Central Nervous System Involvement in Hereditary Neuropathy With Liability to Pressure Palsies

Description of a Large Family With This Association

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Objective: To describe a large family with hereditary neuropathy with liability to pressure palsies associated with central nervous system demyelination.

Design: We examined the 18 members of a pedigree. Genetic analysis was performed on 15 subjects, standard nerve conduction studies on 10 subjects, and brain magnetic resonance imaging studies on 8 subjects.

Results: Hereditary neuropathy with liability to pressure palsies was confirmed in 9 patients of the pedigree. Brain magnetic resonance imaging findings showed multiple areas of demyelination in 6 of 6 affected members and were normal in 2 of 2 healthy relatives. Magnetic resonance imaging abnormalities were predominantly located in the subcortical frontal white matter. All patients had acute and recurrent nerve palsies, while clinical features of central nervous system involvement were not a characteristic of this pedigree.

Conclusions: We demonstrate that this association, previously reported in sporadic cases, is not coincidental. Therefore, patients with hereditary neuropathy with liability to pressure palsies can present central nervous system white matter lesions, and the role of the PMP22 (peripheral myelin protein 22) gene deletion in the central nervous system should be further studied.

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HEREDITARY NEUROPATHY with liability to pressure palsies (HNPP) is an autosomal dominant disorder typically presenting as acute recurrent nerve palsies.

Most HNPP families have a 1.5-megabase deletion on chromosome 17p11.2, an area that contains the PMP22 (peripheral myelin protein 22) gene; PMP22 is an integral membrane glycoprotein of uncertain function. It is mainly localized in the compact part of peripheral myelin. Its expression in central nervous system (CNS) myelin has not been clearly established, although it has been described in rat and mouse brain and spinal cord motor neurons.

Central nervous system involvement has previously been reported in several isolated patients, suggesting an association between central demyelinating lesions and HNPP.

We describe a large family with HNPP caused by a 17p11.2 deletion, demonstrating that the association is not fortuitous.

METHODS

SUBJECTS

We describe 18 members of a family (Figure 1). In all subjects, a standardized neurological examination was performed. Fifteen subjects gave their informed consent for genetic analysis.

ELECTROPHYSIOLOGICAL STUDIES

Nerve conduction studies were performed on 6 patients and 4 healthy relatives. Distal motor latency, motor conduction velocity, and sensory nerve action potentials were recorded for the median, ulnar, and fibular nerves. Normal values from our laboratory and those from another laboratory were used.

DNA STUDIES

Molecular diagnosis of HNPP was performed using polymerase chain reaction amplification of 3 new, highly polymorphic, short tandem repeats covering 0.53 megabase in the center of the Charcot-Marie-Tooth type 1A–duplicated region, including the PMP22 sequence, as previously described.
Cranial magnetic resonance imaging (MRI) was performed using a 0.5-T magnet with a head coil in 8 subjects, 6 patients and 2 healthy relatives with a confirmed genetic study. Imaging sequences consisted of the following: (1) T1-weighted spin-echo sequence in the sagittal and axial planes (repetition time/echo time, 490/25 milliseconds), (2) axial T2-weighted spin-echo sequence (repetition time/echo time, 2450/25.90 milliseconds), and (3) sagittal and axial fluid-attenuated inversion recovery images (repetition time/echo time, 6950/120 milliseconds).

**RESULTS**

**PHENOTYPE**

The proband (III:1) was referred at the age of 24 years for investigation into the cause of an abnormal MRI. The neuroradiological study was performed because she complained of acute right arm weakness and because a cousin (III:4) with similar neurological symptoms was diagnosed as having possible multiple sclerosis (MS). She had experienced recurrent episodes of weakness and/or sensory symptoms in the upper and lower extremities since childhood. The episodes resolved within 1 to 4 weeks and could be related to mononeuropathies. The neurological examination findings were normal, except for right radial hypoesthesia. Signs of generalized neuropathy or CNS pathological features were carefully excluded. Visual, brainstem auditory, and somatosensory-evoked potentials showed no abnormalities. Fluid-attenuated inversion recovery and T2-weighted MRI clearly revealed several foci of a high-intensity signal in the supratentorial white matter, predominantly in the corticomedullary junction (Figure 2C).

Nerve conduction studies demonstrated prolonged distal latencies of the motor nerves and focal motor conduction velocity slowing at the wrist in the median nerve, while study results were normal in the ulnar or fibular nerves across the usual entrapment sites. Sensory potentials could not be elicited in the fibular nerve, but they were of normal amplitude in the median and ulnar nerves. Genetic study confirmed the deletion on chromosome 17p11.2.

**FAMILY MEMBERS**

Clinical and/or electrophysiological studies confirmed the neuropathy in 8 other members of the family in addition to our proband (Figure 1).

Clinical features were similar in all these patients. They complained of episodes of sensory disturbance and/or weakness, which developed suddenly and resolved within several days or weeks. In all patients, the onset of the disease occurred between the second and the third decade of life.

