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Multiple Sclerosis in a Patient With Neurogenic Locus Notch Homolog Protein 3 Mutation

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Dear Editor,

Multiple sclerosis (MS) is an autoimmune inflammatory disease that mostly affects the cerebral white matter.[1] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary degenerative disease that also involves the cerebral white matter. The clinical features and pathophysiology of CADASIL differ from those of MS; nevertheless, CADASIL always needs to be differentiated from MS because of the similarity in their magnetic resonance imaging (MRI) findings. We experienced an MS case with a neurogenic locus notch homolog protein 3 (NOTCH3) gene mutation. The patient had a family history of CADASIL, and it was particularly interesting that brain MRI presented findings that were characteristic of both MS and CADASIL.

An 18-year-old female presented with sudden right facial palsy. She was healthy and had no prior history of any specific disease or medication. Her mother had been diagnosed with CADASIL with a NOTCH3 gene mutation and presented with stroke and dementia.

The initial vital signs of the patient were normal, and a neurological examination revealed peripheral right facial palsy. She did not present with migraine, memory disturbances, or personality changes.

Brain MRI revealed multiple high signal intensities in both the periventricular white matter and infratentorial areas, including the right pontine tegmentum, the right cervicomedullary junction, and the left middle cerebellar peduncle and cerebellum (Fig. 1A-C). Low signal intensities were observed in the same areas in T1-weighted images. Some of the lesions were positive for the central vein sign. Non- and contrast-enhanced lesions also presented simultaneously, some of which showed peripheral enhancement in the form of an open ring (Fig. 1D and E). The patient exhibited confluent fluid-attenuated inversion recovery (FLAIR) hyperintense lesions in the bilateral anterior temporal lobes without external capsule lesions (Fig. 1F and G). No MRI abnormalities in the bilateral optic nerves or spine were noted (Fig. 1F).

A serum antibody assay for aquaporin-4 and myelin oligodendrocyte glycoprotein was negative. Cerebrospinal fluid (CSF) test results were normal, with a cell count of 0, protein level of 27.2 mg/dL, and CSF/serum glucose ratio of 62/118. The CSF was positive for oligoclonal bands (OCBs), and the IgG index was 0.58. She also had a heterozygous pathological variant with c.328C>T (p.Arg110Cys) in the NOTCH3 gene, which had also presented in her mother.

The patient was diagnosed with MS with a NOTCH3 gene mutation and treated using dimethyl fumarate. There was no recurrence during the 8-month follow-up period.

MRI findings suggestive of MS in this case included high signal intensity on FLAIR images, low signal intensity on T1-weighted images, and abnormal enhancement on gadolinium-enhanced images in the periventricular white matter, callososeptal interface, and infratentorial area.[2] Open ring enhancement is a relatively specific sign for demyelination and

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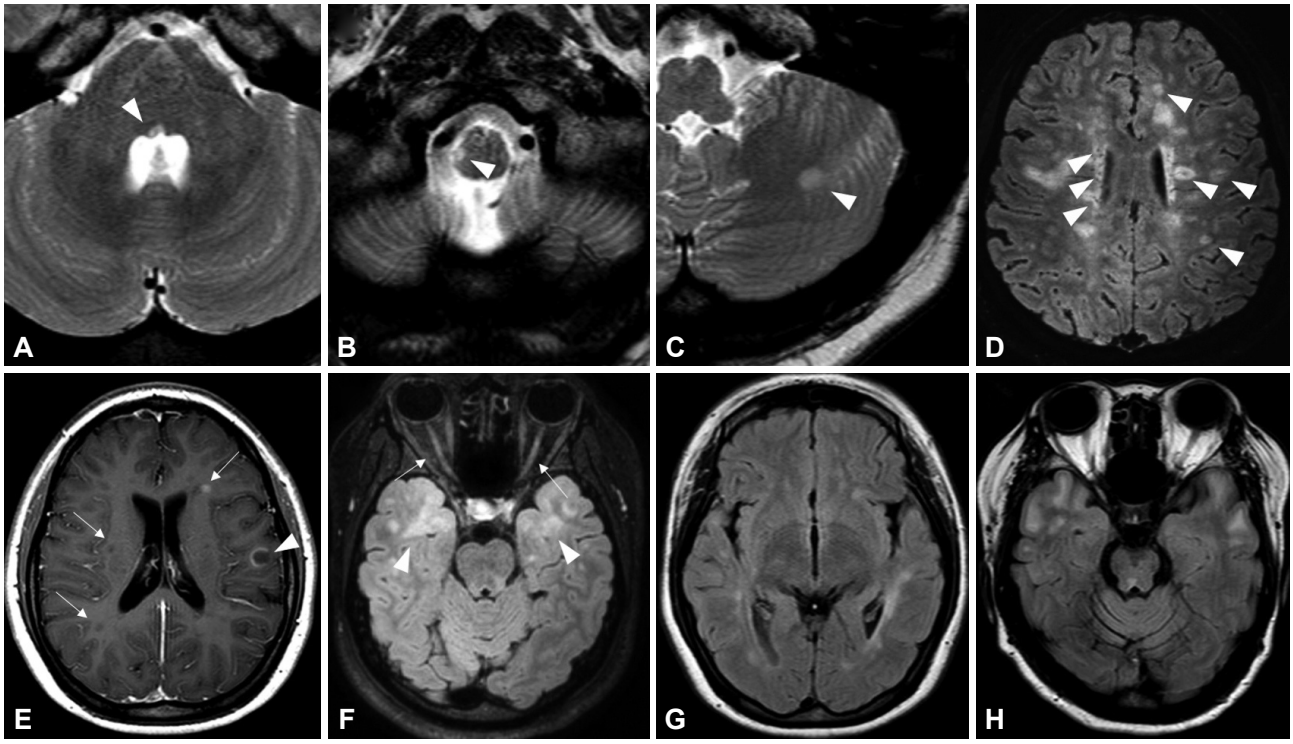

