ELSEVIER

Images in Child Neurology

Magnetic Resonance Imaging Findings in Alexander Disease

Christine A. Matarese, DO, and Deborah L. Renaud, MD

A 22-month-old boy presented for neurologic evaluation secondary to global developmental delay and hypotonia. His fine and gross motor skills were consistent with an 11-month level, and language skills were consistent with a 12-month level. He had been developmentally progressing slowly, without any regression. He was diffusely hypotonic from infancy and had developed a right-hand preference by 3 months of age. Upon examination, his height was below the 3rd percentile and head circumference was at the 90th percentile. Physical examination also demonstrated significant drooling, bilateral fifth finger clinodactyly, diffuse hypotonia, and increased deep tendon reflexes in the lower extremities with bilateral ankle clonus.

Cranial magnetic resonance imaging (Fig 1) demonstrated T_2 hyperintensity in the periventricular and subcortical white matter in both cerebral hemispheres, most prominent in the frontal lobes, with sparing of the occipital lobes and less intense T_2 hyperintensity in the basal ganglia. These findings are consistent with Alexander disease. Magnetic resonance spectroscopy demonstrated elevated, myoinositol and choline in the parietal white matter and a decreased *N*-acetylaspartate/creatine ratio. These spectroscopy findings are consistent with those described by Brockmann et al. [1]. Lactate peaks were not identified in the present patient.

Glial fibrillary acidic protein gene sequence analysis demonstrated a mutation in exon 1 of the *GFAP* gene, a heterozygous missense mutation causing a substitution of a cysteine for the normal arginine at position 79. This mutation is designated R79C and has been described in patients with infantile, juvenile, and adult-onset Alexander disease [2].

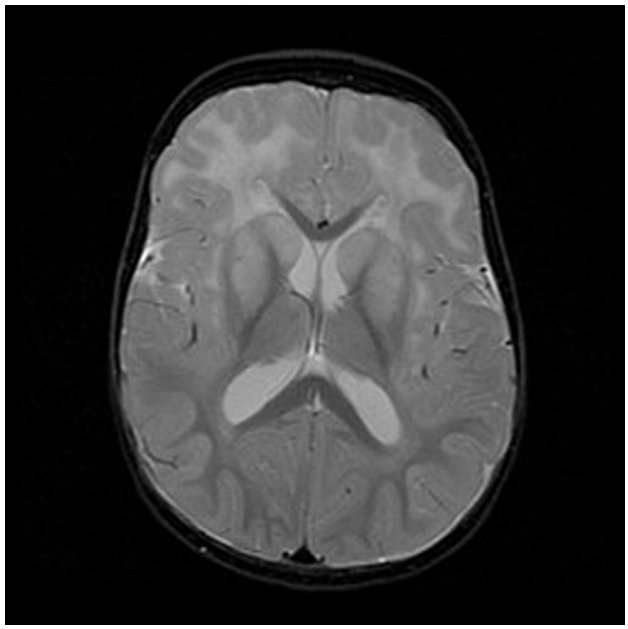

Figure 1. Magnetic resonance imaging in a case of Alexander disease, axial view. Note confluent T_2 hyperintensity in the periventricular and subcortical white matter in both cerebral hemispheres, more prominent in the frontal lobes, with relative sparing of the occipital lobes and less intense T_2 hyperintensity in the basal ganglia.

Alexander disease is a rare, progressive leukodystrophy affecting the central nervous system white matter. The pathologic feature is widespread Rosenthal fibers, which are intracytoplasmic inclusion bodies found in astrocytes. There are infantile, juvenile, and adult-onset disease forms. The infantile form is most common and is characterized clinically by megalencephaly, developmental delay, psychomotor retardation, seizures, and a progressive course, with death usually occurring within the first few years of life [3]. The juvenile form is characterized by pseudobulbar and bulbar signs, such as problems with speech and swallowing. There may also be ataxia, spasticity of the lower extremities, and kyphoscoliosis. The juvenile form also is progressive, but the deterioration is usually slower than that seen with the infantile form. The adult-onset form is the least common and may include features such as palatal myoclonus, ataxia, and dysauto-

From the Division of Child and Adolescent Neurology, Department of Neurology, Mayo Clinic, Rochester, Minnesota.

Communications should be addressed to:
Dr. Renaud; Division of Child and Adolescent Neurology; Departments of Neurology and Pediatrics; Mayo Clinic Foundation and College of Medicine; 200 First Street SW Rochester, MN 55905.
E-mail: renaud.deborah@mayo.edu
Received December 21, 2007; accepted January 2, 2008.

doi:10.1016/j.pediatrneurol.2008.01.004 • 0887-8994/08/$—see front matter

nomia [3]. Heterozygous dominant mutations in the *GFAP* gene account for most cases of Alexander disease. It is unknown exactly how these mutations lead to the disease, but they appear to cause a gain of function as opposed to a loss of function. Treatment is supportive.

Prior to the development of *GFAP* gene sequencing analysis, diagnostic criteria based on magnetic resonance imaging findings were proposed by van der Knaap et al. [4]. They defined five magnetic resonance imaging criteria and based the diagnosis on four of the five being met. These criteria are (1) extensive cerebral white matter abnormalities with a frontal predominance, (2) a periventricular rim of decreased signal intensity on T_2-weighted images and elevated signal intensity on T_1-weighted images, (3) abnormalities of the basal ganglia and thalami, (4) abnormalities of the brainstem, especially the medulla and midbrain, and (5) contrast enhancement of one or more of the following structures: ventricular lining, periventricular tissue, frontal lobe white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, or brain stem structures.

References

[1] **Brockmann** K, Dechent P, Meins M, Haupt M, Sperner J, Stephani U, Frahm J, Hanefeld F. Cerebral proton magnetic resonance spectroscopy in infantile Alexander disease. J Neurol 2003;250:300-6.

[2] **Li** R, Johnson AB, Salomons G, Goldman JE, Naidu S, Quinlan R, Cree B, Ruyle SZ, Banwell B, D'Hooghe M, Siebert JR, Rolf CM, Cox H, Reddy A, Gutiérrez-Solana LG, Collins A, Weller RO, Messing A, van der Knaap MS, Brenner M. Glial fibrillary acidic protein mutations in infantile, juvenile, and adult forms of Alexander disease. Ann Neurol 2005;57:310-26.

[3] **Johnson** AB, Brenner M. Alexander's disease: clinical, pathologic, and genetic features. J Child Neurol 2003;18:625-32.

[4] **van der Knaap** MS, Naidu S, Breiter SN, Blaser S, Stroink H, Springer S, Begeer JC, van Coster R, Barth PG, Thomas NH, Valk J, Powers JM. Alexander disease: diagnosis with MR imaging. AJNR Am J Neuroradiol 2001;22:541-52.