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A case of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia presenting with alien hand syndrome

Dear Editor,

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is characterized by demyelination of brain white matter, swollen axons, pigmented glial cells, local and generalized brain atrophy, and thinning of the cortex and corpus callosum [1]. ALSP is inherited as an autosomal dominant disorder, and CSF1R gene mutation is known to be the most common mutation [1]. The common symptoms of ALSP at disease onset are cognitive impairment, psychiatric symptoms, parkinsonism, gait disturbances, and speech problems [1]. We report the case of a patient who developed isolated alien hand syndrome (AHS) at symptom onset.

A 44-year-old woman visited our hospital complaining of discomfort when using both hands for approximately 2 years. She complained that both hands moved in the opposite or same direction and interfered with each other. For example, when she gets dressed, both hand would move in opposite directions, making it uncomfortable to dress and dropping objects after holding them. Neurological examination showed no specific findings other than clumsiness of the left hand. Her mother was diagnosed with dementia of neurodegenerative disease in her 70's and passed away in her 80's. There was no evidence of other family members having been affected. General cognitive status and gait were normal, and she did not have myoclonus, apraxia, and/or neglect syndrome. Laboratory findings were normal including full blood count, chemistry, thyroid function, vitamin B12, homocysteine, HIV, hepatitis B, syphilis, autoimmune markers, and tumor markers. Brain MRI showed hyperintensity and atrophy of the corpus callosum (Fig. 1A & B). AHS resolved spontaneously. After 2 years, she revisited the hospital with a depressive mood and memory decline. She had mild parkinsonism. Comprehensive neuropsychological battery confirmed early stage dementia. Follow-up brain MRI showed that the diffuse brain atrophy and white matter hyperintensities had progressed (Fig. 1C and D). Whole exome sequencing was performed to differentiate adult-onset leukodystrophy, and CSF1R mutation(c.2330G > A, p.Arg777Gln) was observed. At 48 years of age, she was hospitalized with status epilepticus and then progressed to being bed-ridden.

Here, we consider a number of noteworthy factors. First, this patient developed early AHS without any other symptoms. Motor symptoms are the more frequent initial symptoms in young women (under 30's) [1]. However, more than half of ALSP patients develop two or more symptoms in the early stages of the disease, of which cognitive symptoms and psychiatric symptoms are known to be the most common [1,2]. Second, AHS is caused by heterogeneous pathologies, such as stroke, corticobasal syndrome (CBS), Alzheimer's disease, and Creutzfeldt-Jakob disease (CJD) [3]. The timing of the onset of AHS varies depending on the disease. It has been reported that patients with stroke and CJD developed AHS at the time of symptom onset, patients with CBS approximately one year later, and patients with ALSP about 9 months later [4]. It is unusual for the initial symptom of ALSP as in this case. Third, we did not identify the underlying pathology at the initial presentation of AHS, although the corpus callosum lesion was a possible cause of AHS. It took two years from the hospital visit to the diagnosis. To eliminate the corpus callosum pathology, laboratory tests for infection, inflammation, and toxic or metabolic causes were performed, and all were negative. Ruling out multiple sclerosis was necessary, unfortunately, it was not done. After two years, the clinical features and MRI findings satisfied the diagnostic criteria of ALSP [2], allowing for further diagnosis to be made using genetic testing. Hereditary white matter diseases are difficult to diagnose because their clinical and imaging findings overlap [5]. Although genetic testing is expensive, it is recommended that it should be performed immediately if clinical diagnosis is uncertain after treatable or acquired causes are identified in white matter diseases.

This case of ALSP had a clinical course that started with AHS and progressed to parkinsonism, dementia, and seizures, and involved the corpus callosum and white matter in the brain sequentially. There are still uncertainties regarding the early symptoms and natural course of ALSP. The development of techniques in brain imaging and genetic testing is crucial for early diagnosis of ALSP.

Ethnic statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the Gyeongsang National University Hospital (GNUH 2020–09-007) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A waiver of informed consent was granted by the Institutional Review Board of the Gyeongsang National University Hospital, Korea.

CRediT authorship contribution statement

Bora Chung: Data curation, Writing – original draft. **Minkyeong Kim:** Data curation, Visualization. **Soo-Kyoung Kim:** Data curation, Visualization. **Heeyoung Kang:** Conceptualization, Writing – original draft.

Declaration of Competing Interest

None.

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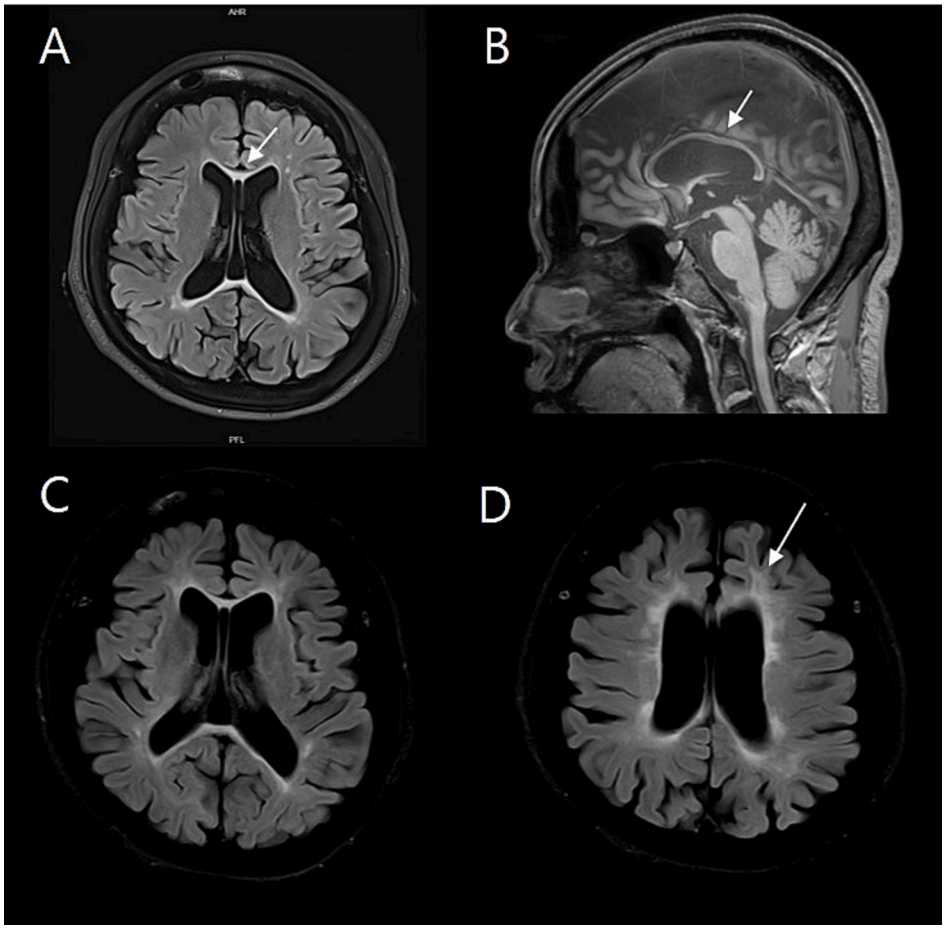

Fig. 1. Initial brain MRI shows hyperintensities (A) and thinning of the corpus callosum (B). Follow-up MRI reveals progressive brain atrophy and abnormal signals in periventricular white matter, especially frontal area (C and D).

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