Case Report

J Korean Soc Radiol 2023;84(3):736-744
https://doi.org/10.3348/jksr.2021.0015
eISSN 2951-0805

JOURNAL of THE KOREAN SOCIETY of RADIOLOGY

Characteristic MR Imaging Features and Serial Changes in Adult-Onset Alexander Disease: A Case Report

성인형 알렉산더병의 자기공명영상 소견 및 추적 관찰상의 변화: 증례 보고

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Received January 21, 2021
Revised July 5, 2022
Accepted October 6, 2022

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Adult-onset Alexander Disease (AOAD) is a rare genetically determined leukoencephalopathy that presents with ataxia, spastic paraparesis, or brain stem signs including speech abnormalities, swallowing difficulties, and frequent vomiting. The diagnosis of AOAD is frequently proposed based on the findings on MRI. We demonstrate two cases (37-year-old female and 61-year-old female) with characteristic imaging findings and changes in follow-up MRI in patients with AOAD, which were confirmed via glial fibrillary acidic protein (*GFAP*) mutation analysis. On MRI, the typical tadpole-like brainstem atrophy and periventricular white matter abnormalities were noted. The presumptive diagnoses were made based on the typical MRI appearances and, subsequently, confirmed via *GFAP* mutation analysis. Follow-up MRI demonstrated the progression of atrophy in the medulla and upper cervical spinal cord. Our report could help raise awareness of characteristic MRI findings of AOAD, thus helping clinicians use *GFAP* analysis for AOAD diagnosis confirmation.

Index terms Alexander Disease; Adult; Magnetic Resonance Imaging

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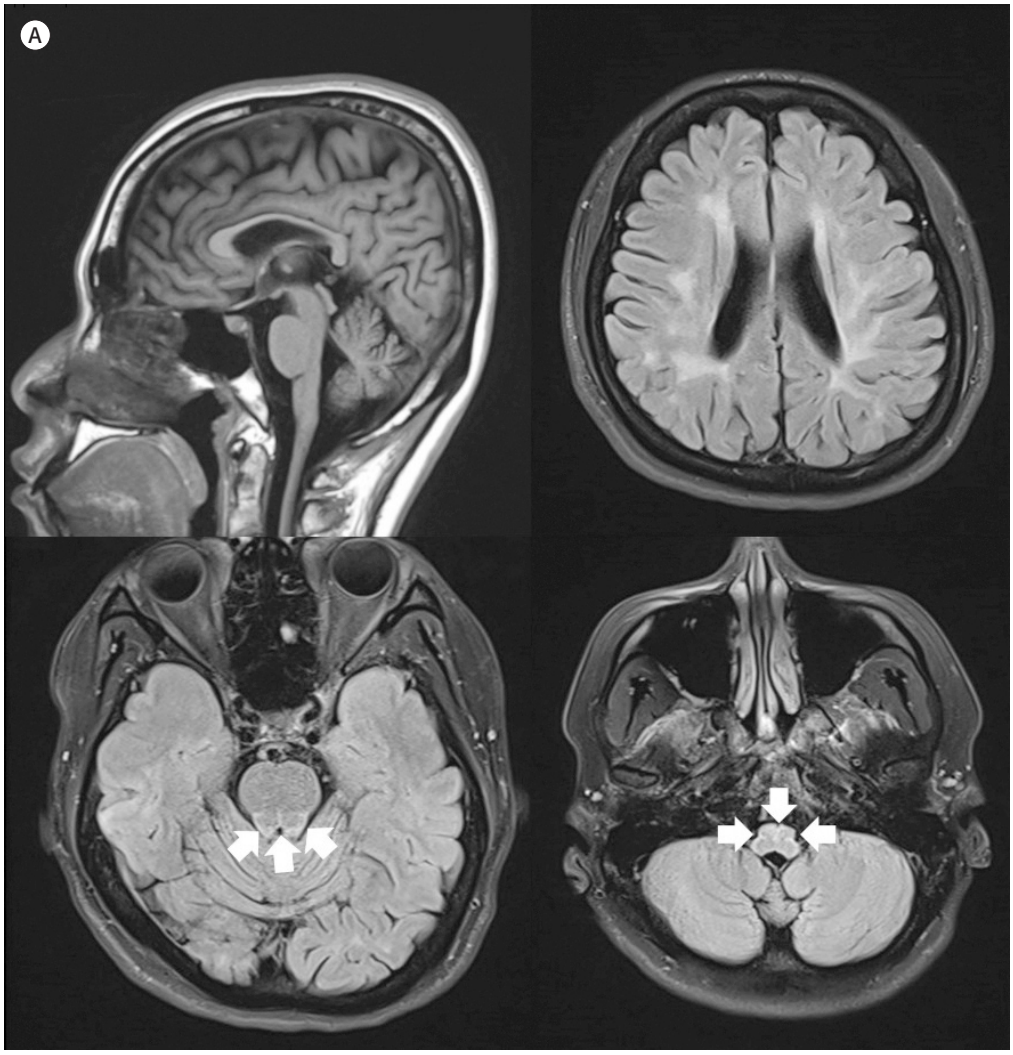
INTRODUCTION

