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Letter to the Editor

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A Case of Adult-Onset Leukoencephalopathy With Axonal Spheroids and Pigmented Glia mimicking Multiple Sclerosis

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Dear Editor,

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare, autosomal dominant white matter disorder that presents with cognitive decline, parkinsonism, pyramidal signs, and gait disturbance.[1] Early diagnosis is often challenging due to its heterogeneous clinical presentation.

A 34-year-old woman presented with right-sided weakness and gait disturbance. Six months later, she developed dysarthria and dysphagia. Neurological examination showed mild weakness (Medical Research Council grade 4) in the right upper and lower extremities and hyperreflexia in both legs. Sensory examination was normal, and cognition was relatively preserved. Brain magnetic resonance imaging (MRI) revealed multiple bilateral T2 hyperintense lesions involving the periventricular, juxtacortical, and deep white matter, with diffusion restriction on diffusion-weighted imaging without splenial involvement or calcification (**Fig. 1A and B**). Cerebrospinal fluid analysis showed normal cell count and protein level, with negative oligoclonal bands. Serum aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies were negative. Based on the 2017 McDonald criteria, she was initially diagnosed with relapsing-remitting multiple sclerosis (MS). Dissemination in space was fulfilled by the presence of periventricular and juxtacortical lesions, while dissemination in time was based on two clinical attacks occurring six months apart (right-sided weakness followed by dysarthria and dysphagia).[2] The patient was treated with intravenous methylprednisolone followed by teriflunomide. Despite sequential treatment with dimethyl fumarate, cladribine, and rituximab, her symptoms progressively worsened. Behavioral and personality changes emerged, including emotional lability, perseveration, and impaired emotional control. At 14 months, follow-up brain MRI demonstrated progressive bilateral frontal-predominant white matter lesions, corpus callosum thinning, and persistent diffusion restriction (**Fig. 1C and D**). The Mini-Mental State Examination score declined from 25/30 at 26 months to 23/30 at 34 months despite 16 years of education. She became bedridden within 3 years after onset.

Given the rapid progression, poor response to multiple immunotherapies, prominent frontal involvement, evolving cognitive and behavioral symptoms, and persistent diffusion

