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Pain and small-fiber affection in hereditary neuropathy with liability to pressure palsies (HNPP)

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Abstract

Background and aims: Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal – dominant hereditary neuropathy caused by a deficiency in the peripheral protein PMP-22, due to deletion on chromosome 17p11,2 or in some rare cases point mutations in the PMP-22 gene. The clinical picture is characterized by recurrent mononeuropathies in nerves which frequently may be exposed to pressure, such as the median, ulnar, radial and peroneal nerves or also a more general neuropathy. Although pain is reported to be an unusual clinical symptom, there have been reports of pain in a surprisingly high proportion of these patients. Since pain may be explained by mechanisms in afferent small unmyelinated C- nerve fibers, an assessment of the function of small nerve fibers has been requested. The purpose of the present study was to investigate the presence of pain and the possible affection of afferent small nerve-fibers, A-δ and C-fibers, by quantitative sensory testing (QST)-assessment of thermal thresholds, as well as quantitative sudomotor axon reflex (QSART), a quantitative, validated assessment of efferent postganglionic sumodotor function. QST values were compared to values of age- and sex matched healthy subjects.

Methods: The 19 patients were investigated clinically, with an emphasis on pain characteristics, with nerve conduction studies (NCS) of major nerves in upper- and lower extremity, small fiber testing (QST, measurement of thermal thresholds) and with QSART.

Results: A total of 10 patients reported numbness in some extremity, suggesting entrapment of individual nerves as well as a general neuropathy, as verified by NCS in nine patients. A total of 15 patients had findings compatible with a general polyneuropathy. A total of eight patients reported pain, seven patients with pain in the feet, described as burning, aching, shooting and six with severe pathological QST values, mainly cold detection, but also four patients with elevated thresholds to warmth. Four of the patients had signs of a severe sensory neuropathy on NCS, with no sural findings. One patient had only pain in the arms, with only minor changes on NCS and with normal QST-values. Cold detection thresholds (CD) were significantly elevated (reduced sensibility) on the dorsum of the foot (mean of two feet), in patients [26.0 °C (19.7–28.0)] as compared with healthy subjects [28.6 °C (27.4–29.6) $p = 0.000$]. There were also significantly elevated warmth detection thresholds (WD) in feet in patients 39.5 °C (36.4–42.9) compared to healthy subjects [37.7 °C (36.1–39.4) $p = 0.048$]. However, there were no significant differences in QST values between patients with and without pain.

Conclusions: Of a total of 19 patients with verified HNPP, eight patients (42.1%) suffered from neuropathic pain, mainly in both feet.

Implications: Due to the high percentage of pain in HNPP, it is important not to disregard this diagnosis in a patient presenting with pain. Since there are no significant differences in QST values in patients with and without pain, routine QST studies in HNPP do not seem necessary.

Keywords: hereditary neuropathy with liability to pressure palsies (HNPP); pain; nerve conduction studies; small fiber affection; quantitative sensory testing.

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1 Introduction

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal – dominant hereditary neuropathy

caused by a deficiency in the peripheral protein PMP-22, due to deletion on chromosome 17p11,2 or in some rare cases point mutations in the PMP-22 gene [1–5]. The clinical picture is characterized by recurrent mononeuropathies in nerves which frequently may be exposed to pressure, such as the median, ulnar, radial and peroneal nerves [1–5]. Brachial plexus affection, either as a sole manifestation [5] or in combination with other mononeuropathies [2] may also occur, as well as a polyneuropathy [1, 3]. The prevalence of HNPP is largely unknown. A study from Northern England has estimated a prevalence of 7.3 per 100,000 [6], but is probably underdiagnosed because of its usually benign course [4, 7].

The typical clinical symptoms are sensory abnormalities (paresthesias, numbness) and eventual motor affections (paresis) fitting with innervation territories of the individual nerves in question. Neurophysiological findings are typical for mononeuropathies with entrapment of median, ulnar, radial nerves in the upper-extremity and the peroneal nerve in the lower extremity [1–3] in addition to findings of a generalized polyneuropathy [1, 3].

