

## Terminal Latency Index (TLI) Abnormalities in Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)

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### Abstract

**Introduction:** The diagnosis of Hereditary Neuropathy with Liability to Pressure Palsy (HNPP) is frequently missed or delayed because of its clinical and electrophysiological heterogeneity. Nonetheless, electrophysiological criteria were published 15 years ago. Our aim was to highlight the Terminal Latency Index (TLI) disorders by describing the electrophysiological characteristics in patients with HNPP.

**Methods:** All the consecutive patients with the clinical and genetic diagnosis of HNPP due to the 1.5Mb deletion of PMP22 or to others mutation or deletion were included. Motor and sensory conductions were studied using surface electrodes placed near the median, ulnar, fibular, tibial, superficial fibular and sural nerves in accordance with standard techniques. The results were compared with our own laboratory standards.

**Results:** All of the 22 included patients had low TLI in the median, ulnar and peroneal nerves, whereas 6% of the patients had low tibial TLI. The other frequent electrophysiological characteristics were increased distal motor latency and low sensory conduction velocity, especially of the median nerve.

**Conclusions:** TLI abnormalities are almost constant in HNPP, which is a great argument to define HNPP as a distally accentuated myelinopathy. TLI disorders should be added to HNPP electrophysiological criteria to improve their diagnosis accuracy.

**Keywords:** Hereditary Neuropathy with liability to Pressure Palsies (HNPP); Variable phenotype; Electroneuromyography; Terminal latency index

### Abbreviations

CMT: Carcot-Marie-Tooth; DML: Distal Motor Latency; EMG: Electromyography; HNPP: Hereditary Neuropathy with liability to Pressure Palsies; Mb: Megabase; PMP22: Peripheral Myelin Protein 22; STR: Short Tandem Repeat; TLI: Terminal Latency Index

### Introduction

Hereditary Neuropathy with liability to Pressure Palsies (HNPP) is classically characterized by recurrent episodes of painless paralysis with paresthesia in the territory of peripheral nerves or plexuses [1-4]. Usually the onset is acute, but progressive weakness may occur. Episodes of peripheral paralysis are often triggered by minor nerve compression or posture; nerves are therefore affected in a zone of anatomical entrapment (the ulnar nerve at the elbow or the fibular nerve at the neck of the fibula, essentially) [5]. Patients can sometimes have symptoms of a distal and length-dependent polyneuropathy [4-7]. In most cases, patients recover in a few days or weeks, but sensitive or motor deficits can persist longer. Neurological examination confirms sensitive and/or motor disorders with depression or loss of tendon reflexes.

HNPP is inherited in an autosomal dominant pattern, and can be confirmed using molecular biology by the presence, in 70 to 85% of cases [8,9], of a 1.5 Megabase (Mb) deletion on chromosome 7p11.2, which codes for PMP22 (Peripheral Myelin Protein 22) [10]. In addition to the well-known 1.5 Mb deletion, new genetic mutations [11-14] and other deletions [15-17] have been discovered, and these enrich the genetic diagnosis of HNPP. De novo mutations exist too. Mutation carrier can be asymptomatic.

HNPP is one of the large group of demyelinating neuropathies, and therefore presents the electrophysiological characteristics common to this group [4]. These include reduced motor and sensory conduction velocity, increased distal motor latency (DML) and conduction blocks, the frequency of which is still a matter of debate [5,18].

Diagnostic criteria for HNPP were published in 2000 [19]. They correspond to clinical and electrophysiological criteria, neuropathological features and molecular genetic data. Electrophysiological criteria are as follows: diffuse electrophysiological abnormalities, such as “bilateral delayed median nerve distal motor latencies, associated with bilateral reduced median sensory nerve conduction velocity at the palm-wrist segment and at least delayed DML or reduced motor nerve velocity in one of the peroneal nerves”, have to be present in all mutations carriers aged more than fifteen years. Other abnormalities can be present to reinforce the HNPP diagnosis: reduction of the ulnar motor nerve velocity at the elbow,

moderate reduction of the motor nerve velocity in lower limbs, and reduction of the sensory nerve action potentials, especially in upper limbs. However, despite of these criteria, the diagnosis of HNPP is frequently missed or delayed. Moreover, HNPP is often under-diagnosed when presenting clinically as a distal and length-dependent polyneuropathy exceeding tunnel compressions.

Terminal Latency Index (TLI) is a well-known electrophysiological parameter which gives a picture of the distal demyelination. Low TLI is a major sign of distal demyelinating neuropathy associated with antibodies to myelin-associated glycoprotein [19,20]. Only a few former studies take into account the TLI for the diagnosis of HNPP [6,7,21], and TLI abnormalities do not belong to the HNPP criteria [22].