Fig. 1. Brain magnetic resonance imaging of the case. A-H: T2-weighted image shows high intensity signal lesions in the (A) right pontine tegmentum (arrowhead), (B) right cervicomedullary junction (arrowhead), and (C) left cerebellar hemisphere (arrowhead). (D) FLAIR image shows periventricular ("Dawson's fingers") and other white-matter lesions, some of which are positive for the central vein sign (arrowheads). (E) Postcontrast T1-weighted image shows the simultaneous presence of non- and contrast-enhanced lesions (arrows), some with the open ring sign (arrowhead). (F) FLAIR image shows no abnormal findings in the bilateral optic nerves (arrows). Confluent hyperintensities in the bilateral anterior temporal lobes (arrowheads). (G) No abnormal lesions in the bilateral external capsule areas. (H) FLAIR image of the mother (with CADASIL) presents similar bilateral anterior temporal lobe hyperintensities. FLAIR, fluid-attenuated inversion recovery.

is particularly common in MS. The lesions were perpendicular to the lateral ventricle, and the central vein sign was positive in most of the plaques, which supported a perivenular distribution, and therefore the possibility of MS.[3]

The subtle lesion in the right pontine tegmentum was symptomatic. Peripheral facial palsy is not commonly observed in patients with MS, and some cases like the present one present with ipsilateral pontine tegmentum lesions on brain MRI, while others have no lesions in the pons. Most of the remaining lesions are often asymptomatic and so are incidentally discovered during brain MRI.[4]

While the patient only experienced had one episode of facial palsy, the brain MRI findings satisfied the dissemination in space and time diagnostic criteria for MS because gadolinium-enhanced and nonenhanced lesions were simultaneously detected in multiple locations in a single scan. A positive CSF OCB was also an abnormal finding that supported the MS diagnosis in this case.

White-matter hyperintensities in the bilateral anterior temporal lobes and deep white matter are radiological findings that are suggestive of CADASIL, but they are not exclusive to the disease.[5] Because the patient was an asymptomatic carrier of the NOTCH3 gene mutation and other MRI features indicative of CADASIL were absent, such as white-matter hyperintensities in the external capsule, lacunes, and cerebral microbleeds, it was debatable whether the anterior temporal lobe lesions were due to MS. However, since lacunes tend to appear later in life, microbleeds are correlated with age, and external capsule lesions (though frequent) are not observed in all CADASIL cases.[6,7] Even with no family history of CADASIL and with clinical, CSF, and radiological findings suggestive of MS, the presence of hyperintensities in the anterior temporal lobe or external capsular and unexpected cerebral microbleeds warrants consideration of a diagnostic workup for CADASIL.

Some authors have considered the acute inflammatory neurological manifestations in CADASIL to represent inflammatory CADASIL; however, there is currently no evidence to support this since MS is very rare in patients with NOTCH3 pathological variants. It may be notable that our case seemed to differ from those in previous reports due to the positive CSF OCBs, symptomatic peripheral facial nerve palsy, and more-distinct characteristic features of MS, including open-ring-type gadolinium enhancement and the central vein sign.[8]

The MRI findings of the mother were typical of CADASIL, including lacunar infarcts, microbleeds, white-matter hyperintensities in the bilateral anterior temporal lobes, and deep and periventricular white matter (Fig. 1H).[6] Notably, no external capsule hyperintensities were observed. Although most MRI lesions in young patients remain suggestive of MS, the number of MRI lesions suggestive of CADASIL may increase as the patient gets older.

Ethics Statement

The study was reviewed and approved by the Institution Review Board of Haeundae-Paik Hospital Hospital (IRB No. 2022-04-027), and written informed consent was obtained from patient.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

Kyong Jin Shin, a contributing editor of the Journal of Clinical Neurology, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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