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E. Vázquez, A. Macaya, N. Mayolas, S. Arévalo, M.A. Poca and G. Enríquez

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Neonatal Alexander Disease: MR Imaging Prenatal Diagnosis

E. Vázquez
A. Macaya
N. Mayolas
S. Arévalo
M.A. Poca
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SUMMARY: Alexander disease (AD) is a rare neurodegenerative disorder characterized by megalencephaly, leukoencephalopathy, and Rosenthal fibers within astrocytes. This report describes the case of a female patient with sonography-detected ventriculomegaly at 32 weeks' gestation and distinctive MR imaging features at 33 and 36 weeks' gestation, at birth, and at 2 months of age, which led to the suggested diagnosis of Alexander disease. Molecular analysis confirmed a missense mutation in the *GFAP* gene. The literature contains little information on the fetal MR imaging findings that may allow prenatal diagnosis of AD.

Alexander disease (AD) is an uncommon neurological disorder with 3 clinical subgroups: infantile, juvenile, and adult. The most distinctive histologic feature of AD is the presence of countless Rosenthal fibers throughout the CNS. The genetic basis is presence of mutations in the glial fibrillary acidic protein (*GFAP*) gene, which encodes *GFAP*, located on chromosome 17q21.[1] Although characteristic neuroradiologic hallmarks of the infantile subtype of AD have been described,[2] prenatal findings had never been previously reported. Presence of prenatal hydrocephalus and abnormal frontal white matter make us rule out AD.

Case Report

A 31-year-old primipara woman was referred to the MR imaging unit from the fetal medicine department to investigate fetal ventriculomegaly discovered on a routine sonography study. The first MR imaging examination performed at 33 weeks' gestation (Fig 1) showed asymmetric ventricular enlargement, questionable abnormal white matter, and slightly swollen fornices. The second MR imaging examination performed at 36 weeks' gestation (Fig 2) showed abnormal hyperintense frontal white matter on T1-weighted images, with a low signal intensity on T2-weighted images; a more evident pseudomass was also seen corresponding to the thickened fornices. The definite diagnosis could not be established, and the child was born at 37 weeks by cesarean delivery, with normal birth parameters. A neonatal MR imaging examination was performed at 2 days of life (Fig 3). The diagnosis of AD was strongly suggested on the basis of the imaging findings. AD was confirmed by molecular genetic analysis, which revealed a previously reported[1] missense mutation in exon 1 of the *GFAP* gene, producing a 73Met<Thr change in the highly conserved rod domain of the protein (Human Genetics Department, Ruhr University, Bochum, Germany).

The patient's clinical status deteriorated during the first weeks of life, with increasing irritability, nystagmus, and accelerated head growth with a bulging anterior fontanel. MR imaging examination at 2 months of age (not shown) demonstrated parenchymal atrophy, abnormal signal intensity involving the thalami and basal ganglia, an obstructed sylvian aqueduct, increased hydrocephalus, and small cavitations in the frontal white matter. A ventriculoperitoneal shunt was inserted, with improvement of signs of intracranial hypertension.

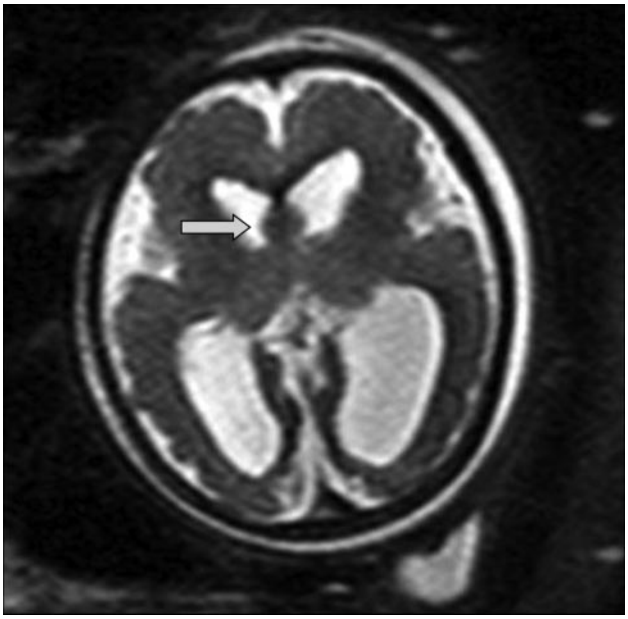

Fig 1. First MR imaging examination at 33 week's gestation. Ventriculomegaly with anterior mass effect (*arrow*) owing to fornix thickening is seen on the axial half-Fourier acquired single-shot turbo spin-echo T2-weighted image. Subtle low signal intensity in the frontal periventricular white matter is questionable.

