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"Ear of the Lynx" Sign in Hereditary Spastic Paraplegia 76

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Dear Editor,

Hereditary spastic paraplegia (HSP) 76 is a rare form of spastic paraparesis caused by mutations in *CAPN1*. It is inherited in an autosomal recessive manner, and about 50 cases have been reported worldwide.[1] The clinical presentation of HSP76 varies from pure spastic paraparesis to a complicated form accompanied by ataxia.[2] Diagnosing the disease may often be challenging, but a previous case report suggested that an "ear of the lynx" sign in brain magnetic resonance imaging (MRI) can be useful.[3] Here we describe an HSP76 patient, including their brain MRI findings.

A 25-year-old female patient presented at our clinic with a 10-year progressive gait disturbance. She had a normal developmental history from infancy through childhood. However, she experienced unsteadiness while walking and sometimes required assistance when going down stairs. Her parents had noticed that her speech had become unclear about 2 years previously. She was diagnosed with type I diabetes mellitus 4 years previously. Her other medical history was unremarkable, and her family history was negative for genetic disease. Her speech was slightly slurred, but a cranial nerve examination including vision, pupil, and eye movements was unremarkable. A motor examination of the upper limbs produced normal findings, while subtle weakness of ankle plantar flexion was noticed along with brisk deep tendon reflexes in both knees as well as ankle clonus. The finger-to-nose test showed bilateral dysmetria and mild terminal tremor. She stood with a wide base and exhibited multiple side steps during the tandem gait test. Other aspects of her nervous system appeared normal.

Serological testing for human immunodeficiency virus, human T-lymphotropic virus 1, vitamin B12, paraneoplastic antibodies, and a vasculitis panel produced negative findings. Brain MRI showed mild cerebellar atrophy in the upper part of the anterior and posterior lobes (Fig. 1A), and revealed vertical and horizontal T2-hyperintense signals at the level of the ventral pons (Fig. 1B). In addition, T2 hyper-/T1 hypointense signals were observed resembling a tuft of hair at the tips of the frontal horns of the lateral ventricles (Fig. 1C and D). Genetic tests for dentatorubral-pallidoluysian atrophy and spinocerebellar ataxia types 1, 2, 3, 6, 7, 8, and 17 were normal.

The targeted sequencing for HSP identified two compound heterozygous variants in *CAPN1*: c.1730-2A>G and c.1442G>A (NM_001198868.2). The c.1730-2A>G variant was novel and was classified as a likely pathogenic variant according to the criteria established by the American College of Medical Genetics and Genomics.[4] The classification was supported by the following evidence: 1) the variant represents a null variant in a gene where loss of function is a recognized disease mechanism,[5] and 2) it is not present in controls in the gnomAD database. Similarly, the c.1442G>A (p.Arg481Gln) variant was also classified as likely pathogenic, based on following evidence: 1) it is located in a region known to have a high mutation density and/or within a critical and well-established functional domain that lacks benign variations, 2) it is not observed in East Asian control samples in the gnomAD database, 3) several computational models predict a deleterious effect on the gene or its

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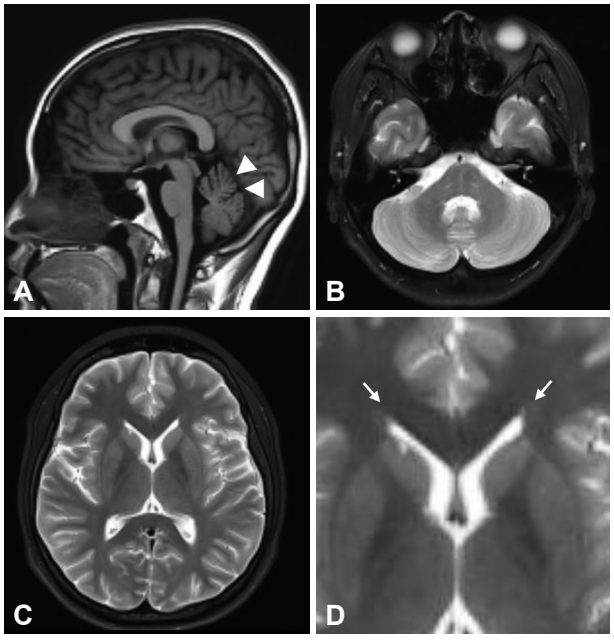

Fig. 1. Sagittal T1-weighted imaging showed no atrophy in the corpus callosum, but mild cerebellar atrophy was observed in the upper part of the anterior and posterior lobes (A, arrow heads). An axial T2-weighted scan exhibited a cruciform T2-weighted hyperintensity in the ventral pons (B) and flame-shaped hyperintensities at the tips of the frontal horns of the lateral ventricles (C and D, arrows).

product, and 4) although a reputable source has recently reported this variant as pathogenic,[6] the evidence was not accessible for independent verification by our laboratory.

The "ear of the lynx" sign has been observed in cases with HSP11, -15, and -78.[7,8] Brain MRI in HSP76 cases has mostly produced normal results or revealed mild cerebellar atrophy,[2] but the "ear of the lynx" sign was described in two HSP76 patients with ataxia.[3] A study including patients with HSP11 and -15 as well as multiple sclerosis found that the finding was sensitive (78%–97%) and specific (90.9%–100%) for the HSP group.[7] Another study observed the "ear of the lynx" sign in a carrier of a heterozygous HSP11 mutation,[9] suggesting that this finding may be associated with the presence of pathogenic variation.[3]

Our case additionally showed vertical and horizontal T2-hyperintensities in the ventral pons resembling the hot-cross bun sign. This sign is known to be associated with the degeneration of transverse pontocerebellar fibers and the medial raphe nuclei, which is implicated in various mechanisms including synucleinopathy, gliosis, Wallerian degeneration, and granule-cell neuronopathy.[10] In a rodent model, knocking out *CAPN1* expression led to a reduction in the cerebellar granule-cell density and clinical ataxia.[11] It is therefore possible that the cruciform T2 hyperintensity in this case might be associated with pathogenic variations of *CAPN1*.

This report adds to the clinicoradiological and genetical spectrum of HSP76. We recommend considering genetic screening for recessive HSP in cases with the "ear of the lynx" sign.

Ethics Statement

The present study was approved by the Institutional Review Board of Pusan National University Hospital (2405-005-139). The written conformed consent for publication of the clinical records were obtained from the subject.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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