Although pain is reported to be an unusual clinical symptom [4, 7–9], there are reports of pain in a surprisingly high proportion of these patients [1, 10–12], also in patients with novel frameshift mutation in the exon 3 sequence of the PMP 22 gene [11]. Some studies report single cases, but in an evaluation of 39 patients, pain was reported by six patients [1] and in a study of 32 patients, Yilmaz et al. reported neuropathic pain in 10 (31%) of the patients [10]. Damage to peripheral small nerve fibers has been suggested to be a crucial factor for neuropathic pain [13], but assessment of small nerve function in HNPP has to our knowledge previously not been performed, as also concluded by Yilmaz et al. [10]. The purpose of the present study was to investigate the presence of pain and the possible affection of small nerve-fibers, A-δ and C-fibers, by QST- assessment of thermal thresholds, allowing evaluation of function of afferent sensory temperature-mediating fibers. We also included QSART (quantitative sudomotor axon reflex), a quantitative, validated assessment of efferent post-ganglionic unmyelinated C-sudomotor fibres [14].

2 Methods

2.1 Material

Nineteen patients above 18 years with genetically verified HNPP were included in the study. None of the patients suffered from other diseases likely to induce neuropathy. The study was approved by the Regional Ethical Committee and the patients have signed informed consents.

2.2 Clinical examination

The patients underwent a clinical neurological examination included testing of motor and sensory function, including reflexes. They were asked about the presence of ongoing, paroxysmal and evoked pain, the distribution and intensity of pain (if present).

2.3 Nerve conduction study (NCS)

The patients were examined with a Keypoint Dantec (Skovlunde, Denmark) with measurements of motor amplitude, distal latency and nerve conduction velocity in the median and ulnar nerve in the upper extremity and the peroneal and tibial nerve in the lower extremities. Sensory amplitudes, distal latency as well NCV were established from the median, ulnar, radial, superficial peroneal as well the sural nerves. All values were compared to normal values in the Keypoint equipment.

2.4 Quantitative sensory testing

Threshold temperatures for the sensation of warmth, cold, heat pain and cold pain were determined using a computerized Thermotest (SENSElab, Somedic A/B, Hörby, Sweden) with a thermode size of 5×2.5 cm. Warmth detection threshold (WD), cold detection threshold (CD), heat pain detection threshold (HP) and cold pain detection threshold (CP) were determined from a baseline temperature of 32 °C with a 1 °C/s rate of change. The subjects were instructed to push a signal-button when the relevant sensation was perceived. When this happened or if cut-off temperature (50 °C and 10 °C) was obtained, the temperature returned to baseline. WD, CD, HP, CP were determined from the right thenar eminence (within the innervation territory of the median nerve) and the dorsum of both feet in all patients (within the innervation territory of the peroneal nerve) as well as the lateral part of both legs, below the knee. For calculations of thresholds, an average of five recordings for WD and CD and the average of three recordings for HP and CP were used. The values were compared with values from age- and sex matched healthy individuals. For individual evaluation of thermal thresholds, these were judged pathological when like or above 95 percentile

of normal controls for warmth (41.1 °C) and like or below 25 percentile for cold (26.8 °C).

2.5 QSART

Evoked sweat response at rest from the dorsum of the feet was measured by the Quantitative sudomotor axon reflex tester (WR medical electronics co, Stillwater, OK, USA).

To evoke axon reflex sweating, iontophoresis (2 mA for 5 min) of 10% acetylcholine (ACh) was started after a stable baseline sweating level had been obtained. A commercially available device (Iontophor ll, Life-Tech Inc., Stafford, TX, USA) was used for this purpose. Axon reflex sweat output during the 5 min of iontophoresis and additional 10 min was recorded via a sweat capsule with an area of 0.767 cm^2 attached to the skin of the dorsum of both feet.

Values were compared with normal values form previous investigations of healthy persons.

2.6 Statistics

Non-parametric statistical methods were used (IBM SPSS Statistics 25), the median as a measure of location and the interquartile range as a measure of distribution, except for age where mean (SD) are reported. Mann-Whitney *U* test was used to calculate significant differences between patients and normal controls and between patients with and without pain. Values of $p < 0.05$ were considered statistically significant.