Alexander disease (AD) is known to be genetically determined leukoencephalopathy usually affecting infants and children that leads to death in 2 months to 7 years (1). Among the subtypes of AD, adult-onset AD (AOAD) is a rare subtype that presents milder symptoms such as ataxia, spastic paraparesis, and/or lower brain stem signs including speech abnormalities, swallowing difficulties and frequent vomiting (2). The diagnosis of AOAD has been made by detecting the mutation of the glial fibrillary acidic protein (*GFAP*) gene since 2001 (3). However, suspecting AOAD based on clinical presentation is challenging because the symptoms may not be specific enough to make the diagnosis of AOAD although the presence of ataxia with palatal

Fig. 1. Case 1. MRI of AOAD in a 37-year-old female.
A. Initial MRI findings. Sagittal T1-weighted image (left upper) shows mild atrophy of the medulla oblongata and cervical spinal cord with relative sparing of the pontine base, consistent with tadpole-like brainstem atrophy. Axial FLAIR image (right upper) shows confluent high signal lesions involving supratentorial periventricular white matter. Pial signal changes appear as a rim of hyperintensity along the surface of midbrain, pons and medulla (arrows) on FLAIR images (lower).
AOAD = adult-onset Alexander disease, FLAIR = fluid-attenuated inversion recovery



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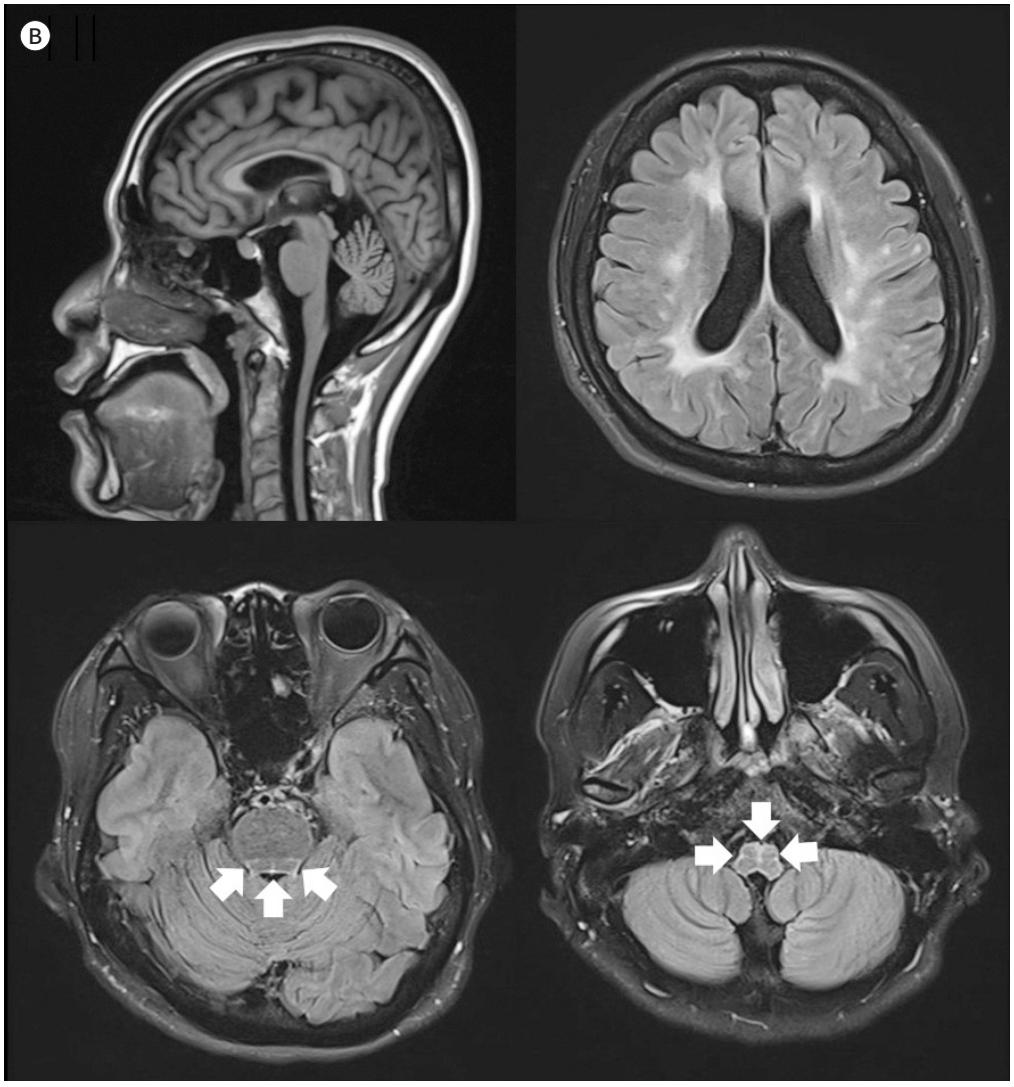
tremor may suggest the possibility of AOAD (4). Therefore, diagnosis is often suggested based on the imaging findings of MRI, and then further genetic testing is recommended. Here, we demonstrate two patients with AOAD who presented with characteristic imaging findings and serial changes on follow-up MRI.

