

# Hereditary Neuropathy with Liability to Pressure Palsies

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## Abstract

*Hereditary neuropathy with liability to pressure palsies (HNPP) is a focal and recurrent hereditary motor and sensory neuropathy inherited as an autosomal dominant trait. First symptoms appear rarely before the age of 20 years. This disorder is characterized by acute episodes of weakness and paresthesia arising in a defined territory of a nerve trunk. These attacks, which often occur after minor injury or prolonged nerve compression, often regress but have the tendency to relapse, either in the same or in a different nerve. Paralysis can remain permanent. The electrophysiological manifestations consist of prolonged distal motor latencies and slowed conduction velocities at usual sites of nerve compression. Sausage-shaped swellings of the myelin sheath (tomacula) are characteristically found on nerve biopsy. In 80% of cases, the genetic anomaly is a 1.5 Mb deletion in chromosomal region 17p11.2 including the PMP22 gene. The deleted region is identical to the region duplicated in Charcot-Marie-Tooth disease type 1a (CMT1A). The identification of this deletion confirms the diagnosis. Point mutations within the PMP22 gene have been identified in rare HNPP cases. Treatment is symptomatic and is aimed at preventing nerve compression.*

## Keywords

Hereditary neuropathy with liability to pressure palsies, HNPP, tomaculous neuropathy, PMP22.

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## Name of disease and synonyms

Hereditary neuropathy with liability to pressure palsies, HNPP, tomaculous neuropathy.

## Name of excluded diseases

Other diseases causing recurrent episodes of nerve paralysis.

## Diagnostic criteria/Definition

HNPP is a special form of hereditary motor and sensory neuropathies (HMSN) and is inherited as an autosomal dominant trait. This disorder is characterized by transient and recurrent episodes of nerve paralysis and/or brachial

paralysis. The diagnosis is based on the association of:

- clinical signs: recurrent episodes of painless, acute-onset nerve paralysis, manifesting with weakness and paresthesia;
- electrophysiological signs: diffuse polyneuropathy with prolongation of distal motor latencies and non-uniform slowing of conduction velocities at usual sites of nerve compression;
- histopathological signs: sausage-shaped swellings of the myelin sheath (tomacula) revealed by nerve biopsy (currently, a nerve biopsy is not indicated as a diagnostic tool);
- and/or molecular alterations: chromosomal deletion at 17p11.2 containing the *PMP22* gene or point mutation in the *PMP22* gene.

A family history correlating with an autosomal dominant transmission is in favor of the diagnosis. If the family history is negative, a probable diagnosis can be made on the basis of characteristic electrophysiological signs and confirmed by detection of the deletion at the molecular-genetic level.

#### Differential diagnosis

HNPP is often not recognized. Unexplained acute onset of nerve paralysis is suggestive of the diagnosis and should prompt the search by taking a detailed history for previous events or familial antecedents. An electrophysiological investigation should also be carried out to confirm or refute the diagnosis.

In case of brachial paralysis, the absence of pain preceding the paralysis enables the differentiation from Hereditary Plexus Brachialis Neuropathy which has a different genotype than HNPP, or from Acute Brachial Plexus Neuropathy.

Acute onset and localized features distinguish HNPP from slowly progressive HMSN, although sometimes HNPP is clinically undistinguishable from chronic HMSN, showing symmetrical weakness and sensory disturbances of the lower legs and fore arms.

#### Incidence

The incidence is unknown. No figure is reported in the literature.

#### Clinical description

First symptoms occur rarely before the age of 20 years (range 8-64 years). This disorder is characterized by acute-onset and recurrent episodes of nerve paralysis, manifesting with weakness and paresthesia ('tingling') or hypo-aesthesia ('dull sensation'). Some patients who are carrier of the gene remain without symptoms.

