *PMP22* mutations had central nervous system abnormalities, 70% of the 15 patients with HNPP had white matter volume reduction. Eleven patients had mild cognitive impairments in executive function, working memory, and verbal episodic memory [17, 71]. Our literature review revealed that three cases involved the central nervous system. A clear cause was found in 61.2% of the cases, most of which were caused by traction and compression trauma. Additionally, four cases were related to temperature changes, adding to the complexity of diagnosis. HNPP is an autosomal-dominant peripheral neuropathy and most patients have a positive family history. In our study, all three probands had clear family histories. Our literature review found that 64.5% of patients had a family history of HNPP, which is crucial for the clinical identification of HNPP. Some family members have had transient symptoms, which must be carefully questioned. Previous reports have emphasized that the age of onset of symptoms is typically between 20 and 30 years [18, 66]. The literature review revealed that the mean age of onset of HNPP was 26.5 ± 18 years (age range: 2–78 years old). However, it is important to note that the disease can occur at any age (Fig. 2). The mean age of diagnosis was 32.7 ± 18.9 years (age range: 10–83 years), and the longest interval from onset to diagnosis was 40 years. Therefore, early identification of the disease can provide patients with timely warnings and help them avoid its causes. In most reports about HNPP, there have been few pediatric patients. In our study, the youngest proband was seven years old and the oldest proband was 16 years old. No significant differences were observed in the male-to-female ratios, which is inconsistent with previous reports [72]. The symptoms of the three probands improved significantly and no obvious sequelae were observed. Over half of the patients recovered completely, typically within days to months; however, relapses occurred frequently, and paresis may last for longer periods [5, 66]. Most patients recover on their own; however, those with unimproved symptoms two years after onset underwent surgical reconstruction for finger and wrist extensions [66]. Therefore, early clinical recognition and intervention are crucial.

EMG characteristics of HNPP

EMG examination is crucial for diagnosing HNPP. In most cases, the EMG manifestations of HNPP are prolonged DML, decreased MNCV, and nerve block at the compression site. Abnormal EMG changes may also be found in asymptomatic nerves or their asymptomatic family members. In our literature review, among 97 patients with detailed EMG descriptions, 82 (84.5%) had prolonged DML, 50 (51.5%) had decreased CMAP, and 76 (78.3%) had decreased MNCV. Additionally, 39 patients (40.2%) had prolonged DSL, 65

(67%) had decreased SNAP, and 73 (75.3%) had reduced SNCV, supporting the EMG characteristics of HNPP. EMG findings in HNPP revealed a distinctive background polyneuropathy independent of superimposed entrapment neuropathies. This condition often occurs in patients with severe symptoms but not extensive myoelectricity, those with mild symptoms but more extensive myoelectricity [21], or those who have experienced mild symptoms, although asymptomatic for many years. However, EMG still revealed extensive multifocal lesions [39]. In our study, three probands were treated for dysfunction or weakness of the right foot with numbness; however, EMG changes were also observed in other clinically unaffected nerves, except for prolonged DML of the common peroneal nerve of the right lower limb. Immediate relatives who had paralysis or numbness in the past or who had never experienced paralysis also showed obvious EMG abnormalities, providing an important basis for clinical diagnosis. Hong et al. compared 50 motor nerves and 39 sensory nerves of eight patients with HNPP, and found that 97% of sensory nerves exhibited slow conduction, 87.5% of motor nerves had abnormally slow conduction at common entrapment sites, and slow conduction was uncommon at non-entrapment sites. Additionally, 80% of nerve DML values were prolonged [73]. De Oliveira et al. conducted a nerve conduction study on 253 motor and 237 sensory nerves in 33 patients. Among them, 98.2% of MNCV values decreased at the elbow joint, and 89.6% of SNCV values decreased in the finger-wrist area. Among the peroneal nerves, 83.0% had at least one abnormal measurement in DML, MNCV, or SNCV. Moreover, 82.8% of median nerve SNCV values decreased in the digital wrist and 100% in the palmar wrist [74]. These studies suggested that EMG changes in patients with HNPP often result in more extensive peripheral nerve damage than the clinical manifestations.

PMP22-related diseases

PMP22 is involved in myelination and is essential for the functional integrity of peripheral nerves. In the human genome, *PMP22* is located on chromosome 17p11.2–12. There are three main types of hereditary peripheral neuropathy caused by its gene mutation: CMT1A due to copy number variation, Charcot–Marie–Tooth type-1E (CMT1E) due to point mutations, and HNPP due to heterozygous deletion [75]. A single genetic mechanism, altered gene dosage due to either deletion or duplication of *PMP22*, is the most common cause of HNPP and CMT1, respectively. However, point mutations in the same gene may also cause different phenotypes [5].