CASE REPORT

CASE 1

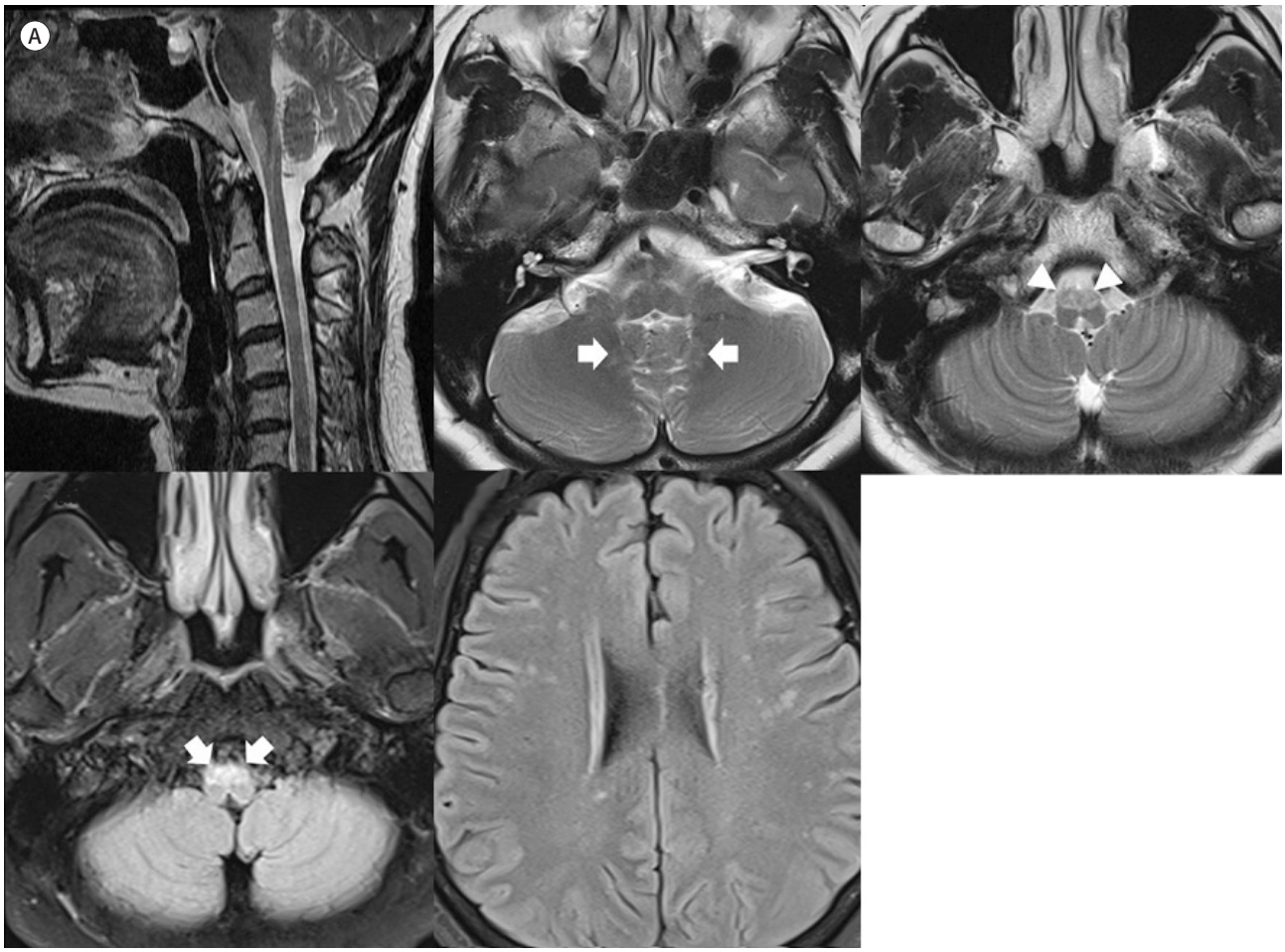
A 37-year-old female visited our hospital with a history of slowly progressive ataxia and spastic paraparesis for a period of 6 years. Spastic gait, increased deep tendon reflex (DTR)