Central nervous system involvement was investigated in all subjects. When she was 27 years of age, patient II:3 complained of right hemiparesis, with complete recovery in 2 weeks (the episode was not monitored by a physician). A second episode, of left hemiparesis and hypoesthesia, occurred when she was 48 years of age. The initial diagnosis was of a probable lacunar infarct because she had a long-standing history of untreated arterial hypertension. She recovered, and her neurological examination findings are normal. Another patient, III:4, had previously been diagnosed as having possible MS when she was 25 years of age, because of punctuate lesions in the supratentorial white matter revealed by MRI after an episode of weakness and paresthesia of the left
arm, with complete remission after several weeks. Before and after the episode motivating the brain MRI, she complained of several episodes of mononeuropathies. Her neurological examination showed no central involvement and the evoked potentials were normal. In summary, the patient did not fulfill the criteria for MS.12

GENETIC ANALYSIS

Genetic study of 15 subjects of the pedigree established the association with the 17p11.2 deletion in all the symptomatic members in whom the study was performed (6 patients). Genetic analysis was not performed in patients II:1, II:7, and II:8 with clinical involvement and electrophysiological confirmation (Figure 1).

ELECTROPHYSIOLOGICAL STUDIES

Ten members of the family were studied, and the results in the 4 nonsymptomatic relatives were normal. In the 6 patients with confirmed deletion of 17p11.2, the studies showed prolongation of distal motor latencies and abnormal sensory nerve conduction as the most prominent features.

MAGNETIC RESONANCE IMAGING

The MRI performed on 6 patients with a deletion of PMP22 showed bilateral supratentorial multifocal lesions in the subcortical white matter in all of them (Figure 2). These hyperintense signals were predominant in the frontal areas. Apparently, the number of lesions did not correlate with the age of the individuals because some members of the second generation presented fewer lesions than members from the third generation, and vice versa. Furthermore, in one patient, the MRI was repeated after 4 years, and the number of lesions remained the same. The results of MRI were normal (not shown) in the only 2 members of the pedigree (III:2 and III:7) who accepted the neuroradiological study and had normal genetic study results and no clinical history of peripheral nerve involvement.

COMMENT

To our knowledge, we describe the first family with HNPP caused by a 17p11.2 deletion in which the affected members present peripheral involvement and CNS demyelination. This association, corroborated by the absence of lesions in the brain MRI of unaffected family members, indicates that the PMP22 deletion may affect myelin not only in the peripheral nervous system but also in the CNS. Of clinical relevance, sensory symptoms and an abnormal MRI result could evoke the diagnosis of MS; this happened in one of our young patients.

Clinically, the disease corresponds to the classic form, with liability to pressure palsy. None of our patients developed generalized polyneuropathy. The results of electrophysiological tests were in agreement with those of previous studies.13 Central nervous system lesions were silent in most of our patients. The patient with clinical CNS involvement had 2 episodes of hemiparesis; however, we cannot prove if this was due to the mutation in the PMP22 gene or to ischemic episodes due to a history of arterial hypertension. The functional outcome of this family over the years is similar to that seen in most HNPP patients, and the CNS involvement has caused no functional involvement in any of the members of the different generations of this family. Furthermore, the number of multifocal areas of increased signal was no larger in patients of the second generation than in those of the third.

This family confirms previously reported isolated cases of HNPP associated with CNS involvement.6-8 However, in these patients, some clinical symptoms, signs, or pathological test results could be attributed to CNS involvement. Speculating on the pathophysiological mechanism(s) involved in these CNS signs and symptoms is difficult. No brain autopsy description is available from patients with HNPP and, unfortunately, no pathological substrate is available from pmp22 0/0 or 0/+ mice.15,19 In fact, in the peripheral nerves, tomaculous structures are diffusely distributed in the nerve fibers and the mechanism(s) involved in the multifocal clinical and electrophysiological findings are not fully understood.

Of clinical interest is that one patient in our family had been diagnosed as having possible MS. Although isolated cases of definite MS in association with some inherited neuropathies, including HNPP, have been reported,10-18 we consider that MRI lesions in our young patient with numbness confused the diagnosis.

Evidence for CNS demyelination has been seen in many patients with chronic inflammatory demyelinating polyneuropathy.19 Therefore, in the absence of a family history, chronic inflammatory demyelinating polynuropathy also has to be considered in the differential diagnosis. This family and the previously described patients indicate that this is not an isolated MRI finding in those with HNPP. Therefore, this neuropathy should be included in the differential diagnosis when a pattern of multifocal lesions in the subcortical white matter is found on brain MRI.

Central nervous system demyelination has also been described in other hereditary neuropathies.20,21 The researchers concluded that central and peripheral involvement was caused by the same genetic disorder. Our family seems to confirm that this would also be the case for HNPP. To our knowledge, the role of PMP22 in the CNS has not been studied in humans. According to the MRI findings in this family, CNS demyelination may be associated with the underexpression of PMP22. It is not known if this finding is a direct consequence of the absence of protein or a defect in gene dosage. Furthermore, whether there is a phenomenon of compensation by other members of the PMP22 gene family22 or by other associated proteins remains to be elucidated.

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