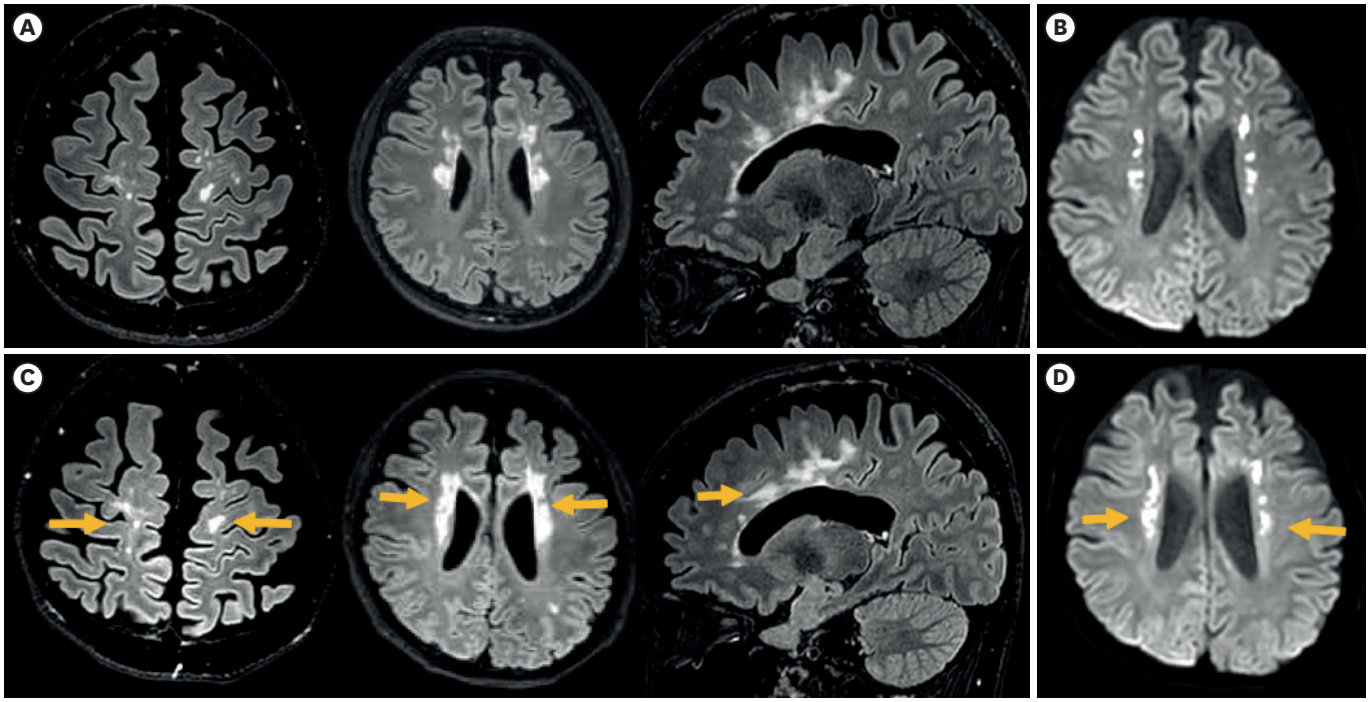

Fig. 1. Serial MRI showing progressive white matter lesions. (A) Initial brain MRI demonstrates multiple T2 hyperintense lesions involving the juxtacortical and periventricular white matter, fulfilling dissemination in space according to the 2017 McDonald criteria. (B) DWI shows diffusion restriction in the periventricular lesions. (C) Follow-up MRI obtained one year later demonstrates progression of the white matter lesions, with increased extent (arrows), along with mild frontal lobe atrophy. (D) Follow-up DWI shows persistent diffusion restriction with progression of the periventricular lesions (arrows), an unusual finding for multiple sclerosis that prompted reconsideration of the diagnosis.
MRI: magnetic resonance imaging, DWI: diffusion-weighted imaging.

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

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restriction, a leukodystrophy was suspected. The patient fulfilled the diagnostic criteria for probable ALSP proposed by Konno et al.[3] Genetic testing identified a heterozygous CSF1R variant (NM_005211.3:c.2381T>C, p.Ile794Thr), which was classified as a pathogenic variant according to the ACMG/AMP guidelines.[4] This missense variant is located within the tyrosine kinase domain of CSF1R, where most pathogenic ALSP-associated variants cluster. The variant has been previously reported in patients with ALSP.[5] Family history was negative for neurodegenerative disease; her father died in his 50s from complications related to alcohol use disorder.

ALSP is occasionally misdiagnosed as MS in the early stage due to overlapping clinical and radiological features.[6] Similar to MS, patients may present with gait disturbance, limb weakness, tremor, and multifocal white matter lesions on MRI.[7] In our case, several factors initially supported a diagnosis of MS, including the patient's young age, unilateral motor symptoms, relative preservation of cognition and psychiatric function at onset, central vein sign in a single periventricular lesion, periventricular white matter lesions, and absence of splenial involvement. However, after reviewing brain MRIs of our patient, several features distinguishing ALSP from MS were identified, such as confluent rather than ovoid lesions, no involvement of the brainstem, cerebellum or temporal lobes, no lesion enhancement, and persistent diffusion restriction on follow-up MRI. Overall radiologic pattern was more consistent with ALSP.

Although no established disease-modifying therapy exists for ALSP,[6] early diagnosis remains important to avoid unnecessary immunotherapy. Emerging evidence suggests that

hematopoietic stem cell transplantation and microglia replacement strategies may have the potential to modify disease progression; however, their efficacy and long-term safety remain to be established.[8] This case highlights that ALSP should be considered in young adults with rapidly progressive, treatment-refractory MS-like presentations. Early genetic testing is essential for accurate diagnosis.

The study was approved by the Institutional Review Board of Samsung Medical Center (IRB No: 2021-05-087) and written informed consent was obtained from the patient.

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