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Neurology 2003;60;1721
DOI 10.1212/01.WNL.0000059262.34846.8A

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.[1] 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. Audiometry 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 CMT1. 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, antiganglioside, and anti-MAG antibodies were not detected.

Sural nerve biopsy, suggesting severe CMT1, revealed marked hypertrophy (total fascicular area, 3.77 mm^2; n.v., 1.34 ± 0.18), severe loss of myelinated fibers (455/mm^2; n.v., 7,511 ± 988), several complex onion bulbs (758/mm^2), Schwannian hyperplasia (nuclei density, 3,250/mm^2), 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 extended to the ganglia. After gadolinium administration, a subtle enhancement depicted the roots.

Molecular analyses demonstrated that the disease segregated with the CMT1A duplication within the family. Quantitative analysis showed that the increase in *PMP22* signal intensity in the proband was larger than in his two children and in our series of duplicated CMT1 patients, indicating homozygosity for the duplication (see figure E-1 on the *Neurology* Web site).[5]

Discussion. Disease expression variability is well known in heterozygous CMT1A. The few reported homozygotes had neuropathy ranging from crippling to mild, suggesting that gene dosage is not the only determinant of disease severity.[1-3] However, *PMP22* tetrasomy in our patient led to overall greater disease severity than seen in average CMT1A. Clinical severity was comparable with severe CMT1A; hearing loss, rare in CMT1A, occurred. CMAPs and MCV were in the lower CMT1A range (upper limb MCV = 7 to 36 m/s; mean, 19.8 ± 5.2, in our 78 CMT1A patients). Nerve biopsy showed more severe demyelination and greater loss of myelinated fibers than usually seen in CMT1A.[4] CSF proteins were much higher than those observed in CMT1A (20 to 122

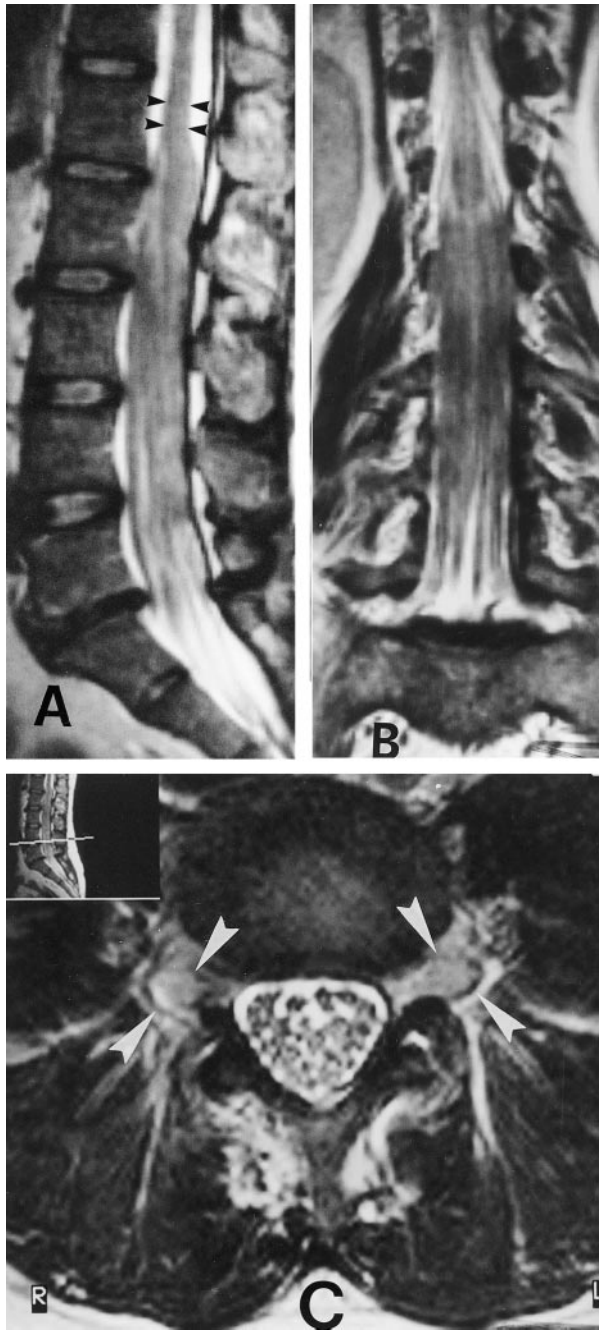

Figure. MRI of the lumbosacral spine. Midline sagittal (A), coronal (B), and axial (C) spin-echo T2-weighted images show thickened nerve roots that completely fill the dural sac. Compare the size of the spinal cord (black arrowheads in A) with the enlarged cauda equina. Marked decrease of CSF causes 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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mg/dL; mean, 58, in 13 of our patients). Finally, he had astonishing root hypertrophy.

