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Hereditary neuropathy with liability to pressure palsy

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Abstract

Hereditary neuropathy with liability to pressure palsy (HNPP) is an autosomal dominant disease with sensory and motor nerve palsies usually precipitated by trivial trauma or compression. In the majority of cases HNPP is caused by deletion of the peripheral myelin protein 22 gene (PMP22) on chromosome 17p11.2. The authors present a family case with genetically proven HNPP.

Key words: *hereditary neuropathy with liability to pressure palsy, children, PMP 22 gene, electrophysiological features*

Introduction

Hereditary neuropathy with liability to pressure palsy (HNPP, MIM #162500) is an autosomal dominant disease with recurrent sensory and motor nerve palsies usually precipitated by trivial trauma or compression [6,8,18]. In the majority of cases HNPP is caused by deletion of the peripheral myelin protein 22 gene (*PMP22*) on chromosome 17p11.2 [6,8,9,13]. The relationship of HNPP to the *PMP22* gene on chromosome 17p11.2 was demonstrated in 1993 [16]. As for today it is the only gene known to be associated with HNPP, although mutations in the *PMP22* gene are also the cause of Charcot-Marie--Tooth Neuropathy Type 1A (CMT1A) [6,19]. Since the breakpoints in HNPP and CMT1A map to the same intervals in 17p11.2, these genetic disorders may be the result of reciprocal products of unequal crossover, resulting in deletion in HNPP or duplication in CMT1A [9,19].

Molecular genetic testing detects a contiguous gene deletion in about 80% of affected individuals. The remaining 20% have a variety of point mutations in *PMP22* that may lead to *frameshifts* or other functional changes in the protein [6,9].

Direct implication of *PMP22* in the pathogenesis of HNPP is unknown. The prevalence of HNPP, known as 2–5 in 100,000 (European study) or 16 in 100,000 (population study of southwestern Finland) seems to be underestimated [17].

In the first report of HNPP in 1947 de Jong described a family with recurrent peroneal neuropathy after prolonged kneeling. Usually all symptomatic patients present with typical HNPP symptoms such as sensor and motor deficits in the nerves liable to compression. The first symptoms occur more frequently in the second or third decade of life. The clinical course varies in severity even within one family. According to the literature the

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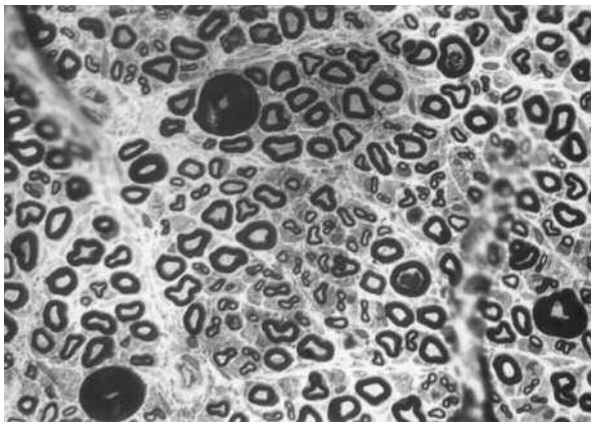

Fig. 1. Transverse section of the peripheral nerve. Single fibre with thickened myelin sheath (Pal--Kulczycki staining, magnification bar 300x)

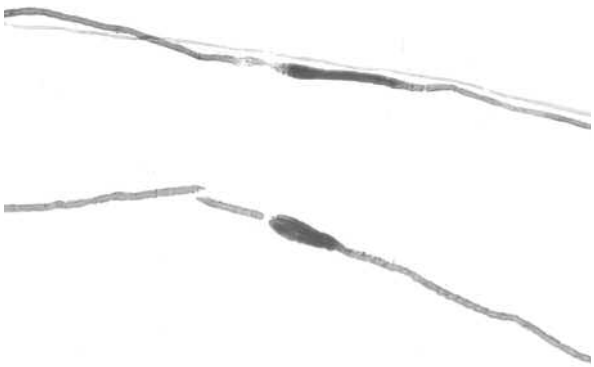

Fig. 2. Teased fibre preparation showing segmental thickening of the myelin sheath (magnification bar 180x)

nerves in HNPP are more susceptible to compression (for example median nerve at the wrist, peroneal nerve at the fibular head or ulnar nerve at the elbow) which is probably caused by reduction of *PMP22* in the Schwann cells [6,11,18,20].