Our aim was to highlight the TLI disorders by describing the electrophysiological characteristics in patients with HNPP due to the 1.5 Mb deletion of PMP22 and to others mutation or deletion.

## Methods

### Schema and study population

This was a retrospective observational study.

All of the patients who had a consultation that included Electromyography (EMG) in the fifteen last years at the Dijon University Hospital, France, and who were diagnosed with HNPP as a result of clinical, electrophysiological and genetic data were included in a consecutive manner.

Patients with other neurological pathologies likely to have been the cause of the neuropathy were excluded.

### Electrophysiological studies

Motor and sensory conduction studies were studied using surface electrodes placed near the median, ulnar, peroneal, tibial, superficial fibular and sural nerves in accordance with standard techniques. The results were compared with our own laboratory standards which were obtained in healthy human subjects (average of the electrophysiological values of healthy male and female subjects of different ages). The normal limits of our own laboratory standards are shown in Tables 1 and 2. The results for motor and sensory amplitudes, motor and sensory conduction velocity and F-wave velocity were expressed as percentages of the lower limit of normal, while the results for distal motor latency (DML) and F-wave latency were expressed as percentages of the upper limit of normal.

The Terminal Latency Index (TLI) was calculated for the motor nerves according to the formula: distal distance in mm / (motor conduction velocity in m/s \* distal motor latency in ms) [21]. A value below 0.25 was considered abnormal.

Motor conduction block was defined as a reduction of at least 20% in proximal motor amplitude compared with distal motor amplitude, with a duration increase of no more than 15% [23].

The motor response M of median nerves was obtained on the abductor pollicis brevis muscle after stimulation at the wrist (amplitude A1) and at the elbow (amplitude A2). The motor response M of the ulnar nerves was obtained on the abductor digiti minimi muscle after stimulation at the wrist (amplitude A1), below the elbow (amplitude A2) and above the elbow (amplitude A3). The motor response M of the peroneal nerves was obtained on the extensor

digitorum brevis muscle after stimulation at the ankle (amplitude A1), at the fibular neck (amplitude A2) and at the popliteal fossa (amplitude A3). The motor response M of the tibial nerves was obtained on the abductor hallucis muscle after stimulation at the ankle (amplitude A1) and at the popliteal fossa (amplitude A2). Negative peak amplitude (in mV), distal latency (in ms) and conduction velocity (in m/s) were obtained for each of the peripheral nerves studied.

F-waves were obtained for each peripheral nerve after distal stimulation: at the wrist for the median and ulnar nerves and at the ankle for the peroneal and tibial nerves. The F-wave velocity (in m/s) was calculated from F-wave latency (in ms) for each peripheral nerve, according to the following formulae:

- For upper limbs at the wrist: F-wave Velocity = (distance elbow – sternum \* 2) / (F-wave latency – M latency – 1)
- For lower limbs at the ankle: F-wave velocity = (patient's height \* 1.25) / (F-wave latency – M latency – 1)

Sensory nerve responses were studied using the antidromic pathway for all sensitive nerves. The amplitude of each response (in  $\mu$ V) was calculated from the positive to the negative peaks. The sensory conduction velocity obtained was expressed in m/s.

Limb temperature was maintained above 32°C.

Concentric needle single fiber electromyography was not taken into account in this study.

### Genetic studies

Patients who underwent EMG at our department of clinical neurophysiology, and in whom the clinical and electrophysiological diagnosis was compatible with HNPP were screened in genetic consultation with a molecular study of the PMP22 gene. First, an indirect diagnostic approach using microsatellite markers (Short Tandem Repeats; STR) was carried out to screen for the classical 1.5 Mb deletion of the PMP 22 gene, the most frequently encountered genetic anomaly in patients with HNPP [10]. If screening for the 1.5 Mb deletion proved to be negative, smaller deletions were screened for using a locus-specific quantitative method (Multiplex Ligation-dependent Probe Amplification (MLPA) technique) [24,25], and mutations of the PMP22 gene were screened for using direct sequencing. Mutations of the MPZ gene for the P0 protein of myelin were also screened for by direct sequencing.

### Statistical analyses

Variables were described as means and standard deviations, or numbers and frequencies. SAS 9.2 (SAS Institute Inc, Cary, North Carolina) software was used for all of the statistical analyses.