3 Results

3.1 Material

Nineteen patients were included, eight men and 11 women (mean age 40.4, median 41.5). Eleven patients were related, from different families (Table 1). All patients had a verified mutation 17p 11.2 PMP22. Clinical findings and results of neurophysiological testing are presented in Tables 1 and 2.

3.2 Results of clinical findings

A total of 10 patients reported numbness in some extremity, most in the arms. The results of clinical examination revealed reduced sensibility to light touch distally in the legs and to some extension also in the hands in nine patients. Absent or weakened reflexes (at the level of the knee or ankle) were found in four of these patients. The clinical findings were compatible with a clinical polyneuropathy, corresponding to the findings of a more generalized neuropathy on NCS, either pure sensory or combined motor/sensory.

In these 10 patients, NCS (Table 1) showed findings of entrapment of several nerves, predominantly the median and ulnar nerve in the arm, peroneal nerve in one patient as well as a more generalized neuropathy in nine and normal results of NCS in one patient. In three patients who reported a combination of both numbness (arms) as well as pain in the feet, NCS showed findings of a general neuropathy in addition to small fiber affection. NCS also showed abnormalities in four patients with no numbness but with pain.

3.3 Results of nerve conduction studies (NCS)

Results of NCS were missing in two of the patients. In the remaining 17 patients, there were pathological findings as indicated in Table 1, either with findings compatible with entrapment of individual nerves alone (n = 2) or in combination with a more general neuropathy (n = 13). Two patients had only findings of a general polyneuropathy.

Of a total of 15 patients with a general neuropathy (with and without pain), NCS showed sural nerve abnormality (n = 8), or a combined motor/sensory neuropathy (n = 7). Twelve of these patients had elevated thermal thresholds, either with elevated both cold – and warm detection thresholds (n = 7), or only cold detection thresholds (n = 5) (Table 1).

Only two patients had a general large fiber sensory neuropathy with normal temperature detection thresholds.

3.4 Patients with pain and small fiber affection

A total of 8/19 patients suffered from pain, mainly distal pain in both feet (7/8). The pain was described as burning, aching, shooting. Six of the seven patients with pain in feet had a severe damage to small nerve fibers, all with elevated cold detection thresholds, but also four patients with elevated thresholds to warmth (Table 2). One of the seven patients had only borderline cold detection

Table 1: Clinical symptoms and results of NCS, QST and QSART.

Patient	Family	Sympt except pain	Pain	NCS	QST: mean of pathological values from both feet	QSART 0: absent response 1: reduced volume
1	Age: 45	Numb	No	EIN (med + uln bilateral) GSN (red NCV sural)	CD: 18.3 °C	Path (0)
2	Daughter of 3, Sister of 4 Age: 32	Numb (feet)	No	EIN (med + uln) GSN: sural missing	CD: 26.7 °C	Normal
3	Mother of 2 and 4 Age: 53	Numb	No	GMSN (no sural nerve, reduced motor NCV)	WD 41.6 °C CD: 26.5 °C	Path (0)
4	Daughter of 3, sister of 2 Age: 35	Numb	No	EIN (med + uln)	CD: 25.0 °C	Path (0) both feet
5	Sister of 6 Age: 50	No	Yes	GSN (sural,med, uln)	CD: 13.9 °C	Normal
6	Sister of 5 Mother 7 Age: 53	No	Yes	EIN (med + uln) GSN: sural mising	CD: 26.5 °C	Normal
7	Son of 6 Age: 24	Numb Scap alatae	No	Missing	Path one foot: CD: 25.6 °C	Normal
8	No Age: 48	Only sciatica bilat	No	EIN (med + uln) GSN red NCV sural	CD: 21.1 °C WD: 42.0 °C	Normal
9	Son of 10 Age: 29	No	Yes	EIN (med + uln) GSN: red NCV sural	CD < 10 °C WD: 48.7 °C	Normal
10	Father of 9 Brother 11 Age: 63	Numb	No	EIN (med + uln) GMSN: all values mising	CD < 10 °C WD > 50 °C	Normal
11	Brother of 10 Age: 46	Missing	No	EIN (med + uln) GSN red NCV sural	CD 26.3 °C	Normal
12	Son of 13 Age: 24	Numb	No	EIN (uln) GMSN: red NCV	Normal	Path (1) one foot
13	Mother of 12 Age: 55	No	Yes	EIN (med + uln) GSN: sural miising	CD 15.4 °C	Normal
14	Age: 27	No	No	Missing	Normal	Path (1)
15	Age: 35	Parest arms	No	EIN (med + uln) GMSN: red NCV	Normal	Path (0)
16	Age: 31	Numb Drop-foot	Yes	EIN (med + peroneal) GMSN: red NCV	CD 25.9 °C right thenar CD: 25.5 °C WD: 43.0 °C	Missing
17	Age: 37	Numb	Yes	EIN (med + uln) GMSN: red NCV and missing sural	CD: 21.6 °C WD: 44.0 °C	Normal
18	Age: 46	Numb	Yes calves, feet and arms	EIN (med + uln) GMSN: red NCV and Sural missing	CD: 23.9 °C WD: 44.0 °C	Path (0)
19	Age: 22	No	Yes, hands	EIN (radial + peroneal)	Normal	Normal

