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Letter to the Editor

Extensive Cerebral White Matter Involvement and Migrainous Headache in a Patient With Aquaporin-4-Positive NMOSD Mimicking CADASIL

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Dear Editor,

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, relapsing neuroinflammatory autoimmune astrocytopathy characterized by the presence of aquaporin-4 antibodies and a relapsing disease course.[1] A brain magnetic resonance imaging (MRI) in NMOSD reveals lesions affecting the peri-ependymal surfaces of the hypothalamus, thalamus, dorsal medulla, and long corticospinal tracts.[1] In general, involvement of cortical gray matter or juxtacortical white matter is rare in anti-aquaporin-4 (AQP4)-immunoglobulin G (IgG) NMOSD, and diffuse extensive subcortical white matter lesions are also very rarely reported.[1,2] We report a case of an AQP4-positive NMOSD patient with extensive cerebral white matter lesions who exhibited cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)-like clinical manifestations, accompanied by migrainous headaches and cognitive impairment.

A 62-year-old woman presented with pulsatile headaches and episodes of paroxysmal nausea and vomiting. Several months prior, she had experienced decreased visual acuity in both eyes, which had since improved, followed by a 2-week episode of unexplained nausea and vomiting. Neurological examination revealed no significant abnormalities; the relative afferent pupillary defect was normal, and optical coherence tomography showed no specific findings, although there was mild decreased visual acuity. Brain MRI revealed multifocal T2/fluid attenuated inversion recovery (FLAIR) hyperintensities involving bilateral cerebral white matter and the external capsules (**Fig. 1**), resembling CADASIL. Notch3 genetic analysis was negative, and anti-myelin oligodendrocyte glycoprotein antibody levels were normal, while AQP4 antibodies were positive, confirming a diagnosis of anti-AQP4 antibody-positive NMOSD. Systemic evaluation excluded other possible causes, such as systemic vasculitis. The patient's family history included cerebrovascular events and migraines, but there was no definitive diagnosis of CADASIL.

Given the patient's prior history of area postrema syndrome and optic neuritis, they were maintained on immunosuppressive therapy with mycophenolate mofetil. Over more than one year, no definite demyelinating events were observed.

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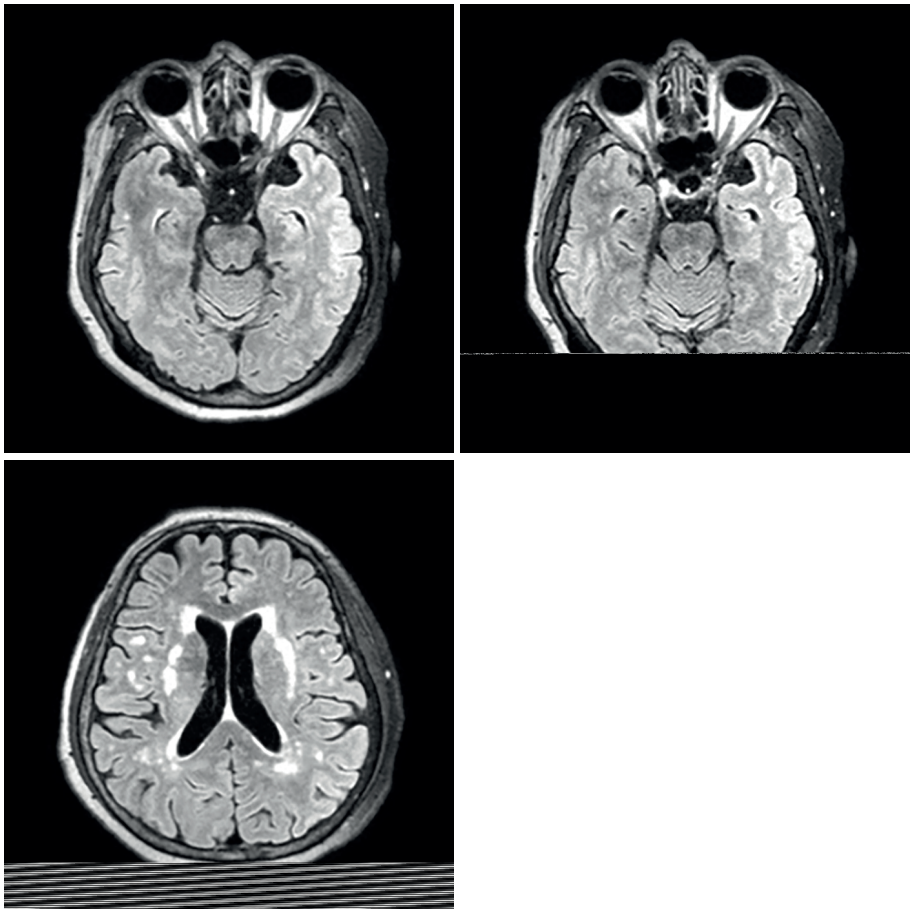

Fig. 1. Brain magnetic resonance imaging axial T2/fluid attenuated inversion recovery revealed symmetrical diffuse white matter hyperintensities, including in the external capsules. There were no significant stenoses in the intracranial vessels or evidence of microbleeds.

