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Alexander Disease: An Important Mimicker of Focal Brainstem Glioma

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Abstract

We report the case of a 6 year old male who was referred to a tertiary oncology center with a focal brainstem lesion which was presumed to be neoplastic. Due to the symmetric nature of the lesion on magnetic resonance imaging, the evaluation was expanded to investigate other possible causes and eventual diagnosis of Alexander's disease was made. Alexander disease is a neurodegenerative disease which must be included in the differential for tumor-like lesions within the posterior fossa.

Keywords

Brainstem glioma; Alexander's disease; brain tumor mimic; neuro-oncology

The differential diagnosis for focal brainstem lesions in children is fairly limited but includes cancer, infection, vascular malformation and consequence of metabolic disease. We present a case of a CNS leukodystrophy presenting as a focal medullary lesion concerning for tumor. Alexander's disease should be included in the differential for focal tumor-like lesions within the posterior fossa.

A 6 year old male with a medical history significant for failure to thrive presented to our institution for an evaluation of a presumed medullary brainstem tumor. He had been born at 35 weeks gestational age and had an unremarkable infancy. At 3 years of age he began to experience intermittent vomiting and was diagnosed with gastro-esophageal reflux. Over the next several years, he developed chronic abdominal pain, anorexia, and failure to thrive for which he was evaluated by endocrinology and gastroenterology. An endoscopy revealed only gastritis and his laboratory evaluation was normal including testing for celiac disease. Prior to his referral to our institution, a magnetic resonance imaging (MRI) of the brain demonstrated a lesion within the brainstem concerning for cancer.

Except for failure to thrive, his medical history was unremarkable. He was meeting all developmental milestones and was excelling in kindergarten with academic achievement at a 3rd grade level. On exam, his head circumference was normal at the 50th percentile, but his weight and height were both below the 3rd percentile. His neurologic exam was normal

except for mild tremor and slightly increased deep tendon reflexes in the left upper extremity.

Repeat MRI was performed at our institution one week after the initial study and showed no changes in the lesion. MRI again demonstrated a well-defined, near-symmetric lesion within the dorsal part of the medulla oblongata (Figure 1A). The lesion involved the obex area and extended into the inferior cerebellar peduncles bilaterally (Figure 1B,C). After intravenous Gadolinium-based contrast agent administration, prominent, near homogeneous enhancement was noted (Figure 1D). The size and topography of the fourth ventricle were normal. No other lesions were seen within the brain parenchyma.

Given the radiographic findings in the setting of a prolonged clinical course and near normal neurologic examination, a diagnosis of low grade glioma was considered. However, the unusually symmetric appearance of the lesion prompted other considerations. In lieu of a biopsy, screening for potential infectious, metabolic and genetic disorders that could mimic a brain tumor was performed. As part of this evaluation, mutation analysis of the glial fibrillary acidic protein (*GFAP*) gene mutation was performed and ultimately revealed a novel pathogenic *GFAP* gene mutation (heterozygous C>T nucleotide substitution in exon 4 at amino acid position 258), confirming the diagnosis of Alexander disease (AD).

Classically described as a central nervous system (CNS) leukodystrophy that primarily affects the frontal white matter, AD is caused by mutation of the *GFAP* gene on chromosome 17q21. Its protein product *GFAP* is the primary intermediate filament in mature astrocytes and, as such, plays an important role in astrocytic motility, structural stability and cell homeostasis.¹ *GFAP* is also critical for the normal interaction between astrocytes and oligodendrocytes. In AD, abnormal *GFAP* accumulates in aggregates called Rosenthal fibers. These aggregates affect normal astrocytic function and induce a stress response.² As a result, demyelination and/or hypomyelination occurs, which causes progressive neurologic dysfunction occurs. Depending upon the area of CNS involvement, patients with AD may exhibit cognitive decline, ataxia, progressive spasticity, dysarthria, dysphagia, breathing problems and/or seizures. The age of presentation for patients with classical AD varies. However, the infantile (presentation prior to age 2 years) and juvenile (presentation between 3 and 10 years) forms of AD are most common, respectively 63% and 24% of cases. Although there are cases of children who survive into the third decade, most children have progressive neurologic decline resulting in death within 10 years of onset.³

Genetic testing for AD became recently available^{4,5} and has expanded the imaging phenotype of AD from classic frontal lobe leukoencephalopathy to include patients with more focal CNS lesions that can mimic a neoplastic process. Despite the significant phenotypic diversity of AD, MR imaging findings in AD are generally believed to be suggestive, on occasions even pathognomonic, especially in cases with dominantly supratentorial imaging manifestations.⁶ However, isolated, mono-focal involvement of the central nervous system structures by AD poses a more challenging differential diagnostic problem for imaging. In 2005, van der Knaap et al. published a series of patients with confirmed AD who demonstrated focal posterior fossa lesions.⁷ Subsequent cases of AD with focal medullary, cerebellar or spinal cord lesions have also been reported.^{8-9,10} Most recently, a tumor-like lesion in the optic chiasm was reported in a child with classic infantile AD.¹¹ Many of these previously reported patients were children initially referred and sometimes treated for presumed cancer. Thus, our report of a patient with a novel *GFAP* mutation and a tumor-like brainstem lesion further contributes to this expanding literature that identifies AD to be an important differential diagnostic consideration for unusual posterior fossa and spinal cord lesions concerning for neoplasm. Unfortunately, at this time there is no treatment for AD and management is primarily supportive. However, to avoid

unnecessary procedures and inappropriate treatment, clinical oncologists need to be aware of AD and should consider genetic testing for *GFAP* gene mutation in patients presenting with atypical tumor-like focal lesions within the posterior fossa.

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Figure 1.
Tumor-like Lesion within the Medulla.