Fig. 1. Case 1. MRI of AOAD in a 37-year-old female.
B. Follow-up MRI after 2 years. Sagittal T1-weighted image (left upper) shows the progression of tadpole-like atrophy of medulla oblongata and upper part of cervical spinal cord. Axial FLAIR image (right upper) shows slightly progressive periventricular white matter abnormalities. Pial signal changes along the brainstem are still present (arrows) on FLAIR images (lower).
AOAD = adult-onset Alexander disease, FLAIR = fluid-attenuated inversion recovery



and Hoffmann signs were present on neurologic examination. MRI examinations of the brain and cervical spinal cord were performed with a 3T machine. On the brain and spinal cord MRI (Fig. 1A), she showed mild atrophy of the medulla oblongata and cervical spinal cord with relative sparing of the basis pontis. She also showed confluent T2 high signal changes, which were prevalent in the posterior periventricular white matter (WM). A hyperintense rim on fluid-attenuated inversion recovery (FLAIR) was present along the surface of the midbrain, pons and medulla. Follow-up MRI after 2 years (Fig. 1B) demonstrated a slight progression of atrophy in the medulla oblongata and upper part of the cervical spinal cord, which is suggestive of tadpole-like atrophy. There was no evidence of atrophy in the pons and midbrain. Finally, AOAD was suspected based on the typical MRI findings. With informed consent, molecular genetic analysis of *GFAP* was performed, and a confirmative diagnosis of AOAD was made.

Fig. 2. Case 2. MRI of AOAD in a 67-year-old female.
A. Initial MRI of AOAD in a 61-year-old female. Sagittal T2WI shows mild thinning of the medulla oblongata and upper cervical spinal. Axial T2WI (upper) and FLAIR (lower) images demonstrated high signal changes involving the corticospinal tract of medulla (arrows) and hilum of the dentate nuclei (arrowheads). Multifocal periventricular white matter high signal lesions are noted on an axial FLAIR image, although it is not as prominent as that in Case 1.
AOAD = adult-onset Alexander disease, FLAIR = fluid-attenuated inversion recovery, T2WI = T2-weighted image