EIN = entrapment of individual nerve; GSN = general sensory neuropathy legs, sural nerve; GSMN = general sensory and motor neuropathy legs.

thresholds. Four of the patients with pain in the feet had signs of a severe sensory neuropathy on NCV, with no sural nerve findings. Only one of the patients had signs compatible with an entrapment of the peroneal nerve. One patient with only pain in the arms, had only minor changes on NCS and normal QST-values. Mean age of patients with pain was 40.4 years (SD 12, 3) at the time of investigation. We have not sufficient information as to conclude on the start of painful symptoms.

When comparing QST values between patients with pain and patients without pain, there were no significant difference at group levels (Table 3).

Table 2: Characteristics of pain.

Patient (from Table 1) and age	Pain	Location of pain	NCS/QST
5, Female Age: 50	Ongoing burning and aching	Both feet	NCS: absent sural QST: CD 13.9 °C
9, Male Age: 29	Deep aching	Started in feet with proximal spreading to thighs	NCS: normal sural QST: CD < 10 WD: 48.7 °C
6, Female Age: 53	Deep aching pain	Feet and calves	NCS: absent sural QST: CD 26.5 °C
13, Female Age: 55	Deep aching pain	Dorsum of feet	NCS: absent sural QST: CD 15.4 °C
16: Female Age: 31	Burning	Feet and calves	NCS: normal sural QST: CD 25.5 °C WD: 43.0 °C
17, Female Age: 37	Intermittent shooting	Feet and calves	NCS: reduced NCV sural QST: CD 21.6 °C WD: 44.0 °C
18, Male Age: 46	Aching pain Deep stinging	Feet and calves arms	NCS: absent sural QST: CD 23.9 °C WD: 42.3 °C
19, Female Age: 22	Deep aching, burning	Both palms	Normal NCS and QST arms

Table 3: Comparison of QST dorsum of feet in patients with pain compared to pain without pain.

	Patients – pain	Patients – no pain
WD foot	41.2 (38.7–43.8)	38.4 (35.7–41.7) non sign
CD foot	22.8 (14.3–26.3)	27.1 (24.1–28.5) non sign
HP foot	47.4 (46.2–48.8)	46.1 (43.9–47.9) non sign
CP foot	10.0 (10.0–16.3)	13.8 (10.0–17.3) non sign

Values in °C, median and interquartile range.

