Pearls & Oy-sters: Adult-Onset Alexander Disease With Transient Swelling of the Medulla Oblongata

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Pearls
- Alexander disease should be considered in patients of all ages, especially in juveniles and adults, with contrast-enhancing lesions in the lower brainstem or upper spinal cord.

Oy-sters
- In adult-onset Alexander disease, the medulla oblongata may swell transiently and atrophy over time.
- In order to avoid sudden respiratory decompensation, patients with adult-onset Alexander disease should be given anticipatory guidance and undergo periodic laryngoscopy, even if the patient has been stable for a long time.

Alexander disease is a rare hereditary neurodegenerative disorder caused by variants of the glial fibrillary acid protein (GFAP) gene. Adult-onset Alexander disease (AOAD) is associated with muscle weakness, spastic paralysis, bulbar palsy, ataxia, and autonomic disorders in a variety of combinations. The MRI findings of AOAD are characterized by atrophy of the medulla oblongata and abnormal signals. However, our patient had transient swelling of the medulla oblongata in the early stages of the disease, which atrophied more than 10 years later, resulting in bilateral vocal cord paralysis. We followed the patient’s symptomatology and imaging changes over a 13-year period. There are no similar reports of transient swelling of the medulla oblongata and long-term AOAD follow-up. This finding has important clinical and pathologic implications for Alexander disease.

Case Report
A 45-year-old man presented at our department with unsteadiness while walking. He was unable to walk in tandem gait, and had nystagmus, diplopia, and slight dysarthria. Both his parents had died of a stroke. His brother and 3 daughters were in good health. Serum angiotensin-converting enzyme levels were not elevated, and the results were negative for interferon-γ release assay, β-D-glucan, and toxoplasma antibodies. The results were also negative for rheumatoid factors, antinuclear antibody, anti-AQP4 antibody, and anti-MOG antibody. Antineutrophil cytoplasmic antibodies levels were within normal ranges. CSF examination showed a total cell count of 6/3 μL (normal 0–10) with 0% neutrophils and 100% monocytes, CSF protein 61 mg/dL (normal 10–40), CSF glucose 59 mg/L (normal 48–75), and immunoglobulin G index 0.6 (normal <0.7). No oligoclonal bands were observed. MRI showed a swelling of the medulla oblongata with a sagittal diameter of 17.0 mm, accompanied by increased signal intensity on T2-weighted images and gadolinium-enhancing effects. Fluorodeoxyglucose (FDG) PET did not show increased FDG uptake in the brainstem. IV methylprednisolone pulse therapy was administered under the assumption of brainstem encephalitis but no clinical or imaging improvements were observed.
At age 51 years, the patient developed intractable hiccups, although no other neurologic symptoms had changed. At 55 years of age, he suddenly developed severe dyspnea and was admitted to our department. On admission, he had marked wheezing and hoarseness. Arterial blood gas analysis (ABG) revealed a pH of 7.328, PaCO₂ of 66.1 mm Hg, PaO₂ of 45.0 mm Hg, and HCO₃⁻ of 33.8 mmol/L. Bilateral vocal cord paralysis was observed on laryngoscopy (figure). After an emergency tracheotomy, his respiratory condition gradually improved without mechanical ventilation (ABG revealed a pH of 7.408, PaCO₂ of 48.8 mm Hg, PaO₂ of 71.3 mm Hg, and HCO₃⁻ of 30.2 mmol/L). MRI revealed mild atrophy of the medulla oblongata, 11.1 mm in diameter (figure).

We listed Alexander disease as a differential diagnosis based on these clinical and imaging features and sequenced the GFAP gene. We identified a novel heterozygous missense variant in exon 6: NM_002055.5: c.972 G > A (GRCh38/hg38 chr17:44,911,405), causing a change from glutamate to lysine at amino acid position 320 (p.E320K). The amino acid sequences surrounding glutamate at position 320 are highly conserved across species (figure), indicating their functional importance. Polyphen-2² and Mutation Taster² predicted that this variant is probably damaging and disease-causing, respectively. The high combined annotation-dependent depletion (CADD) score³ of 32 also indicates that this variant is deleterious. The patient did not require a ventilator at the time of discharge. However, at age 56, he developed night and daytime apnea and had to be placed on a ventilator. At 58, his ataxia had slightly worsened, and the medulla oblongata was atrophied to 9.3 mm in diameter (figure).