## Results

Twenty-two patients had clinical data compatible with the diagnosis of HNPP. Among them, the 1.5 Mb deletion of the gene coding for PMP22 was found in genetic testing in twenty patients, one patient was heterozygous for the Leu145fsX9 (c.434delT) mutation present on exon 1A of the gene coding for PMP22 and one patient presented a heterozygous deletion in 17p12 with a maximal size of around 650 kb (this deletion encompassed PMP22).

### Clinical characteristics of the patients with HNPP

The mean age of the 22 patients included (36 half-bodies tested) was  $32 \pm 16$  years; half of the patients were men.

The most frequent clinical presentation was single or multiple mononeuropathy (15 patients - 68%): in most cases the mononeuropathy affected the ulnar nerve at the elbow (7 patients - 47%), and/or the common peroneal nerve at the fibular neck (5 patients - 33%). The median, radial and sciatic nerve were more rarely affected with four patients (27%), two patients (13%) and one patient (7%), respectively. Other rarer clinical presentations were found in our cohort: sensory-motor polyneuropathy (four patients - 18%) or isolated involvement of the brachial plexus (one patient - 5%). One patient was asymptomatic (5%), identified thanks to his twin brother who had HNPP.

### Electrophysiological characteristics of patients with HNPP

Concerning motor conduction (Table 1), the TLI were always low ( $< 0.25$ ) for the median, ulnar and peroneal nerves, but the TLI for the tibial nerves was almost never pathological (abnormal in only 6% of cases). A total of 100% of patients had increased DML of the median nerve while only 46%, 78% and 23% of patients had increased DML of the ulnar, peroneal and tibial nerves, respectively. Overall, the other motor conduction parameters such as conduction velocity, F-wave latency and velocity, and above all motor response amplitudes were less often abnormal. As for motor conduction block, the median nerve was the least frequently affected: conduction blocks were present in 3% of the cases for the median nerve, 20% for the ulnar nerve, 13% for the peroneal nerve and 32% for the tibial nerve. The other motor characteristics of the patients are described in Table 1.

Electrophysiological characteristics	Patients with the 1,5 Mb deletion of PMP22 gene	Patients with another genetic anomaly of the PMP22 gene	Normal limits of our laboratory	Frequency of abnormal results (%)
	Mean $\pm$ SD	Mean $\pm$ SD		
Median nerve (n = 35)				
Motor CV (m/s)	53.0 $\pm$ 5.1	48.7 $\pm$ 8.5	$\geq 53$	49
DML (ms)	5.2 $\pm$ 1.6	4.7 $\pm$ 0.5	$\leq 3.7$	100
TLI	0.19 $\pm$ 0.03	0.22 $\pm$ 0.03	$\geq 0.25$	100
Motor amplitude A1 (mV)	7.3 $\pm$ 3.4	7.2 $\pm$ 1.6	$\geq 4.8$	17
Motor amplitude A2 (mV)	7.1 $\pm$ 3.4	6.5 $\pm$ 1.4	$\geq 4.8$	17
Conduction block				3
F-wave latency (ms)	30.7 $\pm$ 4.4	32.0 $\pm$ 4.9	$\leq 30.6$	37
F-wave velocity (m/s)	56.4 $\pm$ 5.5	51.7 $\pm$ 8.5	$\geq 54$	23

Ulnar nerve (n = 35)				
Distal motor CV (m/s)	52.8 $\pm$ 5.2	50.7 $\pm$ 7.8	$\geq 53$	54
Motor CV at the elbow (m/s)	36.6 $\pm$ 8.7	34.0 $\pm$ 9.8	$\geq 44$	86
DML (ms)	3.1 $\pm$ 0.6	3.0 $\pm$ 0.5	$\leq 3.0$	46
TLI	0.01 $\pm$ 0.01	0.01 $\pm$ 0.00	$\geq 0.25$	100
Motor amplitude A1 (mV)	8.7 $\pm$ 2.1	7.7 $\pm$ 0.2	$\geq 5.6$	6
Motor amplitude A2 (mV)	8.2 $\pm$ 2.1	6.9 $\pm$ 0.8	$\geq 4.5$	3
Motor amplitude A3 (mV)	6.9 $\pm$ 2.6	6.4 $\pm$ 0.4	$\geq 4.5$	17
Conduction block				20
F-wave latency (ms)	30.8 $\pm$ 7.3	34.0 $\pm$ 6.6	$\leq 32.2$	37
F-wave velocity (m/s)	48.3 $\pm$ 10.5	46.0 $\pm$ 8.7	$\geq 50$	43
	Patients with the 1,5MB deletion of PMP22 gene	Patients with another genetic anomaly of the PMP22 gene	Normal limits of our laboratory	Frequency of abnormal results (%)
	Mean $\pm$ SD	Mean $\pm$ SD		
Peroneal nerve (n = 32)				
Distal motor CV (m/s)	39.4 $\pm$ 4.6	37.0 $\pm$ 9.6	$\geq 41$	59
Motor CV at the fibular neck (m/s)	38.7 $\pm$ 8.8	29.3 $\pm$ 7.5	$\geq 39$	59
DML (ms)	7.3 $\pm$ 2.7	5.3 $\pm$ 1.0	$\leq 5.5$	78
TLI	0.01 $\pm$ 0.00	0.02 $\pm$ 0.00	$\geq 0.25$	100
Motor amplitude A1 (mV)	4.0 $\pm$ 1.7	1.7 $\pm$ 2.2	$\geq 3.3$	28
Motor amplitude A2 (mV)	3.7 $\pm$ 1.7	1.6 $\pm$ 2.1	$\geq 3.0$	28
Motor amplitude A3 (mV)	3.3 $\pm$ 1.7	1.6 $\pm$ 2.3	$\geq 2.9$	38
Conduction block				13
F-wave latency (ms)	57.4 $\pm$ 10.5	62.1 $\pm$ 18.1	$\leq 57.9$	56
F-wave velocity (m/s)	42.2 $\pm$ 5.2	39.5 $\pm$ 12.0	$\geq 43$	66
Tibial nerve (n = 31)				

