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Alexander Disease: A Leukodystrophy That May Mimic Brain Tumor

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Abstract

Alexander disease is a leukodystrophy caused by dominant missense mutations in the gene encoding the glial fibrillary acidic protein. Individuals with this disorder often present with a typical neuroradiologic pattern including white matter abnormalities with brainstem involvement, selective contrast enhancement, and structural changes to the basal ganglia/thalamus. In rare cases, focal lesions have been seen and cause concern for primary malignancies. Here the authors present an infant initially diagnosed with a chiasmatic astrocytoma that was later identified as having glial fibrillary acidic protein mutation-confirmed Alexander disease. Pathologic and radiologic considerations that were helpful in arriving at the correct diagnosis are discussed.

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Alexander disease is a heritable cerebral white matter disorder caused by dominant missense mutations in 1 allele of the glial fibrillary acidic protein (*GFAP*) gene.[1-3] Alexander disease is classified into type I and II by clinical course and age at onset of disease: type I often begins before 4 years with seizures, macrocephaly, developmental delay, failure to thrive, intractable vomiting, encephalopathy and is sporadic with de novo mutations in *GFAP*; type II is a continuous spectrum of clinical features from juvenile to adulthood with distinct features of bulbar dysfunction, palatal myoclonus, autonomic dysfunction and often without significant encephalopathy.[2] It is more likely to be inherited from an affected parent. Five magnetic resonance imaging (MRI)–based criteria for diagnosis of typical Alexander disease have been described and are most often seen in type I Alexander disease: (1) frontal predominance of central white matter involvement manifested by T2 hyperintensity and T1 hypointensity; (2) a periventricular rim of T2 hypointensity and T1 hyperintensity; (3) abnormal T2 signal, swelling or atrophy of basal ganglia/thalamus; (4) abnormal T2 signal of the brain stem; and (5) contrast enhancement of selected structures.[4] These diagnostic criteria help prompt *GFAP* sequencing analysis to confirm the diagnosis. However atypical MRI findings such as focal supratentorial cerebral lesions and isolated brainstem abnormalities have been described in genetically confirmed cases of Alexander disease.[5,6] In some cases of Alexander disease these focal lesions cause concern for primary malignancies. Here the authors report an infant initially diagnosed with a chiasmatic astrocytoma, subsequently identified as having *GFAP* mutation-confirmed Alexander disease.

Case Presentation

The authors' patient is a 2-year-old boy born of an uneventful term pregnancy with vaginal delivery with birth weight of 3170 g. Birth occipito-frontal circumference (OFC) was not available. The patient was identified as having concomitant Hemoglobin SC disease with no clinical symptoms. Family history was not contributory. He initially presented with macrocephaly (48.5 cm

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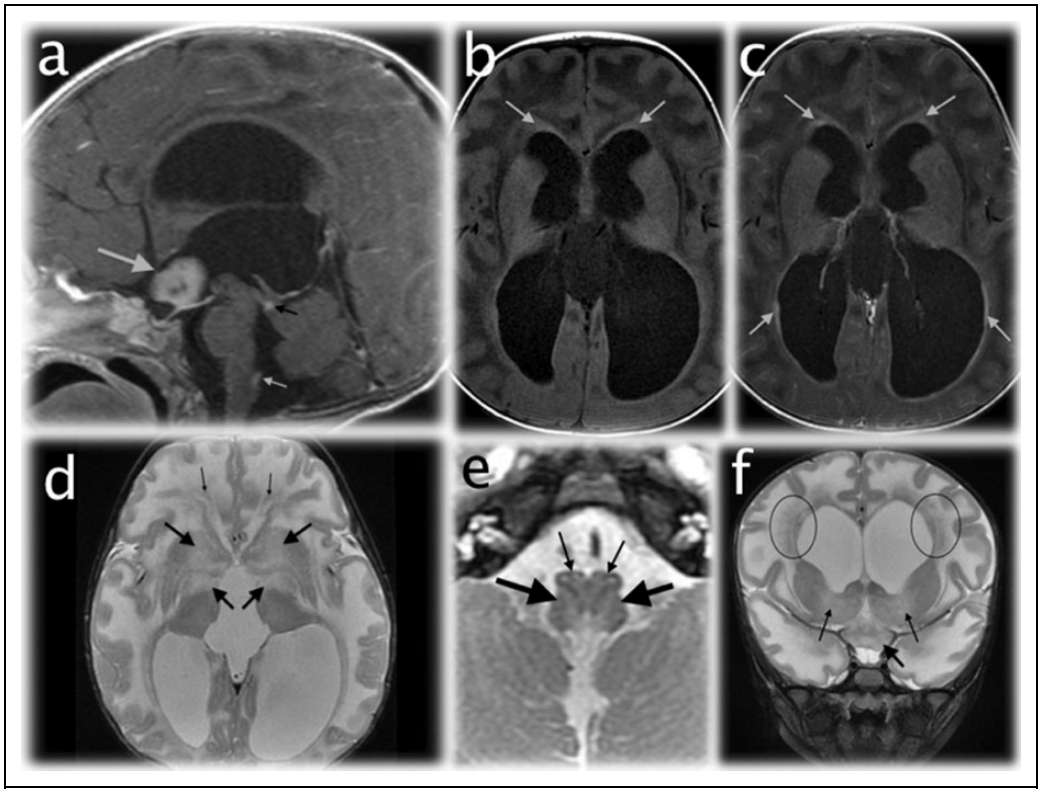