3.5 QST values of patients compared to healthy subjects

Cold detection thresholds (CD) were significantly elevated (reduced sensibility) on the dorsum of the foot (mean of two feet), in patients [26.0 °C (19.7–28.0)] as compared with healthy subjects [28.6 °C (27.4–29.6) $p = 0.000$]. Warm detection thresholds were also elevated in patients [39.5 °C (36.4–42.9)] as compared with healthy subjects [37.7 °C (36.1–39.4)] $p = 0.048$. Also warmth detection threshold in the hand was elevated in patients [34.7 °C (33.9–35.3)] as compared to healthy subjects [33.9 °C (33.3–34.4) ($p = 0.013$)]. Cold pain threshold was also reduced (higher temperature) on the thenar eminence in patients 15.5 (11.8–16.8) compared to heathy subjects [10.0 (10.0–12.5) ($p = 0.001$)] compatible with a relative cold allodynia in the patients. There were no significant differences in other thresholds (Table 4).

Table 4: Comparison of QST in patients with HNPP compared to healthy subjects.

	Patients	Healthy subjects
Wd hand	34.7 (33.9–35.3)	33.9 (33.3–34.4) $p = 0.013$
Cd hand	30.1 (28.1–30.6)	30.4 (29.0–34.4) non sign
Hp hand	44.2 (42.0–48.0)	42.3 (41.0–47.5) non sign
Cp hand	15.5 (11.8–16.8)	10.0 (10.0–10.0) $p = 0.001$
Wd foot	39.5 (36.4–42.9)	37.7 (36.1–39.4) $p = 0.048$
Cd foot	26.0 (19.7–28.0)	28.6 (27.4–29.6) $p = 0.000$
Hp foot	47.2 (44.7–47.9)	46.7 (44.0–43.9) non sign
Cp foot	10.0 (10.0–15.6)	10.0 (10.0–12.5) non sign

Values in °C, median and interquartile range (25–75). Values in feet are mean of two feet.

3.6 QST-changes related to entrapment of individual nerves

QST was performed on the thenar eminence, within the innervation of the median nerve, and on the dorsum of the feet, within the innervation territory of the peroneal nerve. A total of 14 patients had NCS findings showing affection of the median nerve (only sensory for some patients, but combined motor and sensory in most patients), but only four of these patients had pathological QST values, two patients with elevated cold detection thresholds, one patient with borderline cold detection threshold, and one patient with elevated warmth detection threshold.

Several patients had NCS findings of peroneal nerve affection (in a general neuropathy), but only one patient had a verified entrapment of the peroneal nerve at the level of the knee (Table 1).

3.7 The effect of age

Comparing patients with and without pain, the mean age was [40.4 (SD 12.33)] in patients with pain and [39.2 (SD 12.7)] in patients without pain, but the difference was not significant ($p = 0.78$).

3.8 Autonomic findings

Seven patients had reduced QSART volumes from the dorsum of the feet, absent responses in five patients, reduced on the dorsum of the feet in one patient, and only reduced on one foot in one patient indicative of a damage of autonomic efferent sudomotor small unmyelinated C-fibers. Five of these patients had a general motor-sensory polyneuropathy. In one patient NCS was missing and in one of the patients with absent response, NCS was normal. Only two of these patients had elevated thermal thresholds on both feet. Only one patient with absent response and elevated thermal thresholds suffered from pain. There were no report of abnormal or reduced sweating.

4 Discussion

The main result of the present study was the report of pain in 8/19 (42.1%) patients with a genetically verified HNPP. The pain was described as burning, shooting and aching, all frequent qualities of neuropathic pain, and with a distribution as in a length-dependent polyneuropathy, involving both feet and with a proximal spreading in seven patients. Four of these patients had a general neuropathy as verified by nerve conduction studies and five had a severe small fiber affection, while two had a moderate/slight small fiber pathology. Cold detection thresholds (presumed to reflect A δ fiber function) were elevated in all of these patients, while elevation of warmth detection thresholds (presumed to reflect C-fiber function) was found in four of seven patients. One patient had pain in hands only. Although the material is small (19 patients, but still considerable for a rare disease such as HNPP), the presence of pain in 42.1% of patients indicates, that contrary to previous belief, pain is not uncommon in HNPP. This is in accordance with findings of Yilmaz et al. [10], with 10/32 (31%) reporting pure neuropathic pain.