Headaches in NMOSD have been reported in various forms, including cervicogenic headache and trigeminal autonomic cephalalgia, and may occasionally present as an early clinical symptom.[3] In AQP4-positive NMOSD, inflammatory mediators like interleukin-6 are often elevated and, along with astrocyte dysfunction, may contribute to central sensitization and an increased susceptibility to headaches. In this case, a migrainous headache accompanied by extensive white matter lesions initially suggested a diagnosis of CADASIL. Due to the overlapping clinical and radiologic features, CADASIL-associated migrainous headache was considered in the differential diagnosis before confirming NMOSD. In NMOSD, it can primarily present as intracerebral diencephalic lesions, dorsal brainstem lesions, or poorly defined contrast-enhancing lesions. Additionally, it may manifest as lesions in the large cerebral hemispheres or as longitudinal lesions along the corticospinal tract.[1,4] However, as demonstrated in this case, the coexistence of migrainous headache and white matter lesions resembling a CADASIL-like pattern in NMOSD is rare.[1,2,4]

Brain MRI findings in NMOSD often show lesions in areas with high aquaporin-4 expression, particularly in the periependymal regions surrounding the third and fourth ventricles, including the hypothalamus and area postrema. Lesions in the dorsal brainstem, especially near the fourth ventricle, are considered characteristic and are frequently associated with severe nausea, vomiting, and hiccups. Extensive tumescent or fusiform lesions

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in the hemispheric white matter may mimic acute disseminated encephalomyelitis or neoplasms. Corticospinal involvement is also commonly seen, typically presenting in a longitudinally extensive and symmetrical pattern.

In this patient, the brain MRI revealed symmetric T2/FLAIR hyperintensities in the periventricular white matter, centrum semiovale, and external capsule, along with lacunar infarcts in the basal ganglia. This pattern closely resembles that seen in CADASIL and differs from the characteristic lesions typically associated with NMOSD, which more often involve the periependymal regions of the brainstem, diencephalon, and area postrema. Therefore, these imaging findings suggest an alternative etiology that is not typical of NMOSD.

Differentiating NMOSD from CADASIL and other leukodystrophy-like conditions is crucial due to overlapping radiological findings and differing treatment approaches.[2,5] Such cases often exhibit symmetrical confluent white matter involvement, including subcortical regions and the external capsules, which makes diagnosis challenging.

While CADASIL is characterized by microangiopathy resulting from Notch3 mutations,[6] NMOSD pathology is driven by AQP4-IgG-induced astrocytopathy, which leads to demyelination and secondary changes in white matter.[1,5] In addition, leukodystrophies or toxic-metabolic leukoencephalopathies should be considered when extensive white matter changes are observed on brain imaging.[5] Comprehensive serological testing for AQP4 antibodies and genetic studies are essential for distinguishing these entities.

Although typical brain MRI findings of NMOSD were absent in this case, the patient's clinical history included episodes suggestive of area postrema syndrome and optic neuropathy, which were not assessed through neuroimaging or antibody testing at that time. While the visual symptoms partially improved spontaneously, they remained persistently impaired, indicating the possibility of optic neuritis. The symmetric white matter lesions initially raised suspicion for CADASIL, prompting NOTCH3 genetic testing, which returned negative results. Considering the patient's seropositivity for AQP4 antibodies and the clinical context, we explored CNS inflammatory etiologies. This case highlights the importance of including NMOSD in the differential diagnosis, even when imaging patterns resemble leukodystrophies or hereditary small vessel disease.

In this case, the symmetrical pattern of white matter hyperintensities initially suggested CADASIL. However, the absence of Notch3 mutations and the presence of AQP4 antibodies confirmed NMOSD. In conclusion, our report indicates that when headaches are accompanied by extensive white matter lesions, the presence of additional symptoms—such as visual impairment or unexplained nausea and vomiting—should prompt consideration of NMOSD as a potential diagnosis.

REFERENCES

1. Kim HJ, Paul F, Lana-Peixoto MA, Tenembaum S, Asgari N, Palace J, et al. MRI characteristics of neuromyelitis optica spectrum disorder: an international update. Neurology 2015;84:1165-1173. PUBMED | CROSSREF
2. Lee JS, Choi MK, Lee JJ, Seok HY. A little-known brain imaging feature in neuromyelitis optica spectrum disorder: a leukodystrophy-like pattern. J Clin Neurol 2019;15:256-258. PUBMED | CROSSREF

3. Masters-Israilov A, Robbins MS. Headache in neuromyelitis optica. Curr Pain Headache Rep 2017;21:20. PUBMED | CROSSREF
4. Kim SM, Kim SJ, Lee HJ, Kuroda H, Palace J, Fujihara K. Differential diagnosis of neuromyelitis optica spectrum disorders. Ther Adv Neurol Disorder 2017;10:265-289. PUBMED | CROSSREF
5. Bersano A, Kraemer M, Burlina A, Mancuso M, Finsterer J, Sacco S, et al. Heritable and non-heritable uncommon causes of stroke. J Neurol 2021;268:2780-2807. PUBMED | CROSSREF
6. Yamamoto Y, Liao YC, Lee YC, Ihara M, Choi JC. Update on the epidemiology, pathogenesis, and biomarkers of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. J Clin Neurol 2023;19:12-27. PUBMED | CROSSREF