Figure 1. Magnetic resonance imaging brain in Alexander disease affected infant. Postcontrast sagittal SPGR T1 (TR/TE msec, 600/13) (a) demonstrates an enhancing optic chiasmatic mass (large white arrow) and nodular enhancement along the posterior margin of the cerebral aqueduct (small white arrow) and obex (small black arrow). There is aqueductal stenosis and consequent noncommunicating hydrocephalus manifested by marked supratentorial ventriculomegaly, upward bowing of the corpus callosum, and expanded third ventricular recesses. Precontrast (b) and postcontrast (c) axial T1-weighted images (TR/TE msec, 567/10) show intrinsic high signal along the subependymal regions (arrows, b) and abnormal subependymal enhancement (arrows, c). Most of the remaining cerebral white matter is abnormally hypointense, relatively sparing the occipital lobes, consistent with an anteroposterior gradient of white matter disease (b and c). Axial T2-weighted image (TR/TE msec, 3200/90)(d) depicts hyperintense signal in the cerebral deep gray nuclei (large arrows) and hypointense periventricular white matter signal along the frontal horns of the ventricles (small arrows). Axial T2-weighted image (TR/TE msec, 3200/90) (e) through the medulla oblongata shows ill-defined hyerintense signal infiltrating the pyramids and olives (small arrows) and dorsal medulla (large arrows). Coronal T2-weighted image (TR/TE msec, 4450/98) (f) demonstrates a hyperintense chiasmatic mass lesion (large black arrow), signal hyperintensity in the striatum (small arrows), and radially striated hypointense signal in the cerebral white matter (ovals) on the background of more diffuse cerebral white matter hyperintensity and swelling.

at 5 months, >2SD above the norm) and failure to thrive at the age of 5 months. On examination at the time of presentation, the infant was found to be emaciated in appearance and presented with weight loss (<6 kg at 6 months and well below the 3rd percentile for age), macrocephaly, sun-setting eyes and hypotonia. He was able to track objects but visual fields could not be formally tested. Brain ultrasonography showed ventriculomegaly and a diagnosis of hydrocephalus was made. Brain MR performed for further evaluation revealed a mass-like enlargement and contrast enhancement of the optic chiasm thought to be responsible for a diencephalic syndrome (Figure 1-a). Neither clinical signs nor family history for neurofibromatosis type I was present. A brain biopsy and ventriculoperitoneal shunt placement was performed. Pathology of the lesion demonstrated glial proliferation with nuclear atypia and scattered Rosenthal fibers, morphologically reminiscent of pilocytic astrocytoma. Ki67 proliferation index was elevated to 5%. There were no microcysts, myxoid substance or eosinophilic granular bodies (Figure 2). Analysis of pathologic specimens was negative for BRAF duplication and V600 mutations. Based on the diagnosis of unresectable symptomatic pilocytic astrocytoma, the infant was started on chemotherapy with carboplatin and vincristine. The planned induction schedule was interrupted after 2 weeks due to thrombocytopenia and hyponatremia. Because of continued failure to thrive, he ultimately required gastric tube placement with Nissen fundoplication for nutritional supplementation. At the end of second week of chemotherapy, 5 weeks after initial presentation, he presented to the emergency department with a new onset afebrile partial seizure. A second MRI was performed that showed contrast enhancement along the subependymal regions of the lateral ventricles, aqueduct, and obex with extensive cerebral white matter signal abnormality. This was felt to represent an intrinsic white matter abnormality rather than hydrocephalus related interstitial edema or chemotherapeutic toxicity, because the signal was not confined to the

