Letters

COMMENT & RESPONSE

Proximal Lower-Limb Weakness in Charcot-Marie-Tooth Disease

To the Editor We read with interest the article by Lee et al[1] describing hereditary motor and sensory neuropathy with proximal dominance, a rare type of autosomal dominant adult-onset Charcot-Marie-Tooth disease (CMT). It is indicated that detailed magnetic resonance imaging analysis revealed a distinct pattern of muscular involvement consisting of marked hyperintense signal changes in the hip muscles compared with those in the thigh or the leg muscles. According to the authors, these signal changes are different from the ones in patients with CMT with length-dependent neuropathy.[2,3] Although accepting this position, we wish to draw attention to the fact that, late in the clinical course, a small subset of patients with CMT type 1A (CMT1A), the most common form of CMT, may exhibit florid involvement of thigh and pelvic musculature.[4,5] One of our patients with CMT1A, aged 53 years, was serially evaluated over 3 decades. Initial examination at age 23 years showed mild phenotype including pes cavus, areflexia, stocking hypoesthesia, and nerve enlargement.[4] At age 34 years and throughout the subsequent 4 years, she developed gradually progressive and symmetric leg amyotrophy and weakness, obliging her to use foot orthotics. As of age 43 years, she developed progressive deterioration of gait, her walk becoming ungainly and waddling with bilateral steppage obliging her to continuously use a cane. At her last examination, her stance was wide based and also possible only with support (see Figure 1 in the article by Berciano et al[4]), and there was positive Gowers maneuver in getting up from a chair. At that time, magnetic resonance imaging of the pelvic, thigh, and calf musculature showed extensive fatty muscle atrophy comparable with that illustrated by Lee et al[1] (Figure 2I-P). Worthy of note is the fact that marked fatty atrophy of gluteus medius and minimus muscles was an outstanding finding in both studies,[1,4] accounting for the observed waddling gait. In short, involvement of pelvic and thigh musculature, which is a characteristically inaugural manifestation of hereditary motor and sensory neuropathy with proximal dominance, may exceptionally occur late in the clinical course of CMT1A.

José Berciano, MD
Elena Gallardo, MD

Author Affiliations: Services of Neurology, University Hospital Marqués de Valdecilla (IFIMAV), University of Cantabria, and Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Santander, Spain (Berciano); Services of Radiology, University Hospital Marqués de Valdecilla (IFIMAV), University of Cantabria, and Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Santander, Spain (Gallardo).

Corresponding Author: José Berciano, MD, Service of Neurology, University Hospital Marqués de Valdecilla (IFIMAV, UC, and CIBERNED), Avda Valdecilla s/n, Santander, Spain 39008 (jaberciano@humv.es).

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In Reply We are grateful for the comments on our recent magnetic resonance imaging (MRI) data from patients with hereditary motor and sensory neuropathy with proximal dominance (HMSN-P).[1] We have carefully read the article on outstanding findings of lower-limb MRI patterns in Charcot-Marie-Tooth disease type 1A (CMT1A)[2] and compared our observation on the atrophies of gluteus medius and minimus muscles in HMSN-P.

Some patients with CMT1A showed proximal weakness; however, the time of appearance seemed to be different from HMSN-P. It was early in the clinical course of HMSN-P; whereas, it was late in CMT1A.[1,2] The predominant clinical signs of CMT1A are distally accentuated muscle weakness and wasting in the lower limbs.[3] As the disease advances, more proximal muscles may become weak, although paresis of the proximal limb muscles is extremely rare.[2] On the other hand, HMSN-P is characterized by predominant proximal muscle weakness.[4]

We performed lower-limb MRIs in 4 patients with HMSN-P.[1] A 23-year-old man did not mention having any symptoms, and MRIs of the hip, thigh, and lower leg revealed normal findings. A 48-year-old woman with a 2-year disease duration showed atrophy and fatty changes in gluteus minimus and medius muscles but relatively preserved gluteus maximus muscle. At the thigh level, there was a selective severe involvement of the semitendinosus muscles, but the other muscles in the posterior compartment were relative sparing. On the lower leg, mild fatty change was found in the gastrocnemius muscle; however, it was not involved in the tibialis anterior muscle. A 51-year-old man with a 3-year disease duration revealed more progression of fatty infiltrations than his younger sister. In a 56-year-old man with an 11-year disease duration, we observed diffuse severe atrophy and fatty change of whole lower-limb muscles, including the hip, and a relatively intact anterior compartment especially the tibialis anterior muscles in the lower leg.

