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Letter to the Editor

Degenerative inferior olivary nucleus and medullary tegmentum produced the characteristic magnetic resonance imaging signs in Alexander disease: A case report

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Dear editor:

Alexander disease (AxD) is a rare neurodegenerative disease that is pathologically characterized by the presence of Rosenthal fibers in astrocytes. Ninety-eight percentage of AxD patients have detectable pathogenic variants in glial fibrillary acidic protein (GFAP) gene. Clinically, AxD is categorized into subtypes based on the age of onset, and the adult-onset AxD (AOAD) constitutes approximately 33% of affected individuals [1]. As a radiological finding in AxD, "tadpole appearance," which is characterized by the presence of relatively preserved pons and severely atrophied medulla oblongata on magnetic resonance imaging (MRI) [2], is well known. In addition, some patients with signal abnormalities in the anterior portion of the medulla oblongata have been reported, and Yoshida et al. called the findings the "eye spot" of the *Taenaris* sign [3]. The pathological background resulting in this "eye spot" sign is not well identified. Herein, we report the case of an autopsied patient with AxD, presenting the "eye spot" sign on MRI.

1. Case report

A 51-year-old woman, who had a history of scoliosis and no family history of neurological disease, presented with progressive dropped head syndrome (DHS) and gait disturbance for the past 6 years. Neurological examination revealed dysarthria, dysphagia, mild weakness of neck extensor muscle and extremities, and positive bilateral plantar reflex. Her gait was short-stepped and spastic. There was no evidence of ataxia, nystagmus, and palatal tremor (PT). She had urinary frequency and constipation. Electromyographic studies of the paraspinal muscles and extremities showed no neurogenic or myopathic changes. Brain and cervical magnetic resonance (MR) imaging revealed atrophy of the medulla oblongata and spinal cord. Moreover, T1-weighted MR image of the brain showed bilateral hyperintense basal ganglia, and T2-weighted MR image showed bilateral oval-shaped hyperintense areas in the anterior portion of the medulla oblongata [Fig. 1(A)]. As these imaging features were suggestive of AxD, we sequenced the GFAP gene and identified a heterozygous p.L123P (c.368T > C) missense mutation in the patient. On the basis of this information, the patient was clinically diagnosed as having AxD, and the clinical presentation of the patient was reported in 2017 [4][5:Patient NO.19]. Only two patients with the mutation have been reported [4–6]. The patient pursued a slowly progressive clinical course. She died suddenly when she was 53 years old, and an autopsy was performed.

The formalin-fixed brain weighed 1290 g. Macroscopically, severe atrophy of the medulla oblongata and spinal cord was observed. An old contusion was noted in the inferior side of the left frontal lobe. The cerebral hemispheres, basal ganglia, thalamus, and pons appeared normal. Microscopically, the inferior olivary nucleus (IO) and medullary pyramid demonstrated atrophy. Additionally, neuron loss was detected in the IO and reticular formation of the medulla oblongata. The demyelination of the medullary tegmentum was severe in the reticular formation, although the neuronal losses in the hypoglossal nucleus and dorsal nucleus of the vagus were relatively preserved. In the cerebellum, the white matter showed discolored myelin sheath and numerous Rosenthal fibers. A decrease in the number of Purkinje cells and an increase in the number of Bergmann glia were also observed. Calcification of the perivascular areas of the caudate nucleus, internal capsule, putamen, and globus pallidus was observed. The number of GFAP-reactive astrocytes decreased drastically in the medullary tegmentum as compared with the normal control. Rosenthal fibers appeared in the caudate nucleus, putamen, pons, periventricular area, and the cerebellar white matter [Fig. 1(D)]. In the caudate nucleus and putamen, discoloration of myelin and swelling and/or anaplastic nuclear changes of astrocytes were observed. The spinal cord showed severe atrophy and rarefaction of the ventral and lateral funiculus; the dorsal funiculus was spared. The anterior horn showed severe atrophy with no neuron loss. Both large and small fibers in the corticospinal tract (CST) were atrophic and decreased in number. The neurons of the sacral segment were relatively preserved. There was no apparent axonal loss in the anterior and posterior nerve roots. The muscles of the posterior region of the neck did not exhibit any remarkable change. The pathological diagnosis was AxD, which coincided with the clinical diagnosis.