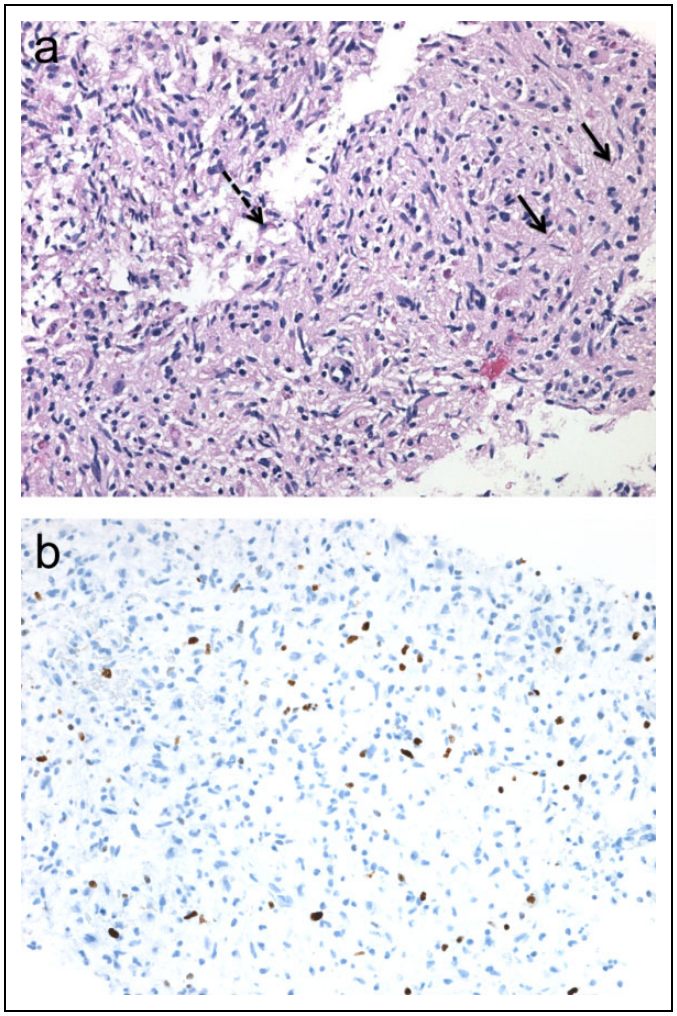

Figure 2. Pathology of the mass-like lesion in Alexander disease. (a) Hematoxylin and eosin (H&E) stain shows astrocytic proliferation with nuclear atypia and scattered Rosenthal fibers (black arrows). Note that occasional astrocytic cells harbor Rosenthal fiber-like inclusions in the cytoplasm (dotted line arrow). (b) Ki67 proliferation index is approximately 5%. 200× magnification.

periventricular region and the occipital white matter was spared (Figures 1b, 1c, 1d, 1e). Furthermore, there was abnormal striated white matter hypointensity on T2-weighted images in the periventricular regions (Figure 1f). In addition, basal ganglia signal abnormality was seen (Figure 1-d).

Chemotherapy was discontinued due to the presumptive diagnosis of Alexander disease and the chiasmatic lesion spontaneously involuted with no further treatment. *GFAP* full gene sequencing using automated fluorescence dideoxy sequencing methods at age of 7 months showed 2 adjacent heterozygous variants of uncertain significance: c.228C>A and c.227T>A, which if in cis (on the same allele) would result in p.Leu76Glu, and if in trans (on different alleles) would result in p.Leu76His. Parental testing was negative which confirms the de novo inheritance of the variants identified. Although these changes were novel, variants have been previously identified at the same amino acid locus in Alexander disease affected individuals.[2]

His later course was notable for persistent poorly controlled seizures treated with topiramate and levetiracetam. His macrocephaly and hydrocephalus stabilized and he gained weight gradually over time (now at 95% for age). When last examined at 2 years of age, he cannot roll or sit without support. He has no words. He no longer tracks visually. He has diffusely increased appendicular tone and decrease truncal tone. He has a persistent asymmetric tonic neck reflex. His clinical course is felt to be consistent with Type I Alexander disease.