The most commonly affected nerve trunks include the peroneal nerve by compression against the head of the fibula (squatting, sitting with legs crossed), the ulnar nerve by prolonged resting on the elbow, and the radial nerve by compression in the spiral groove half way the upper arm (prolonged sitting with an arm around a person). The brachial plexus is also frequently affected. It is painless, in contrast to Hereditary Plexus Brachialis Neuropathy and Acute Brachial Plexus Neuropathy. Other nerve trunks may be affected after prolonged use of a tool, or intense or unusual sport activity. Although HNPP may present as carpal tunnel syndrome, it is not a major cause. Rarely, involvement of the facial nerve (weakness of the facial muscles) or recurrent laryngeal nerve (weakness of the vocal cord: hoarseness) may occur.

These episodes often occur after minor injury or prolonged nerve compression (e.g. squatting). The manifestations (i.e., weakness and sensory disturbances), often regress over days to months, but have the tendency to relapse, involving the same or a different nerve. Repeated episodes in the same nerve territory can cause permanent weakness or loss of sensation. In some patients the repeated nerve injuries lead to generalized polyneuropathy, although some patients have no clear history of previous episodes of nerve paralysis. Associated features include pes cavus (hollow feet) and scoliosis in a proportion of patients.

#### Management including treatments

There is no cure for HNPP. Management of persistent paralysis is based on physiotherapy in order to avoid muscle retractions and referral to rehabilitation medicine in case of disabilities (e.g. ankle-foot orthoses if there is severe foot drop, splints to overcome wrist extensor weakness). The patients should be cautioned against prolonged static positions, in particular work-related, and the use of compressive plaster casts for fractures.

#### Etiology

HNPP is due to defective synthesis of PMP22 protein (peripheral myelin protein 22), caused in 90% of the cases by a 1.5 Mb deletion of region 17p11.2 including the *PMP22* gene. The deleted region is identical to the region duplicated in [Charcot-Marie-Tooth disease type 1a \(CMT1A\)](#). These duplication/deletion within the same genomic sequence are caused by an unequal crossing over promoted by the presence of highly homologous sequences, the CMT1A-REP, that flank the locus disease. Point mutations within *PMP22* gene have been identified in rare HNPP cases.

## Diagnosis

Diagnosis includes taking of the (family) history, electrophysiologic investigation and molecular-genetic analysis. EMG abnormalities are suggestive of the diagnosis, but not sufficient, unless there is a positive family history. The molecular-genetic diagnosis is based on the identification of the deletion in region 17p11.2 including *PMP22*. The deletion is detected in Southern-blot analysis of DNA that is double digested with *EcoRI* and *SacI* and hybridized with a probe specific to CMT1A-REP p57.8: in 75% of patients carrying the deletion, a 7.8 kb junction fragment is present, whereas 2 bands, of 5 and 6 kb respectively, showing different dosage (copy number) can be seen in the 25% of remaining cases. These rearrangements in the CMT1A-REP sequences provide evidence for unequal recombination. These results are confirmed by hybridizing the same Southern blot with the probe VAW405 (specific to the deleted region) and a control probe, SF85, which localizes to chromosome 21; the observation of a dosage 1/2 confirms the presence of the deletion. When the deletion is absent, sequencing can be performed to identify a point mutation within the *PMP22* gene.

## Genetic counseling

HNPP is inherited in an autosomal dominant manner. Each affected individual is at 50% risk of transmitting the mutation to each of his children, whatever their gender. In about one-third of the patients there is no family history. The manifestation of the disorder is very variable within the same family. Some individuals carrying the *PMP22* deletion show no symptoms. On the other hand, the EMG always shows abnormalities in individuals carrying the deletion.

## Prenatal diagnosis

Prenatal diagnosis is usually not asked for in this rather benign disease.

## Unresolved questions

The function of *PMP22* is not known, and therefore the exact mechanism that causes the disease is as yet unexplained.

Deletion or point mutations are not found in 10% of HNPP cases fulfilling the clinical, electrophysiological and histopathological disease criteria. These cases could be caused by mutations arising in sequences regulating *PMP22* or due to anomalies in other gene(s) encoding protein(s) that interfere with *PMP22*.

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