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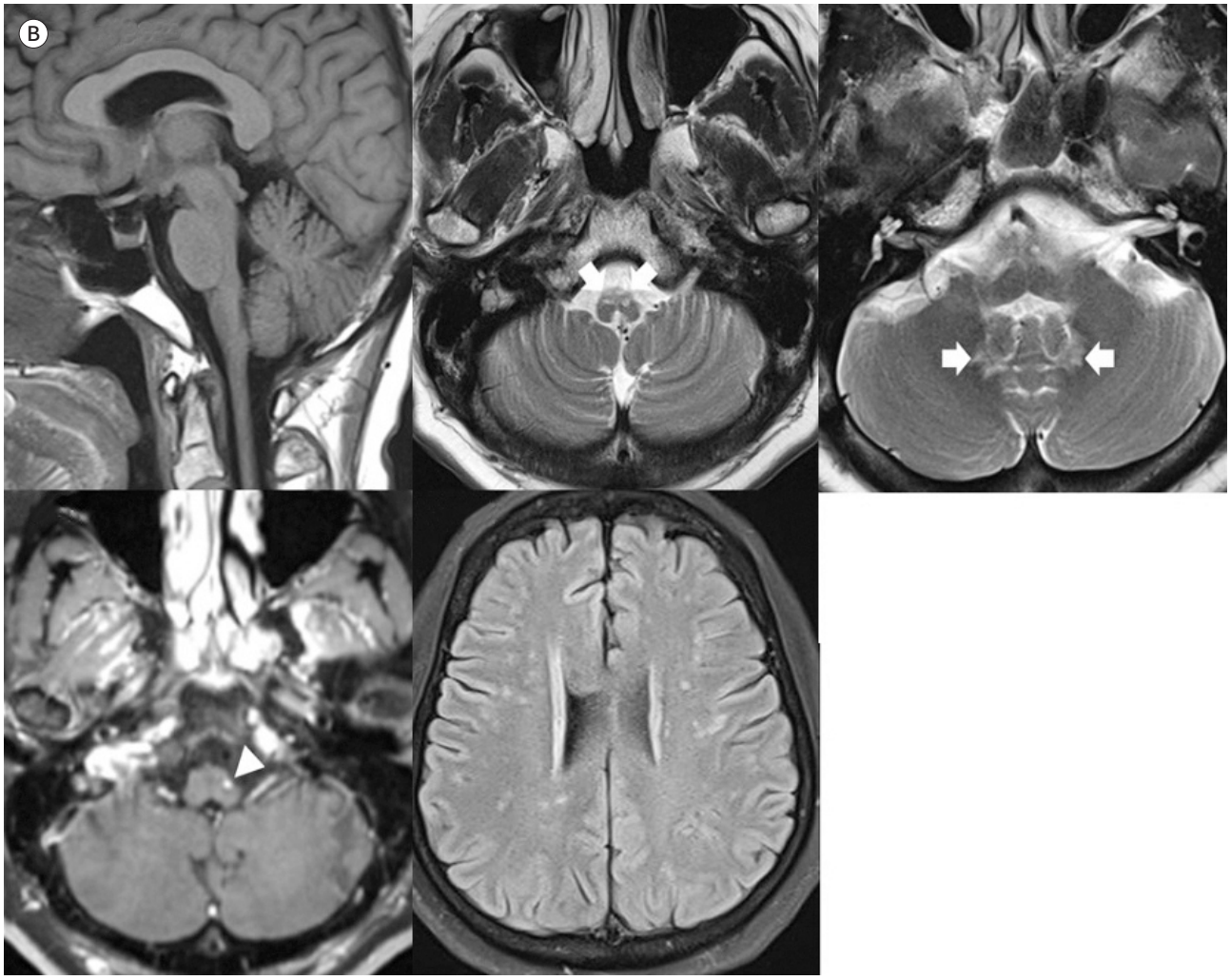
CASE 2

A 61-year-old female was referred to our hospital with a history of slowly progressive right leg paresthesia, hemiparesis, and a non-whirling nature of dizziness for 4 years. She showed increased DTR and positive Babinski signs on neurologic examination. MRI examinations of the brain and cervical spinal cord were performed. Subsequent brain and spinal cord MRI (Fig. 2A) showed typical tadpole-like brainstem atrophy. She also showed multifocal T2 high signal lesions in the periventricular WM that were less prominent than in Case 1. High signal intensities in the anterior half of the medulla oblongata were noted on the T2WIs, which corresponds to the areas of the medial lemniscus and the corticospinal tracts. Additionally, a small area of contrast enhancement was present in the medulla oblongata. Abnormal high signal lesions were also present in the hila of bilateral dentate nuclei on the T2WIs and FLAIR

Fig. 2. Case 2. MRI of AOAD in a 67-year-old female.
B. Follow-up MRI after 3 years. Sagittal T1WI shows slightly progressed atrophy of the lower medulla and upper cervical spinal cord. Axial T2WI (right) demonstrated the increased extent of high signal lesions involving the hilum of the dentate nuclei (arrows) and slightly progressed atrophy and high signal change involving the ventral medulla (arrows). T1WI (lower left) shows a tiny contrast-enhanced lesion on the left side of the medulla (arrowhead). Axial FLAIR (lower right) shows slightly progressive periventricular white matter abnormalities.
AOAD = adult-onset Alexander disease, T1WI = T1-weighted image, T2WI = T2-weighted image



images. Follow-up MRI after 3 years (Fig. 2B) demonstrated a slight progression of the atrophy in the medulla oblongata and upper part of the cervical spinal cord. Based on the MRI findings, *GFAP* mutation analysis was performed with informed consent, and thereby AOAD was confirmed.