Discussion

Alexander disease is considered an astrocytopathy because the mutated glial fibrillary acidic protein accumulates in glial fibrillary acidic protein highly expressing astrocytes together with heat shock proteins and ubiquitin, forming cytoplasmic protein aggregates called Rosenthal fibers.[7] Rosenthal fibers accumulating in the brain are thought to contribute to the pathogenesis of Alexander disease and can cause additional complications: for example when accumulating in cerebral spinal fluid pathways may cause obstructive hydrocephalus even in utero.[8-11] However, Rosenthal fibers are also seen in astrocytic tumors such as astrocytomas. Typically, clinical and radiologic features differentiate Alexander disease from central nervous system malignancies.

Type I Alexander disease and type II Alexander disease can present with focal mass like lesions[5,8] that may result in diagnostic confusion as seen in the authors' patient. Conversely, brain tumors like primary CNS lymphoma and glioblastoma multiforme can resemble some of the key radiologic features of Alexander disease. Spread along the ependymal surfaces cause ventricular lining enhancement as seen in Alexander disease In the setting where hydrocephalus complicates a primary brain tumor white matter signal change representing interstitial edema can be seen similar to the findings in Figure 1.[12,13] However, accompanying basal ganglia signal changes and brainstem signal abnormality may alert the clinician to the appropriate diagnosis, as these are unlikely to be present in non-neurofibromatosis-related low-grade gliomas.

Pathologic data of mass-like lesions in Alexander disease is relatively scarce, because these lesions are usually not biopsied. *GFAP* mutations were already reported in patients initially diagnosed as having low-grade glioma, also presenting as thickened chiasm.[6,14-17] These lesions showed mass effect and contrast enhancement, indicating that Alexander disease may mimic a tumor in some cases. When a biopsy was performed, the finding of Rosenthal fibers and the appearance of additional MRI white matter signal abnormalities led to a suspicion of Alexander disease. Based on morphology alone, it may be difficult to differentiate mass-like lesions in Alexander disease from low-grade astrocytomas due to the proliferative nature of the astrocytic lesions. The increased cellularity, cytonuclear atypia and abundant Rosenthal fibers observed in the mass-like lesions in Alexander disease are nearly indistinguishable at biopsy from the features of pilocytic astrocytoma. Nevertheless, lack of biphasic morphology and eosinophylic

granular bodies are subtle histologic clues that may be used to distinguish Alexander disease from low-grade astrocytomas. Taken together, these data suggest that the tumor-like lesions observed in Alexander disease patients may be due to a brisk proliferation of mutant astrocytes, possibly followed by astrocytic death explaining the spontaneous regression. This highlights the relationship between abnormal astrocytic proliferation, *GFAP* mutations and Rosenthal fibers, which remains to be elucidated.

Correct identification of Alexander disease in patients with mass like lesions is particularly important because it is plausible that putting the astrocytes under additional cellular stress from chemotherapy may worsen the underlying disease. Children with Alexander disease often present following a febrile illness, and cytokine analysis has demonstrated that glial fibrillary acidic protein induced microglial activation and T cell infiltrates may contribute to neuronal dysfunction and seizures.[18] These potential adverse effects warrant considering genetic testing before initiating therapy in a patient with atypical pilocytic astrocytoma and features of Alexander disease, particularly if the lesion is mildly symptomatic. In conclusion, Alexander disease should be considered in any patient with mass-like brain lesion in association with diffuse white matter signal abnormalities with brainstem and basal ganglia abnormalities.

Authors' Note

AT, TA, and CYH contributed equally.

Author Contributions

AT, TAMB, JREIH, EMW, and RP reviewed clinical information and wrote the initial draft of the manuscript. CTH and MB provided analysis and imagery for neuropathology data. MW, MSVDK, and AV reviewed MRIs and contributed to MRI imaging and diagnosis. AV led this project. All authors provided critical review of this manuscript and final edits.

Declaration of Conflicting Interests

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Ethical Approval

This patient was enrolled in the Myelin Disorders Bioregistry Project, an IRB approved registry at Children's National, with patient informed consent.

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