The patients complaining about pain were above 40 years old, indicating that pain is a relatively late symptom. This is also in accordance with the findings of Yilmaz et al. [10], finding the mean age at pain onset later than the general onset of symptoms (35.3 years vs. 22.5 years). In their study, pain was localised to arms and or legs in seven patients, while three patients complained about pain at compression sites, while we demonstrate pain mainly in the feet corresponding to a general neuropathy. Symptoms in HNPP usually appear in the third decade [15].

Yilmaz et al. [10] suggest small fiber testing in these patients, but have not tested for small fiber function themselves. The present study shows that patients do have a significant both A δ fiber and C fiber affection, as shown by elevated thresholds to cold and warmth, compared to healthy subjects, but there was no significant difference in QST values in the feet when comparing patients with pain and patients without pain. We may therefore not conclude that the pain may be due to the finding of small-fiber dysfunction. This is in accordance with other studies on QST-results in patients with and without pain, both in patients with peripheral nerve damage [16] and also polyneuropathy [17, 18].

This implies that the finding of elevated thresholds by QST may be a relevant finding of degeneration of small afferent nerve fibers, by may not reflect the mechanisms of neuropathic pain, which rather may be linked to spontaneous firing of nociceptive C-fibres and predominantly the so called mechano- and heat insensitive nerve fiber [19], fibers which may not be evaluated by routine small-fiber testing such as QST. Consequently, we may not fully explain the pain experienced by these patients by performing QST, but conclude that there is an involvement of small fiber damage, involving mainly the cold-mediating A δ fibers as compared with healthy subjects, but also the warmth-mediating C fibers. Also, since mechanisms of pain are associated with neurophysiological alteration of subgroups of afferent C-nociceptive fibers and not the A δ fibers, the finding of elevated cold detection thresholds may obviously not be related to the pain. The finding of elevated warmth detection thresholds would only indicate degeneration of small unmyelinated C-fibers and not explain the pain in the patients [20].

Pain is in this material largely part of a general neuropathy (large and/or small fibers) and not due to

entrapment of individual nerves. Since pain is not traditionally thought to be associated with HNPP [7, 9], and since pain in some cases may precede the more classical symptoms, pain may delay the diagnosis of HNPP [21].

NCS-findings of a general neuropathy was present in a large majority of the patients, with and without pain (n = 15). Since a general neuropathy involving the large myelinated nerve fibers, often also show pathological results from testing of small nerve fibers [22, 23], small fiber affection is not a surprising finding. However, in a general neuropathy or a pure SFN, both A-δ fibers as well as C-fibers are normally affected. Although C-fibers are affected in the present material, as compared to healthy subjects, cold detection thresholds are elevated in a larger number of patients than warmth detection thresholds. Mechanisms of a predominantly A-δ fiber involvement is not known.

It is of interest to note that similar findings have been reported in another cohort of patients with polyneuropathy, CMT-1 also with a genetically similar disorder 17p11.2 (PMP22) [24]. In spite of CMT-1 being a demyelinating neuropathy, presumably only affecting the large myelinated nerve fibers, a small fiber affection was demonstrated in 12% of the patients, and elevated CDT in as many as 53% of the patients. As in the present study, there was a significantly higher occurrence of pain in patients above 40 years and, mainly localized in the feet. Other studies have also demonstrated small fiber involvement in CMT 1 A patients [25], while others did not find any pathological findings [26].

In addition to the finding of an affection of afferent A δ fibers, we also report a damage to efferent autonomic sudomotor C-nerve fibers which was demonstrated in seven patients, all with a severe general neuropathy, but only two with elevated QST-values, indicating that small nerve fibers may be affected separately. There were no reports of abnormal or reduced sweating.

In conclusion, pain is not uncommon in HNPP, more due to a general neuropathy than caused by entrapment of individual nerves. The finding of elevated thresholds to cold and warmth in the feet indicate degeneration also of small nerve fibers, but may not explain the pain of the patients, since there is no significant difference in QST thresholds in patients with and without pain, and pain mechanisms such as spontaneous activity in afferent primarily heat – and mechano insensitive C-fibers may not be evaluated by QST. Routine QST investigation of the patients does not seem necessary. It is however important to be aware that pain may be present also in HNPP, not risking a lack of correct diagnosis in these patients.

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