The results of genetic testing for spinocerebellar ataxia (*SCA*)-1, *SCA*-2, *SCA*-3, *SCA*-6, *SCA*-7 and *SCA*-17, and spastic paraplegia (*SPG*) 3A and *SPG*4 genes show that mutations were not present in either case. In addition, there were no abnormalities in the enzyme activities of arylsulfatase A and ß-galatocerebrosidase in leukocytes or in the concentration of very long chain fatty acids in either patient.

The Institutional Review Board of our hospital waived informed consent for use of the data due to its retrospective nature (IRB No. 2020-04-013).

DISCUSSION

Herein, we report two patients with sporadic AOAD, who showed typical MRI findings. Similar to previous studies, the patients in our study showed tadpole-like brainstem atrophy, signal changes involving the periventricular WM, dentate nuclei, and medulla with pial high signal changes on FLAIR images, and a contrast-enhanced lesion in the brainstem (5). These characteristic MRI findings allowed us to perform *GFAP* gene tests for diagnosing AOAD. Thus, we reconfirm that these characteristic MRI findings could help physicians to effectively select patients who need genetic testing for *GFAP* to make an appropriate diagnosis and a proper management plan.

Recent studies have proposed that subtypes of AD can be classified into two categories according to clinical and neuroimaging findings: type I, which is characterized by early onset, seizures, and megalencephaly and type II, which is characterized by a later age of onset and brainstem features, and atypical MRI findings as for our study (6). Compared with infantile form of AD, periventricular WM involvement was relatively sparse in AOAD (7). Moreover, periventricular WM lesion of AOAD does not always show frontal predominance (4, 8). In addition, pial FLAIR signal abnormalities, signal changes in the middle cerebellar peduncle and contrast-enhanced lesions in the brain stem of AOAD are previously unrecognized imaging features in the infantile form of AD. A recent study suggested that pial signal abnormality in FLAIR image mainly located on the surface of the medulla may help to differentiate AOAD from other disease involving the brainstem (5). Farina et al. (3) showed that patients less than 40 years old demonstrated periventricular WM abnormalities, and contrast enhancement more frequently in patients over 40 years.

It is challenging to diagnose AOAD if the patients do not present with typical clinical features such as ataxia with palatal tremor or typical MRI finding. For the radiologic differential diagnosis, several disorders such as demyelinating disease, encephalitis, or mitochondrial disease occasionally considered (2, 3). In the first case in our study, demyelinating disease such as multiple sclerosis or mitochondrial disease were included in the differential diagnosis list before focusing on the atrophy of medulla and upper cervical spinal cord on the initial MRI. However, the distribution of periventricular WM abnormalities and the high signal intensities along the surface brain stem do not support to diagnose as demyelinating disease.

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Furthermore, mitochondrial disease frequently involves the midbrain and pontine tegmentum than in the lower brainstem (2). Therefore, awareness of the characteristic imaging finding of AOAD allow radiologists to suggest AOAD. The results of a previous study show marked atrophy of the medulla is present in about 90% cases of AOAD, and this characteristic atrophy is highly specific of AOAD (9). As in patient 2 of our case, there are few reports about the signal changes selectively involving the medial lemniscus and the corticospinal tracts (3, 10). One report suggested that this finding may associated with a mutation in an alternative *GFAP* transcript, which is modulated by a non-neutral HDAC6 variant, but it is difficult to draw firm conclusion about the relationship between this genetic variant and this imaging finding due to insufficiency of previous research results.

Especially, the tadpole-like brainstem atrophy, which means the atrophy of the medulla oblongata and upper cervical spinal cord, is strongly suggestive of AOAD (3, 6). A case report followed a patient from 1998 to 2005 showed development and progression of atrophy of the medulla oblongata and spinal cord was the most striking feature among MRI findings (2). Another study demonstrated that two patients showed progressive atrophy of the medulla for 7 years follow-up period (3). Consequently, follow-up MRI might be helpful for young adult patients with unexplained lower-brainstem symptoms and signs.

