plays a major part in the perception of intraoral sensation, whereas facial sensation projects to the medullary portion of this nucleus.

As our case indicates, a small lesion at the lateral pontine tegmentum can cause a pure and crossed orocutaneous deficit, by involvement of the rostral spinal trigeminal nucleus and the lateral side of the spinotemporal tract, where the respective sensory fibres from the mouth and the lower part of the body are immediately adjacent (figure, C).

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Hereditary neuropathy with liability to pressure palsies with a partial deletion of the region often duplicated in Charcot-Marie-Tooth disease, type 1A

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder characterised by recurrent peripheral nerve palsies, paraesthesiae, and less often by a prominent symmetric polyneuropathy. Nerve biopsies show thickening of myelin called tomaculae. Chance et al. found such patients to have a large chromosomal deletion located in this region as in Charcot-Marie-Tooth disease (CMT) neuropathy, type 1A. This region contains a gene for peripheral myelin protein 22 (PMP22). The role of this gene in the pathogenesis of HNPP has been shown by the discovery of a frame shift mutation creating a null mutation and resulting in the HNPP phenotype. In the case of deletion/duplication, a gene dosage effect has been proposed.

In a family affected with HNPP, we found a deletion at locus D17S122 including the PMP22 gene and sparing distal loci (D17S61 and D17S125), hence confirming the expectation that deletion of a smaller region than that previously described, but including PMP22, is capable of causing HNPP, and therefore supporting the role of PMP22 in HNPP.

Patient I.1 developed leg weakness at the age of 30. Since the age of 26, he had noticed episodes of paraesthesiae on multiple nerve trunks, at first transient, then lasting and needing several surgical decompressions. At the age of 58, he had bilateral pes cavus, distal weakness, severe muscle atrophy, and areflexia in the lower limbs with transient paraesthesiae and cramps; sensory examination showed hypoesthesia in the left peroneal nerve territory. In the upper limbs, only muscle atrophy and mild weakness of interosseous muscles were noted. All tendon reflexes were absent. Motor nerve conduction velocities (MNCVs) were severely slowed in median nerves (42 m/s on the right and 40 m/s on the left) and radically altered in the ulnar nerves (32 m/s on the right and 24 m/s on the left at the elbow). A nerve biopsy showed severe loss of myelinated fibres, some having an overthin myelin sheet. Rare onion bulbs were present. Tomaculae were found in 7% of the 200 interneurons studied on teased fibres.

His daughter (patient II.1), had presented since the age of 26 with paraesthesiae and episodes of weakness of one or two weeks’ duration in the peroneal, ulnar, or median nerve territories. At the age of 27, she had pes cavus, severe peroneal muscle atrophy, weakness, and distal extrapoluminal and partially lemniscal sensory impairment in the lower limbs. Mild sensory impairment was noticed in the left ulnar and median nerve distribution. Tendon reflexes were all absent. In the upper limbs, MNCVs were normal in 1990, but in 1995 a bilateral entrapment of the ulnar nerve at the elbow and a left carpal tunnel syndrome were proved. In brainstem cross sections of the sural nerve showed a slightly reduced large myelinated fibre density, tomaculae, and lesions of remyelination. All the teased fibres presented features of tomaculae and of demyelination and remyelination. Tomaculae were found in 9% of the interneurons.

Molecular genetic studies were carried out for both patients by southern blotting analysis (figure, A) and pulsed field gel electrophoresis (PFGE) (figure, B).

Probe pVAW409R3a (D17S122) disclosed only one band for both patients whereas probes pBW401HE (D17S61) and pVAW412R3HEc (D17S125) were heterozygous for the second patient. Density scanning showed the presence of a single pVAW409R3a allele in both patients, and the presence of two alleles for the other probes in the first patient. The same technique showed only one copy of the PMP22 gene in the patients (not shown).

In PFGE analysis, hybridisation of Eagle-digested DNA with CMT1A-REP probes usually detects deletion and duplication junction fragments in HNPP and CMT1A, respectively. No such junction fragments were found for our patients with HNPP.