The main clinical manifestations of CMT1A are progressive muscle weakness and atrophy in the distal extremities, often accompanied by sensory disorders, "crane leg," foot droop, arcuate foot changes, and weakening or disappearance of tendon reflexes. Multiple studies have confirmed that in rodents, increasing the copy number variation of *PMP22* results in protein overexpression, producing a pathological phenotype similar to that of human CMT1A [75]. EMG is characterized by demyelinating damage, uniform symmetrical deceleration of motor and sensory conduction velocities, and almost equal conduction velocities in different segments of the same nerve, even within different limbs [75]. In contrast, acquired demyelinating neuropathies, such as Guillain–Barré syndrome and chronic inflammatory demyelinating polyradiculopathy, are often asymmetrical and uneven in terms of clinical presentation and nerve conduction.

CMT1E is a rare subtype of CMT1 that accounts for 1–5% of all CMT1 cases and is caused by a point mutation in *PMP22*. Its clinical phenotype is often indistinguishable from that of other CMT1 subtypes, ranging from mild HNPP-like neuropathy to severe early-onset myelin dysplasia neuropathy. Given the phenotypic heterogeneity, CMT1E must be confirmed by *PMP22* gene testing. Most patients with CMT1E may present with impaired motor development, distal muscle weakness, foot malformations, and loss of deep tendon reflexes, and a few patients may present with clinical symptoms of axonal neuropathy. EMG manifestations include reduced MCV and prolonged DML [75].

Patients with HNPP primarily present with recurrent numbness and weakness in the affected innervation area after slight tension or compression of the nerve in the vulnerable area. Approximately 80–90% of the pathogenic mutations in patients with HNPP had heterozygous deletions of chromosome 17p11.2, and 10–20% had point mutations, including nonsense, missense, frameshift, or splicing mutations [76, 77]. Our literature review found that 77.4% of patients had heterozygous deletions of PMP22, 7.26% had point mutations in PMP22, and 15.34% had other PMP22 gene mutations in PMP22 (microdeletions, frameshift mutations, splice site mutations, missense mutations, single-nucleotide deletions, or PMP22 heterozygous deletions combined with other gene mutations). Compared to patients with a heterozygous deletion of *PMP22*, the phenotype of patients with other *PMP22* mutations is typically less typical. Some of the phenotypes ranged between those of CMT1A and HNPP: lighter than the CMT1A phenotype but heavier than the HNPP phenotype [5, 17]. The finding that a single deletion mutation of *PMP22* produces the same phenotype as the deletion of heterozygosity on chromosome 17p11.2 confirms that *PMP22* is the cause of the disease rather than other genes located on chromosome 17p11.2 [78]. Bai et al. made a mouse model of HNPP ($PMP22^{\pm}$) and found in the compression sensitivity study on normal mice ($PMP22^{+/+}$) and HNPP mice that the induction time of block in HNPP mice was significantly shorter than that in normal mice. Additionally, the recovery of nerve block in

HNPP mice was also delayed. These results suggest that the action potential propagation of the HNPP-diseased nerve is impaired, making the HNPP nerve susceptible to conduction blocks when subjected to mechanical stimulation [79].

Diagnosis and treatment recommendations for HNPP

In summary, the increased diagnosis rate of HNPP is primarily based on the following: recurrent single or multiple nerve injury in clinical practice; a positive family history; beyond the lesion nerve and involves a wider range of neurological changes, as detected by EMG; and genetic testing showing *PMP22* heterozygosity deletion. Early diagnosis of the disease can avoid unnecessary and excessive examinations and can help family members perform early prevention education. This is beneficial for reducing the family's economic burden. Currently, no effective treatments exist for HNPP in clinical practice. Early diagnosis, symptomatic supportive treatment such as rehabilitation training, and protective measures to protect vulnerable parts of entrapment and avoid repeated movements are crucial for the prognosis of HNPP. Patients with HNPP and their family members should limit and avoid heavy physical work and trauma and reduce movements that can cause nerve compression in daily life. With the continuous development of genetic engineering technology, gene correction treatment for the disease is expected to reduce long-term symptoms and even cure the disease. However, there is currently no relevant research. Therefore, further research is required to address this gap and advance our understanding of the topic.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-024-12839-7.

Author contributions LC and JL contributed to the conception and design of the study. LC, HZ, CL, NY, and JW were in charge of the data analysis. LC prepared Figs. 1, 2, 3, Table 1, and Supplementary Table 1 and drafted the manuscript. HZ and JL commented on and revised the draft. All authors have read and approved the final version of this manuscript.

Funding This work was supported by the National Nature and Science Foundation of China (No.82271509 & No.81771396), the Foundation of Jilin Provincial Key Laboratory of Pediatric Neurology (No. YDZJ202102CXJD021), the Project of Jilin Provincial Science and Technology Development Plan (No.YDZJ202201ZYTS676), the Natural Science Foundation of Jilin Province (No. YDZJ202201ZYTS090) and the Project of Jilin Medical and Health Talents (No. JLSWSRCZX2021053).

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval and consent to participate This study was approved by the Ethics Committee of Bethune First Hospital of Jilin University. Informed consent was obtained from all the participants and their legal guardian involved in the study.

Consent to publication Written informed consent from all the participants and patient's parents was obtained before conducting the gene test, including the patient's clinical and EMG details in the manuscript for publication.

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