2. Discussion

The patient had a heterozygous c.368T > C missense mutation in

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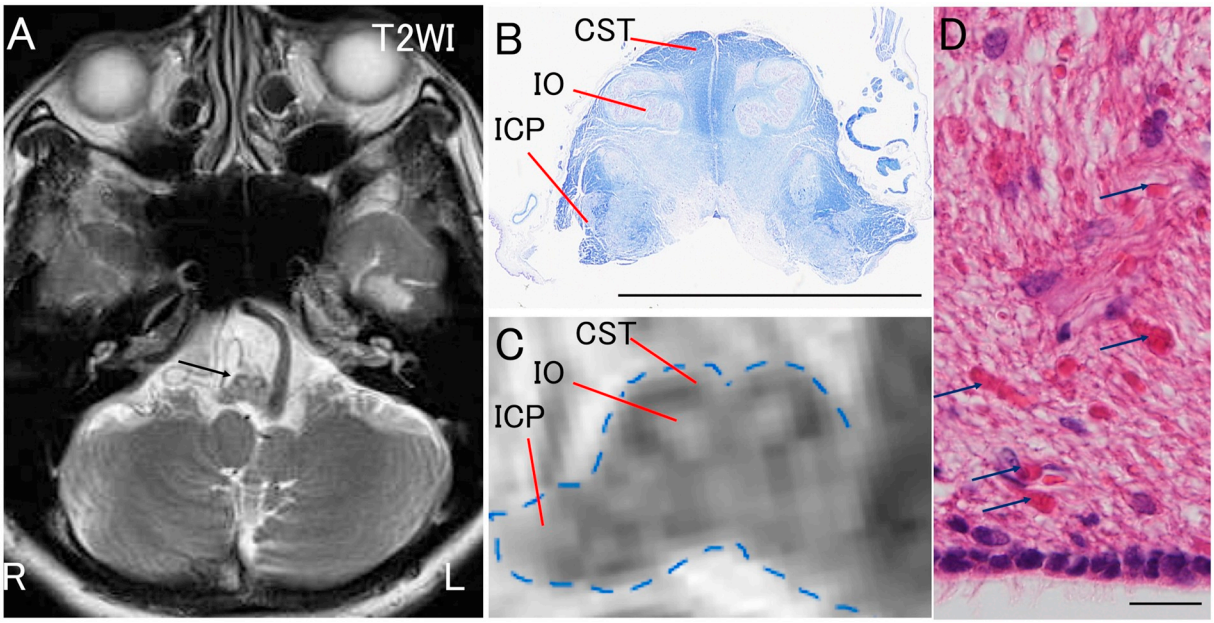

Fig. 1. T2 weighted MR image showed abnormal signal in the anterior portion of the medulla oblongata, which is called "eye spot" of taenaris (arrow) (A). Pathology specimen and enlarged view of the medulla oblongata on MRI indicates "eye spot" coincides with the IO and the medullary tegmentum (B) (C). B:Klüver-Barrera staining scale:1 cm. Rosenthal fibers in the pons (arrow) (D). Hematoxylin-Eosin staining scale:20 μm. Abbreviations: IO = inferior olivary nucleus; CST = corticospinal tract; ICP = inferior cerebellar peduncle.

GFAP, and based on the autopsy, the mutation is pathogenic. Tadpole appearance, which is characterized by the presence of relatively preserved pons and severely atrophied medulla oblongata, is a well-known radiological feature of AOAD. In 2015, Yoshida et al. reported 4 cases of AOAD in which the anterior portion of the medulla oblongata demonstrated an MRI signal abnormality resembling the "eye spot" of *Taenaris* [3]. We identified nine cases (reported in English) in which signal abnormality in the anterior portion of the medulla was observed [1,7–11]. The abnormal signal had been presumed to indicate that the CST or medial lemniscus was affected [3,7]. However, our case suggests that the signal could be compatible with IO and medullary tegmentum [Fig. 1(B) (C)].

PT is a characteristic symptom of AOAD and is exhibited in 41% of patients [8]. In AOAD patients with PT, one case of hypertrophic olivary degeneration on T2-weighted MR image was reported [12]. Patients with the "eye spot" sign may have atrophic IO, and none of the 10 reported cases, including our case, exhibited PT. More cases are required to discuss the relationships between PT in AxD and IO.

As we have previously reported, the chief complaint in the current case was DHS; previously, three cases of AxD with DHS were reported [4]. The autopsy showed that the motor neurons in the anterior horn of the spinal cord were preserved and that the muscles of posterior region of the neck did not present remarkable change. Although it was difficult to elucidate the mechanism of DHS, disturbance of the CST and extrapyramidal problems, such as dystonia, were considered to play a role in the symptom.

In conclusion, the "eye spot" sign indicates that the IO and medullary tegmentum are affected and that DHS in AxD may be caused by pyramidal or extrapyramidal dysfunction.

Consent form

Written informed consent was obtained from the husband of the patient for autopsy and publication of this case report and any accompanying images.

Conflicts of interest

None.

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