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Does CMT1A homozygosity cause more severe disease with root hypertrophy and higher CSF proteins?

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Charcot-Marie-Tooth type 1A (CMT1A) is associated with a peripheral myelin protein-22 (PMP22) gene duplication on chromosome 17p11.2. CMT1A patients have three PMP22 copies and a gene dosage effect, leading to increased PMP22 protein expression, is the hypothesized pathogenic mechanism. Homozygosity for the duplication has been reported in patients from three families, with both parents carrying the duplication and transmitting the mutation to their offspring, who had PMP22 tetrasomy and variable disease severity.1-3

We report a homozygous CMT1A patient with rather severe disease, high CSF proteins, and astonishing root hypertrophy.

Case report. The patient is a 45-year-old man born to first-cousin parents. His parents, two sisters, one brother, and two sons had pes cavus and lower limb weakness (see figure E-1A on the Neurology Web site). He developed pes cavus and walking difficulties at age 11 years, scoliosis at age 16, and slowly progressive lower limb weakness until age 42, when he had more rapid worsening with difficulty climbing stairs, loss of balance, and hand weakness. Hearing loss started at age 33 years. On admission, he had marked foot deformities (walking with support), moderate scoliosis, bilateral hearing loss, muscle wasting and weakness (severe distally in lower limbs, moderate in hands and thighs), generalized areflexia, distal sensory loss, and marked palpable enlargement of ulnar nerves.

Motor nerve conduction velocities (MCV) were 10 to 12 m/s in ulnar, median, and tibial nerves, with distal latency prolongation (5.6, 8, 11 to 11.3 ms) and moderate-severe compound muscle action potential (CMAP) amplitude decrease (4.4, 0.75, 0.2 to 0.4 mV). Peroneal nerve M-responses were absent. F-waves and sensory action potentials could not be evoked. Asymmetry, temporal dispersion, and conduction blocks were not detected. Audiology confirmed moderate sensorineural hearing loss.

CSF proteins were high (388 mg/dL; n.v. <45), raising, with the recent worsening, the hypothesis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) superimposed on CMT1A. Two courses of high-dose IV immunoglobulin were administered, as were steroids for several weeks. CSF proteins slightly decreased (288 mg/dL), but there was no objective clinicoelectrophysiologic improvement. Monoclonal gammopathy, antiangiolside, and anti-MAG antibodies were not detected.

Sural nerve biopsy, suggesting severe CMT1, revealed marked hypertrophy (total fascicular area, 3.77 mm²; n.v. 1.34 ± 0.18), severe loss of myelinated fibers (455/mm²; n.v., 7,511 ± 988), several complex onion bulbs (758/mm²), Schwannian hyperplasia (nuclei density, 3,250/mm²), unimodal fiber size distribution (mean diameter, 4.4 μm), no large myelinated fiber >8 μm, G-ratio = 0.59 ± 0.13 (n.v., 0.60 ± 0.08), and demyelination of 19% of teased fiber internodes (CMT1A >45 years = 8.1 ± 3.9).4 We did not find inflammatory infiltrates, edema, focal predominance of abnormalities, immunoglobulin, or complement fragment deposition on myelin sheaths.

On lumbar MRI, cauda equina roots were markedly hypertrophic, much thicker overall than the cord itself, and almost completely filled the spinal canal (figure). Root enlargement is extended to the ganglia. After gadolinium administration, a subtle enhancement with difficulty climbing stairs, loss of balance, and hand weakness. Hearing loss started at age 33 years. On admission, he had marked foot deformities (walking with support), moderate scoliosis, bilateral hearing loss, muscle wasting and weakness (severe distally in lower limbs, moderate in hands and thighs), generalized areflexia, distal sensory loss, and marked palpable enlargement of ulnar nerves.

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Figure. MRI of the lumbosacral spine. Midline sagittal (A), coronal (B), and axial (C) spin-echo T2-weighted images show thickened nerve roots that completely fill the dural sac. Compare the size of the spinal cord (black arrowheads in A) with the enlarged cauda equina. Marked decrease of CSF causes poor definition of the conus and proximal nerve roots. In C (L4-L5 level), the white arrowheads indicate the hypertrophic ganglia.

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Hemicrania horologica ("clock-like hemicrania")
Franco Granella, MD; and Giovanni D'Andrea, MD

In 1747, the German physician Oppermann described a peculiar clinical picture.1 A 35-year-old woman suffered from excruciating daily headache attacks, lasting 15 minutes, which occurred exactly every hour, day and night, with extraordinary precision. Oppermann defined this peculiar headache "hemicrania horologica" (clocklike hemicrania). It has been suggested2 that Oppermann's case was the first known of chronic paroxysmal hemicrania (CPH). We describe here a similar case.1

Case report. A 69-year-old man was headache-free until the age of 66, when he began to complain of strictly unilateral headache attacks on the left side. The pain started behind the ear and then spread ipsilaterally over the temporal and zygomatic regions or over the neck and shoulder. The pain, of throbbing quality, was mild at the beginning of the attacks and afterward became severe, reaching a 5-minute plateau before slowly subsiding. Photophobia, phonophobia, nausea, and vomiting were lacking, as was any local autonomic sign except for modest bilateral facial sweating. No trigger factors were detectable. The attacks, lasting 15 minutes, occurred exactly every 60 minutes, day and night, i.e., the subsequent attack occurred exactly 60 minutes after the end of the previous one. During 24 hours, therefore, 19 attacks occurred (figure). At the beginning, the attacks occurred only 1 day every 2 weeks or 1 month; after 6 months, however, the headache occurred daily. The patient had been unsuccessfully treated with paroxetine and corticosteroid injection of the left great occipital nerve. He had discovered by himself that a small amount of nimesulide (100 mg twice daily) and nimesulide (100 mg twice daily). We treated the patient with nimesulide, 100 mg twice daily, for 3 months and thereafter withdrew the drug. The attacks reappeared soon after. The treatment was restarted and continued for another 4 months, when the patient spontaneously interrupted it, without any recurrence. Subsequently, he has been headache-free for 6 months.

Discussion. Our patient is remarkably similar to Oppermann's.2 Are both cases of CPH? Our patient does not fulfill all the criteria for CPH, as he did not have nausea or vomiting and remained alert during the attacks. However, the attacks were strictly unilateral, with a fixed frequency of exactly 60 minutes, and were of severe intensity. Therefore, we believe that this is a case of CPH. The attacks were not responsive to several treatments, including paroxetine, corticosteroids, and nimesulide, which suggests that CPH is a distinct entity from other types of headache.

References.

Figure. Distribution of the headache attacks during the 24-hour period (■ = attacks lasting 15 minutes).

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