Motor CV (m/s)	42.1 ± 4.0	40.7 ± 5.9	≥ 41	39
DML (ms)	5.4 ± 1.1	4.5 ± 0.9	≤ 6.0	23
TLI	0.32 ± 0.05	0.39 ± 0.03	≥ 0.25	6
Motor amplitude A1 (mV)	8.1 ± 3.0	4.2 ± 0.4	≥ 6.6	32
Motor amplitude A2 (mV)	6.8 ± 2.2	3.8 ± 0.9	≥ 5.4	32
Conduction block				32
F-wave latency (ms)	56.3 ± 7.3	60.7 ± 19.6	≤ 59.2	35
F-wave velocity (m/s)	41.1 ± 3.7	40.7 ± 11.0	≥ 42	58
Abbreviations: HNPP: Hereditary Neuropathy with liability to Pressure Palsies; SD: Standard Deviation; CV: Conduction Velocity; DML: Distal Motor Latency; TLI: Terminal Latency Index; m/s: meter/seconde; ms: milliseconde; mV: millivolt; µV: microvolt.				

**Table 1:** Electrophysiological motor nerves' characteristics of the patients with HNPP due to the 1.5 Mb deletion of the PMP22 gene (n = 33 half-bodies tested) and due to another mutation or deletion (n = 3 half-bodies tested).

Concerning the sensory conduction (Table 2), anomalies in sensory conduction velocity were the most frequent: 100% of the median nerves, 91% of the ulnar nerves, 69% of the superficial peroneal nerves and 66% of the sural nerves tested had low sensory conduction velocity, while sensory response amplitude was low in only 71% of median nerves, 69% of ulnar nerves, 72% of superficial peroneal nerves and 53% of sural nerves.

Electrophysiological characteristics	Patients with the 1.5 Mb deletion of PMP22 gene	Patients with another genetic anomaly of the PMP22 gene	Normal limits of our laboratory	Frequency of abnormal results (%)
	Mean ± SD	Mean ± SD		
Median nerve (n = 35)				
Sensory CV (m/s)	37.0 ± 8.6	40.3 ± 6.1	≥ 50	100
Sensory amplitude (µV)	12.7 ± 9.4	7.9 ± 1.5	≥ 15	71
Ulnar nerve (n = 35)				
Sensory CV (m/s)	38.3 ± 9.4	28.0 ± 24.3	≥ 50	91
Sensory amplitude (µV)	13.1 ± 9.2	6.2 ± 5.4	≥ 15	69
Superficial peroneal nerve (n = 32)				
Sensory CV (m/s)	35.4 ± 13.0	39.3 ± 6.4	≥ 41	69
Sensory amplitude (µV)	8.1 ± 10.1	2.7 ± 0.6	≥ 8	72

Sural nerve (n = 32)				
Sensory CV (m/s)	34.2 ± 11.0	41.3 ± 7.4	≥ 40	66
Sensory amplitude (µV)	7.6 ± 9.0	2.3 ± 0.1	≥ 7	53
Abbreviations: HNPP=Hereditary Neuropathy with liability to Pressure Palsies; SD=Standard Deviation; CV=Conduction Velocity; m/s=meter/seconde; ms=milliseconde; mV=millivolt; µV=microvolt.				