Electrophysiological examination with conduction slowing at entrapment sites has become a reliable tool in diagnostics of patients suspected of having HNPP [1,5,6,14,22]. Nerve biopsy reveals the typical focal myelin sheath thickening (sausage-like) referred to as "tomaculae". The other neuropathological changes include "onion-bulb" formations and axonal degeneration [23].

Case report

A 13-year-old girl, the third child of unrelated parents. She was born from normal pregnancy, at term by vaginal delivery with birth weight of 3150 g and Apgar score of 10 points. First symptoms appeared at the age of 12 years. The patient presented with a 3-month history of painful paresthesias (numbness, sensory loss) of the fourth and fifth fingers of the left upper limb not precipitated by compression or trauma. The sensory phenomena were connected with cooling and cyanosis of these fingers.

Physical examination did not show abnormalities. In neurological evaluation sensory loss of the fifth finger and ulnar surface of the fourth finger of the left upper limb and reduced muscle strength of the abductor digiti minimi (4-according to Lovett's scale) were observed. IQ was 97. MRI of the head and cervical part of the spine did not reveal abnormalities involving CNS structures. EEG, X-ray of the craniocervical border and the bones of the left forearm were normal.

ENG study showed slowing of the nerve conduction velocity in the sensory fibres of the median (right median nerve – 32.6 m/s, left median nerve – 34.6 m/s, normal values >50 m/s) nerves bilaterally and left ulnar nerve (35.4 m/s), lowering of the amplitude with slowing of conduction velocity in the left sural nerve (0.04 μV; 30.8m/s), lowering of the amplitude of the peroneal nerves bilaterally (left peroneal nerve – 1.6 μV, right peroneal nerve – 1.8 μV). EMG (m.abductor digiti minimi) displayed denervation with regeneration.

Cerebrospinal fluid examination yielded normal results except for slightly elevated protein level (46.5 mg%). Visual and brainstem auditory evoked potentials were correct. Somatosensory evoked potentials (SSEP) revealed prolonged latency of N13 and slight interlatency.

Ultrasonography of the intracranial and extracranial vessels showed increased blood flow in the left median artery, more likely on the vasoconstrictive basis. Capilaroscopy of the left hand was normal. We excluded other possible aetiologies of neuropathy, connective tissue disorder, multiple sclerosis and boreliosis.

The patient underwent sural nerve biopsy. On the transverse and longitudinal section stained with haematoxylin-eosin (H-E) no signs of inflammatory, vascular changes or storage were seen. Also connective tissue proliferation was not found. On transverse section with Pal-Kulczycki staining the myelinated fibre count was within normal values. No morphological

features of segment demyelination were observed. Single fibres had thickened myelin sheath.

Teased fibre preparations showed the focal thickening of the myelin sheath. Electron microscopy examination did not reveal axonal degeneration.

Molecular analysis (set of 17 microsatellite markers – method described at Seeman P et al. Int J Mol 2000) revealed the typical HNPP deletion. The same mutation was identified in the patient's father (0.93 Mb), which is consistent with autosomal dominant mode of inheritance.

The mother of the patient was free of HNPP symptoms and her clinical, neurological and electrophysiological evaluation was normal. The father suffered from painless paresthesias and pes cavus on the right side. His electrophysiological examination revealed decreased conduction velocity in the right peroneal nerve (36 m/s). EMG (right extensor digiti brevis) showed denervation.

Discussion

Hereditary neuropathy with liability to pressure palsies (HNPP) is associated with deletion of the peripheral myelin protein 22 (*PMP22*). Probably *PMP22* is involved in cellular growth regulation. The genetic defect can be found in about 80% of affected individuals [6,8,9,20,21]. The same 1.5-megabase (Mb) interval is duplicated in Charcot-Marie-Tooth disease type 1A (CMT1A). It is worth noting that based on the clinical picture patients with HNPP could be misdiagnosed as being affected with CMT1A [19].