Figure Laryngoscopy and MRI Findings, Clinical Course, and Conservation Data of GFAP Amino Acid Sequence Among Different Species

(A) The vocal cords were observed using a laryngoscope. On expiration, bilateral vocal cords are closed (upper figure). The bilateral vocal cords are almost closed during inspiration (lower figure). (B) T2-weighted image at the age of 45 years shows a high signal range from the medulla oblongata to the superior cervical cord. (C.a) T1-enhanced image after gadolinium contrast at age 45 years shows an enhancing effect in a portion of the medulla oblongata. (C.b-F) Brainstem median sagittal section of MRI taken between the ages of 45 and 58 years. (C.b) T1-enhanced image after gadolinium contrast at the age of 45 years. The sagittal diameter of the medulla oblongata (MO) is defined as the vertical distance from just above the posterior kink at the cervicomedullary junction to the anterior surface of the medulla oblongata. MO at age 45 years was 17.0 mm. (D) MO at age 50 years was 14.3 mm. (E) MO at age 55 years was 11.1 mm. (F) MO at age 58 years was 9.3 mm. (G) Clinical course. (H) Conservation of GFAP amino acid sequence among different species (UCSC Genome Browser on Human; December 2013 [GRCh38/hg38 Assembly]).
Discussion

Alexander disease is classified according to the age at onset as infantile (IOAD), juvenile (JOAD), or AOAD, each of which has its own peculiar imaging characteristics. MRI features of IOAD include cerebral white matter abnormalities in the frontal lobe and signal abnormalities indicating swelling or atrophy of the basal ganglia and thalamus and periventricular rim. AOAD is characterized by brainstem lesions; abnormal signals in the white matter, basal ganglia, and thalamus are less frequent. JOAD may present with imaging features similar to those of IOAD or may have brainstem lesions as in AOAD.

Atrophy, from the medulla oblongata to the superior cervical cord, is a well-known feature of AOAD in MRI, and the sagittal diameter of the medulla oblongata (<9.0 mm) is useful for the diagnosis of the disease, with high sensitivity and specificity. However, in this case, the medulla oblongata did not atrophy to less than 9 mm, even 13 years after the onset of the disease. It was rather swollen in the early stages of the disease. We compared the sagittal diameter of the medulla oblongata in this case with the diameter of the cases in the control group included in a previous study. The medullary diameter (mean ± SD) of the control group was 12.3 ± 1.5 mm and the Z scores at each age (45, 50, 55, and 58 years) in this case were 3.13, 1.33, −0.80, and −2.00, respectively. In IOAD, swelling of the white matter and basal ganglia is sometimes observed. This is thought to be related to hyperplasia of astrocytes as well as the accumulation of Rosenthal fibers. The same pathophysiology may be assumed for the swelling in this case.

The disease course of this case provides insight into the classification of Alexander disease. Given the paucity of reports on long-term follow-up before and after the onset of AOAD, the medulla oblongata may be transiently swollen in the early stages of this disease. A previous study reported a similar course in a case of JOAD and made an interesting hypothesis about the phenotype of Alexander disease: that the brainstem atrophy of AOAD is a sequential condition from JOAD. Another study statistically classified Alexander disease into 2 groups: those with white matter lesions (type I) and those with brainstem lesions (type II). They proposed that type II includes a wide age range from infantile to adult-onset cases. This may be related to the fact that brainstem lesions in Alexander disease progressively change with patient age.

We listed brainstem encephalitis and Alexander disease as the differential diagnoses in this case. Other differential diagnoses included sarcoidosis, neuromyelitis optica, and brain tumors, such as gliomas. Inflammatory and immune mechanisms were ruled out because of the lack of response to steroids. A brain tumor was ruled out because of the lack of increased uptake on FDG-PET. AOAD might be a possible differential diagnosis in cases considered as refractory brainstem encephalitis.

This patient initially presented with hiccups and vocal cord paralysis, and eventually, apnea during the process of atrophy of the swollen medulla oblongata. There are several reports on cases with AOAD that resulted in obstructive or central respiratory failure. As in our case, one study showed vocal cord paralysis on laryngoscopy in a case of AOAD, suggesting that there are other similar cases. Therefore, we recommend that patients with AOAD should undergo laryngoscopy and polysomnography for assessment.

In this case, we found a GAP variant (c. 972 G > A) that had not been registered in any database. Based on the guidelines proposed by the American College of Medical Genetics and Genomics, this variant fulfills one moderate criterion (“The absence of the variant in population databases”) and 2 supporting criteria (“multiple lines of computational evidence supporting a deleterious effect on the gene” and “missense variant in a gene with a low rate of benign missense variation and in which missense variants are a common mechanism of disease”). This would only qualify for a “variant of unknown significance (VUS).” Although genetic analysis of the parents was not performed in this case, there was no family history of the disease. Based on this fact, if we judge this variant to be a de novo variant, it satisfies the “likely pathogenic” classification. Even if the variant only qualifies as VUS under the guidelines, the clinical picture of this case is consistent with Alexander disease. This is paradoxically important for clinicians. It suggests that even among genetic variants that are not considered highly pathogenic by the guidelines, there may be pathogenic variants that are buried because there are not enough data to classify them as such. Hence, it is important for clinicians to provide personalized medicine based on the clinical picture, not just on guidelines.

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