Compared with CMT1A, there was a distinct pattern of muscular involvement in HMSN-P.[5,6] Patients with HMSN-P showed that tibialis anterior muscles were relatively intact, while gluteus medius and minimus muscles were severely damaged. In the early clinical course of CMT1A, anterior compartment muscles, including the tibialis anterior, were shown to be severely involved, while gluteus medius and minimus muscles were sparing.[2] However, in the late stage, a small proportion of patients with CMT1A develop severe proximal weakness in the legs and marked fatty atrophy in all 4 leg muscle compartments and the gluteus medius and minimus muscles. Although the involvements of pelvic and thigh muscle occur late in the clinical course of CMT1A, patients with HMSN-P show the earliest and most severe changes in the gluteus minimus and medius muscles. Moreover, the most severe case showed relatively intact anterior compartment muscles especially the tibialis anterior. Therefore, in patients with HMSN-P, marked hyperintense signal changes in the hip muscles and those in the thigh or the lower-leg muscles were well related with the proximal dominancy. It seems that these were different from that of patients with CMT1A having length-dependent neuropathy. Therefore, we suggest a distinct proximal dominant and sequential pattern of muscular involvement in HMSN-P with different pattern of CMT1A.

Ki Wha Chung, PhD
Sang Soo Lee, MD
Young Bin Hong, PhD
Jeong Hyun Yoo, MD
Byung-Ok Choi, MD

Author Affiliations: Department of Biological Science, Kongju National University, Gongju, Korea (Chung); Department of Neurology, Chungbuk National University School of Medicine, Chungbuk, Korea (Lee); Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (Hong, Choi); Department of Radiology, Ewha Womans University School of Medicine, Seoul, Korea (Yoo).

Corresponding Author: Byung-Ok Choi, MD, Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong Gangnam-Gu, Seoul 135-710, Korea (bochoi@skku.edu).

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Creutzfeldt-Jakob Disease

To the Editor In their article, Angus-Leppan et al[1] presented a comprehensive and highly interesting report of a 68-year-old patient exhibiting a rapidly progressing array of symptoms including insomnia, personality change, myokymia, and eventually cognitive decline. As concluded by the authors, Morvan syndrome[2] was suspected, and indeed, serum antibodies to the voltage-gated potassium channel complex were found. Brain biopsy findings were conclusive, with definite Creutzfeldt-Jakob disease (CJD). The combination of CJD and antibodies indicating a possible treatable immune-mediated encephalopathy is intriguing and raises concern of how to proceed with patients considered to have CJD especially as this combination does not seem to be a singularity. In 2012, we cared for a 67-year-old patient presenting with a 3-week rapidly progressive personality change and cognitive decline, as well as gait instability. Initially talkative, mildly disoriented, and ataxic, his condition deteriorated rapidly and he became bed bound, dysarthric, and dysphatic after 2 weeks; as time went on, he became mute and without any reaction to outside stimulus. No metabolic disturbances, besides known chronic renal failure, were detected. Repeated magnetic resonance imaging scans using diffusion-weighted imaging showed progressive extension of cortical hyperintensity bilateral parietooccipital with cortical ribbon sign highly compatible with the diagnosis of CJD.[3] On electroencephalography, diffuse slowing without periodicity was seen. Results from repeated lumbar punctures did not show pleocytosis or elevated protein. Findings from neoplastic screening, including full-body positron emission tomography–computed tomography, were negative. Serum and cerebrospinal fluid antibody testing results were positive in 2 separate laboratories for Caspr-2 at a titer of 1:32. A course of high-dose steroids and plasmapharesis did not change the progression of the disease, and the patient died 4 weeks after hospital admission. The family refused brain biopsy or postmortem analysis. In concert with Angus-Leppan et al, the probability of 2 rare diseases in our patient was extremely low and magnetic resonance imaging did not support a diagnosis other than CJD. Unmasking of epitopes due to rapid neurodegeneration and secondary antibody appearance might explain the concurrent findings, but we argue that the low titer in both cases make it more probable that the antibodies were false positive and not involved in the disease pathophysiology in accord with their detection in control populations.[4] Future research is urgently needed to clarify the relationship between the occurrences of antineural antibodies in CJD, especially to formulate screening and treatment guidelines and define cutoffs for antibody titers. Thus, more patients with rapid progressive dementia could be helped effectively, while others are spared from strenuous and highly expensive, yet ineffective, treatment.

Felix F. Benninger, MD, PhD
Israel Steiner, MD

Author Affiliations: Department of Neurology, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Benninger, Steiner).