HNPP is characterized by recurrent sensory and motor nerve palsies usually precipitated by minor trauma or compression with electrophysiological abnormalities at anatomic sites of nerve entrapment (wrists, elbows, knees). The onset of the disease is acute and painless (85% of cases). Progressive weakness may also be present. Tendon reflexes may be diminished (15–30%) or absent (such as absent ankle reflexes in 50–80%); sometimes pes cavus (20–40%) or skeletal abnormalities may appear [6,8,9,11,13,18,20,22].

Typical symptoms in the form of focal mononeuropathy (sensorimotor demyelinating neuropathy) may concern the median nerve causing carpal tunnel syndrome (90% of HNPP patients), the peroneal nerve causing foot drop, the ulnar nerve producing hypothenar and interossei muscle weakness and atrophy with sensory loss of the lateral part of the hand, the brachial plexus and radial nerve with transient sensory symptoms and hand pain [5,10]. Recovery from these episodes is complete at first and may progress to partial recovery.

According to Mounton et al., besides the typical pictures of HNPP also other phenotypes are possible such as: recurrent positional short-term sensory symptoms, progressive mononeuropathy, Charcot--Marie-Tooth disease-like polyneuropathy, chronic sensory neuropathy, chronic inflammatory demyelinating polyneuropathy-like, recurrent subacute polyneuropathy [18]. There are also asymptomatic patients. A very interesting analysis performed by Pareyson et al. proved the phenotypic heterogeneity in HNPP [20]. Two thirds of the 39 studied cases experienced episodes of acute mononeuropathy (involving upper limbs or brachial plexus, less frequently the peroneal nerve), 41% were unaware of their disease (mild and sporadic paresthesias), 24% were asymptomatic; in one third chronic symptoms (cramps, paresthesias, exercise-induced myalgias, muscle weakness) were observed and four older patients complained of polyneuropathy.

The great variability of symptoms in HNPP explains other findings reported in a few patients: proximal muscle atrophy and severe respiratory insufficiency, hypoglossal nerve paralysis, motor brachial paralysis, lesions of the CNS white matter [2–4,7,12,15,21,24]. In the latter case MRI images displayed bilateral periventricular, frontal and parietal white matter areas of high signal intensity consistent with demyelination or subcortical vascular encephalopathy [4].

The electrophysiological profile of our patient is that of sensorimotor demyelinating polyneuropathy with conduction abnormalities preferentially localized at common entrapment sites and distal nerve segments. On clinical and laboratory grounds we excluded known causes of peripheral nerve disorders.

The electrophysiological abnormalities observed in HNPP patients seem to be unrelated to clinical severity and may be found in clinically unaffected nerves [1]. The key electrophysiological criteria described by Gouider et al. include: bilateral slowing of sensory and motor median nerve conduction at the carpal tunnel with at least one abnormal parameter for motor conduction in one peroneal nerve [6]. Most studies have shown distal slowing. Probably frequent traumas lead to axonal damage secondarily to myelin abnormalities. A study performed by Li et al. disclosed the unique electrophysiological presentation

in HNPP [14]. This pattern consists of prolonged distal motor latencies (DML) in the median and peroneal nerves and with minimal or absent DML in the ulnar and tibial nerves. Infante et al. found it necessary to evaluate the sensory conduction study in the sural nerve and motor conduction in at least two nerves at the entrapment sites [13,14].

The pathologic examinations of biopsied nerves show diffuse sausage-like swellings in the nerve fibres referred to as "tomacula" [20,22,23]. Tomaculae are characteristic of HNPP but are not specific. They may be observed in Charcot-Marie-Tooth disease type 1, neuropathies associated with IgM paraproteinaemia and anti-MAG activity, and sporadically in chronic inflammatory demyelinating polyneuropathy [12,23]. The typical myelin thickenings were also observed in our patient.

Nowadays nerve biopsy has been replaced by molecular genetic testing, although it is still valid in nondeleted patients with characteristic electrophysiological changes.

The history of neuropathy without any triggering factor, nerve conduction abnormalities, and presence of "tomacula" in numerous fibres at nerve biopsy allow the clinician to suspect HNPP. Many relatives are clinically free of symptoms and they were demonstrated to be HNPP affected only by electrophysiological and molecular studies. That is especially important because due to the benign course of neuropathy and the great heterogeneity of clinical symptoms many cases remain still unrecognized or misdiagnosed.

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