According to the results of previous studies, mutation of the *GFAP* gene results in the accumulation of intracytoplasmic inclusions in the Rosenthal fibers, and this process is thought to be related to most cases of AD (4). It is known that the accumulation of Rosenthal fibers is predominantly distributed in the end-feet of the perivascular astrocytes, which are part of the blood–brain barrier (3). This pathophysiological process may contribute to the characteristic or various MRI findings in patients with AOAD; that the findings depend on the time of presentation and the disease course. In our study, the first 37-year-old patient showed pial signal changes on FLAIR images, whereas there were no such signal changes in the second 61-year-old patient. Moreover, supratentorial periventricular WM abnormalities were more extensive in the younger patient, whereas, were less apparent in the older patient. These findings might reflect different amounts and distribution of Rosenthal fibers, which might have differed according to the age of the individual at disease onset. Because Rosenthal fibers are thought to be distributed in the subpial, perivascular, and subependymal astrocytes, the pial signal changes on FLAIR images along the surface of the brainstem in our younger patient can be explained by the massive subpial prevalence of Rosenthal fibers (8, 10). Conversely, the absence of pial lesions in our older patient might reflect a substantial decrease in the amounts of the Rosenthal fibers with age increase. Moreover, malfunction of the blood-brain barrier due to the Rosenthal fibers might explain the contrast-enhanced lesion in the medulla of the second patient.

So far, the infantile form of AD typically leads to patient death within a few years whereas the bulbar dysfunction in AOAD usually shows slow progress (1, 4). Some authors have assumed that further progression of the contrast-enhanced lesions tends to be related to the severe degeneration and atrophy of brainstem structures (9). Our patients showed a symptom duration ranging from 4 to 6 years before the confirmative diagnosis and showed a slight progression of the tadpole-like brainstem atrophy in the follow-up MRI. Spasticity and paresthesia were slightly improved following conservative management. Therefore, the natural course

and exact pathogenic explanations of AOAD according to phenotypic diversity and the age of onset, remain as challenging issues.

In conclusion, we report two cases of AOAD showing characteristic MR imaging findings. Tadpole-like atrophy and high signal changes in the medulla oblongata to the upper cervical spinal cord and periventricular WM abnormalities were present, and these lesions showed progressive atrophy in the follow-up MRI. Awareness of these peculiar MRI findings in patients presenting with undetermined progressive spastic ataxia could help clinicians to make an appropriate diagnosis and management plan by selecting patients who need genetic testing for *GFAP* gene abnormalities.

Author Contributions

Conceptualization, Y.R.G., O.H.Y.; data curation, Y.R.G., O.H.Y.; formal analysis, Y.R.G., K.O., L.W.; investigation, all authors; project administration, Y.R.G., O.H.Y., L.J.Y.; resources, all authors; supervision, Y.R.G., L.J.Y.; visualization, Y.R.G., O.H.Y., L.J.Y.; writing—original draft, Y.R.G., O.H.Y.; and writing—review & editing, Y.R.G., O.H.Y., L.J.Y.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding

None

Acknowledgments

The authors acknowledge Hye Young Han of the medical library for her valuable contribution.

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성인형 알렉산더병의 자기공명영상 소견 및 추적 관찰상의 변화: 증례 보고

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성인형 알렉산더병은 운동 실조, 경련성 마비 또는 뇌간 징후를 나타내는 드문 유전 질환이다. 성인형 알렉산더병의 진단은 흔히 자기공명영상 검사 소견을 통해 내려진다. 이에 저자들은 glial fibrillary acidic protein (이하 *GFAP*) 유전자 변이 분석을 통해 확진된 37세와 61세 성인형 알렉산더병 환자의 특징적인 자기공명영상 소견과 추적 검사상 변화 사례에 대해 보고하고자 한다. 자기공명영상에서 환자들은 전형적인 뇌간 위축과 백질 이상 소견을 보였다. 특징적인 자기공명영상을 바탕으로 추정진단을 내렸으며 이후 *GFAP* 유전자 변이 분석을 통해 확진되었다. 또한, 추적 관찰 검사에서 연수와 상부 경부 척수 위축의 진행을 보였다. 이러한 성인형 알렉산더병의 특징적인 자기공명영상 소견에 대한 이해를 바탕으로, 감별진단을 위한 *GFAP* 유전자 검사 시행 결정에 도움이 될 수 있을 것이다.

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