Hypertrophy of spinal roots, rarely symptomatic, has been occasionally reported in hypertrophic neuropathy (CMT1, Dejerine–Sottas disease, CIDP).[6,7] Most of these patients were not genetically characterized, and the true incidence of root hypertrophy in CMT1A is unknown. Therefore, the mechanism whereby some patients show greater hypertrophy is unclear. In our patient, it is likely that *PMP22* tetrasomy was a further stimulus to nerve hypertrophy. Not only were the cauda equina roots hypertrophied but also the ulnar nerves were markedly enlarged, and the biopsied sural nerve showed relevant hypertrophic changes. The onion bulb number was comparable with that of a series of 20 CMT1A patients,[4] but Schwann cell hyperplasia was considerable, indicating the presence of more complex onion bulbs than in almost all these patients.[4] The somewhat rapid deterioration during the past 3 years and high CSF proteins suggested CIDP superimposed on CMT1. However, we found no confirmatory evidence in laboratory, electrophysiologic, and morphologic findings. Root hypertrophy is the likely cause of increased CSF proteins, probably through leakage from enlarged roots and partial block of CSF circulation.

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Supported in part by a grant from the Italian Ministry of Health to Drs. Taroni and Pareyson (Progetto Ricerca Finalizzata ICS 030.3/RF00.174).

Received October 23, 2002. Accepted in final form January 15, 2003.

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Hemicrania horologica ("clock-like hemicrania")

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In 1747, the German physician Oppermann described a peculiar clinical patient.[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 suggested[2] 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 (a nonsteroidal anti-inflammatory drug [NSAID] of widespread use in Italy), taken before sleeping, was able to avoid the nocturnal attacks. Therefore, he took this drug every night before going to bed.

Medical history was remarkable for the removal of a prostatic cancer at age 68 years. Physical and neurologic examinations were unremarkable, except for marked tenderness at the palpation of the left great occipital nerve. A psychiatric interview and the Minnesota Multiphasic Personality Inventory 2 were normal. The routine blood examinations, including erythrocyte sedimentation rate (ESR), were normal. Brain MRI was normal, too.

At our first observation, the patient was asked to withdraw from nimesulide and to complete a headache diary for 1 week. During this period, the attacks occurred, as previously described by the patient, every 60 (± 2) minutes, with absolute regularity, and lasted 15 minutes.

We treated the patient with low-dose indomethacin (25 mg twice daily) for 1 week, which resulted in a prompt disappearance of the attacks. However, the attacks occurred again 12 hours after drug withdrawal. The same effect was obtained with other NSAIDs, such as ibuprofen (600 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.[1] Are both cases of CPH? Our patient does not fulfill all the

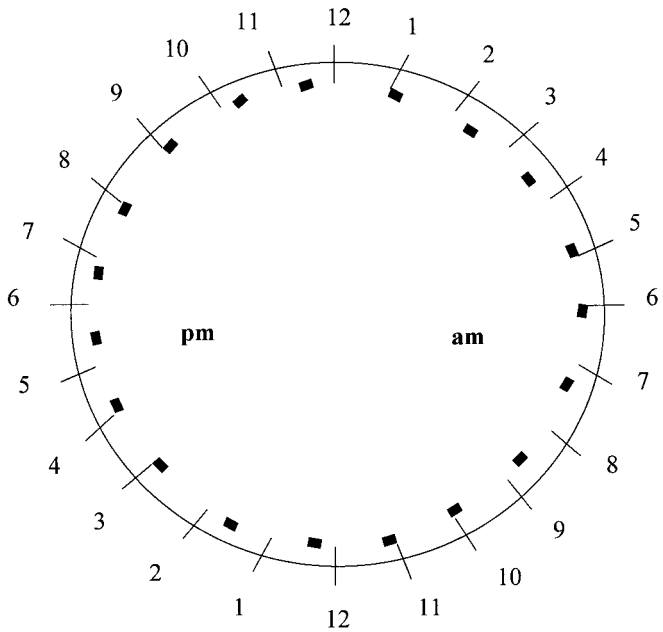

Figure. Distribution of the headache attacks during the 24-hour period (■ = attacks lasting 15 minutes).