(A) Hybridisation profiles obtained with probes positioned in the region often deleted in HNPP (loci D17S122, D17S61, and D17S125) and with control probe localized telomeric outside this region (locus D17S124). Probe pVAW409R3a detected three alleles with sizes of 2-8, 2-7, and 1-9 kb for locus D17S122, probe pFW401HE detected two alleles with sizes of 5-5 and 4-4 kb at locus D17S61, and probe pVAW412R3HE detected two alleles with sizes of 2-6 and 1-7 + 0-7 kb for locus D17S125. Lane 1, unaffected homozygous control; lanes 2 and 3, patients; lane 4 unselected heterozygous control. Probe pVAW409R3a (D17S122) did not detect 1-9 kb alleles. Both alleles of locus D17S61 and D17S125 are present in patient I.1. A correct familial relation was proved with VNTR probes. The presence of one allele in locus D17S122 was proved by densitometric scans from 1-7 to 10-5 kb of the external control (D17S124). (B) Eagl Southern blot hybridised with the CMT1A-REP probe pNEA102. The lanes contain the DNA of a normal subject, a CMT1A patient with the 1-5 Mb duplication, a patient with HNPP with the 1-5 Mb deletion, and the patient with HNPP (patient II.1). Patients with HNPP with a 1-5 Mb deletion show a 370 kb junction fragment. No such fragment was found in patient I.1. Lanes 270 and 220 kb fragments are from normal chromosomes and 150 kb is a junction fragment specific for CMT1A patients with a 1-5 Mb duplication.
Thus in our patients, molecular genetic analysis disclosed a smaller deletion than that previously reported by Chance et al, spanning about 1-5 Mb and including all markers mapping within the CMT1A duplication. In both our patients, the PMP22 gene, the dosage effect of which is thought to be responsible for the neuropathy, was deleted as well as locus D17S122, whereas both alleles D17S61 and D17S125 were present.

In addition to the deletion described by Chance et al, other molecular results underlying HNPP have been reported: a 267 bp deletion was described by Nicholson et al, by sequencing exon 1 of the PMP22 gene, and resulting in a reading frame shift mutation. In these affected patients, analysis of DNA disclosed the presence of two alleles for D17S122 and PMP22 probes. Mariman et al reported an absence of deletion in a family with HNPP established by biopsy. Moreover, these authors were able to exclude linkage of the PMP22 gene and the surrounding region with the disorder present in this family. Finally, Thomas et al described histological features of tomaculous neuropathy in two patients with clinical findings of CMT associated with a mutation of the P0 gene.

We emphasise the unusual character of our patients, in which they present a clinical CMT phenotype associated with the pathological features of HNPP. Prominent motor and sensory neuropathies with or without nerve palsies and HNPP pathological features have already been mentioned, but genetic analysis has only been reported by Thomas et al. However, Nicholson et al did not find any difference in the phenotype of patients either with or without the typical deletion of HNPP. In the study of Mariman et al, the clinical signs in the family with no “HNPP deletion” were those of HNPP. Further studies could help to find out whether atypical clinical features are associated with a certain genotype.

Both HNPP and CMT1A are thought to result from a reciprocal DNA deletion or duplication of a fragment of 1-5 Mb on chromosome 17. A partial deletion in our patients was not unexpected as partial duplications of the concerned region have also been described in CMT and the present case could be a reciprocal recombination product of such a duplication.

Probe pNEA102 detected a 7-8 kb proximal and a 6-0 kb distal fragment belonging to CMT1A-REP repeat sequences flanking the duplicated region in CMT1A. In unaffected persons, two copies of the 7-8 kb fragment and two copies of the 6-0 kb fragment are present, whereas patients with HNPP lack one distal CMT1A-REP sequence and thus show loss of one copy of the 6-0 kb fragment with a subsequent difference in band density. We did not find a density difference between the 7-8 and 6-0 kb fragments of our patients with a partial deletion. Similarly, pulse field gel electrophoresis did not show the deletion junction fragments specific for patients with HNPP with a 1-5 Mb deletion. This finding suggests that sequences other than those detected by the pNEA102 probe are involved in the mutation process of this partial deletion.

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