**Table 2:** Electrophysiological sensory nerves' characteristics of the patients with HNPP due to the 1.5 Mb deletion of the PMP22 gene (n = 33 half-bodies tested) and due to another mutation or deletion (n = 3 half-bodies tested).

## Discussion

The present study showed that low TLI were almost constant in HNPP, which was a great argument to define HNPP as a distally accentuated myelinopathy. Other electrophysiological abnormalities suggesting demyelinating neuropathy were also present: increased DML, low sensory conduction velocity and conduction blocks in zones of anatomical entrapment.

The electrophysiological anomalies revealed in our cohort of were consistent with the definition of HNPP, which belongs to the large group of demyelinating neuropathies. We thus underlined the electrophysiological criteria of demyelination [21,26]: on the one hand for motor nerves with prolonged motor latency, decreased conduction velocity, conduction block (in zones of anatomical entrapment), prolonged F-wave latency and reduced F velocity, and on the other hand for sensory nerves, decreased conduction velocity. To a lesser degree, our cohort revealed a slight reduction in the amplitude of motor and/or sensory responses, which is a sign of axonal degeneration secondary to demyelination. Among these abnormalities, the most characteristic disorders of HNPP are prolonged distal motor latency and decreased sensory conduction velocity with better preserved motor conduction velocity [3,5,7,21,27-28]. In our series, conduction blocks were quite rare, from 3 to 32% depending on the nerve, even though the definition used was large: reduction of at least 20% in proximal motor amplitude compared with distal motor amplitude, with a duration increase of no more than 15% [23]. Almost all were in zones of anatomical entrapment (median nerve in the carpal tunnel, ulnar nerve at the elbow or peroneal nerve at the fibula neck). The presence of conduction block is suggested by a body of evidence: predominance of motor involvement, absence of amyotrophy and cure despite several episodes of peripheral nerve paralysis. The frequency of motor conduction block is a matter of debate in the literature, and ranges from 10-15% [5] to 100% of cases [18]. Most case series are in agreement with the present study, and show a low frequency of conduction block [3,5,27]. Moreover, because of the high sensitivity of the conduction block definition used, conduction block may be over-estimated, in particular for the tibial nerves. However, we always stimulate the tibial nerve at the popliteal fossa with a 1 millisecond-duration stimulus in order to minimize the decrease of the response's amplitude.

Whereas the first studies on HNPP focused on electrophysiological anomalies situated in zones of anatomical entrapment, several patients with the classical 1.5 Mb deletion of the PMP22 gene have the clinical presentation of distal and length-dependent polyneuropathy [2,5,29], like four patients of our cohort. This clinical feature is corroborated by decrease (<0.25) of the TLI which was found for all patients in the

median, ulnar and peroneal nerves in our study. A low TLI was explained by the fact that the distal motor latencies were prolonged to a greater extent than that suggested by the motor conduction velocity detected in the most proximal segment of the limb. Low TLI confirms the presence of a distal and length-dependent demyelinating neuropathy in HNPP. Only two former studies take into account the TLI for the diagnosis of HNPP [6,7], and TLI abnormalities do not belong to the HNPP criteria published in 2000 [19]. The existence of an underlying neuropathy can probably be explained by the fact that HNPP are the consequence of genetic anomalies that affect certain myelin proteins (PMP22), leading to diffuse damage to peripheral myelin. From a physiopathological point of view, there is an overlap between HNPP and Charcot-Marie-Tooth disease type-1A (CMT-1A), a consequence of PMP22 duplication [21,27,30].

Our study, however, had several limitations. First of all, it was a retrospective study, which raises the possibility of bias due to classification differences and to missing data, leading to a reduction in the power of the study. Secondly, the number of patients was quite small (22 patients for 36 half-bodies tested). This limitation also reduces the power of our study. Finally, we did not include groups of control patients or patients with diseases of the peripheral nervous system other than HNPP for comparison purposes.

In conclusion, the present study observed that low TLI in median, ulnar and peroneal nerves is a major HNPP characteristic. It is a strong argument to describe HNPP as a distally accentuated demyelinating neuropathy. It is reinforced by the fact that several patients have distal and length-dependent polyneuropathy leading to the diagnosis of HNPP. Other known electrophysiological features of HNPP are also underlined in our study, such as increased distal motor latencies, low sensory and motor conduction velocity, as well as the previous reports. This finding is very interesting because TLI abnormalities do not belong to the HNPP criteria published in 2000, which are the reference in France for the diagnosis of HNPP. It should be an argument to add TLI disorders into HNPP electrophysiological criteria to improve their diagnosis accuracy.

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