Discussion

Since the first description of this disease by Alexander in 1949,[3] various clinical subtypes have been recognized: infantile (birth to 2 years), juvenile (2–12 years), and adult. Infantile AD is the most common, accounting for approximately 80% of cases. A neonatal variant has been reported,[4] characterized by onset within the first month of life, rapid progression leading to severe disability or death within the first 2 years of life, seizures as an early and obligatory symptom, hydrocephalus caused by aqueduct stenosis, severe motor and mental retardation without prominent spasticity or ataxia, severe white matter abnormalities with frontal predominance, extensive pathologic periventricular enhancement, involvement of the basal ganglia and cerebellum, and elevated CSF protein concentration.

The most distinctive pathologic feature of AD is widespread deposition of cytoplasmic inclusions, termed "Rosenthal fibers," mainly in perivascular, subpial, and sub-

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From the Departments of Pediatric Radiology (E.V., N.M., G.E), Pediatric Neurology (A.M.), Fetal Medicine (S.A.), and Neurosurgery (M.A.P.), Área Materno-Infantil, Hospital Universitari Vall d'Hebron, Universidad Autónoma de Barcelona, Barcelona, Spain.

Please address correspondence to Elida Vázquez, MD, Pediatric Radiology Department, Hospital Universitari Vall d'Hebron, Universidad Autónoma de Barcelona, Ps. Vall d'Hebron, 112–119, 08035, Barcelona, Spain; e-mail: evazquez@vhebron.net

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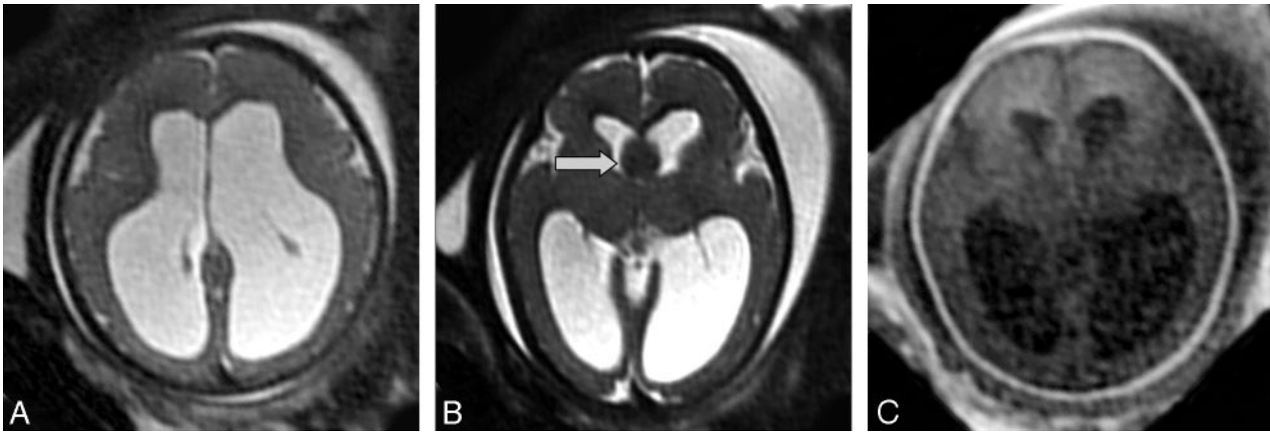

Fig 2. Follow-up prenatal MR imaging at 36 weeks' gestation. *A* and *B*, Ventriculomegaly (*A*) and anterior mass effect (*B*, *arrow*) are both more pronounced than previously on half-Fourier acquired single-shot turbo spin-echo T2-weighted images. *C*, It is difficult to assess the presence of white matter abnormalities, though an abnormal hyperintense periventricular rim is present on the T1-weighted image.

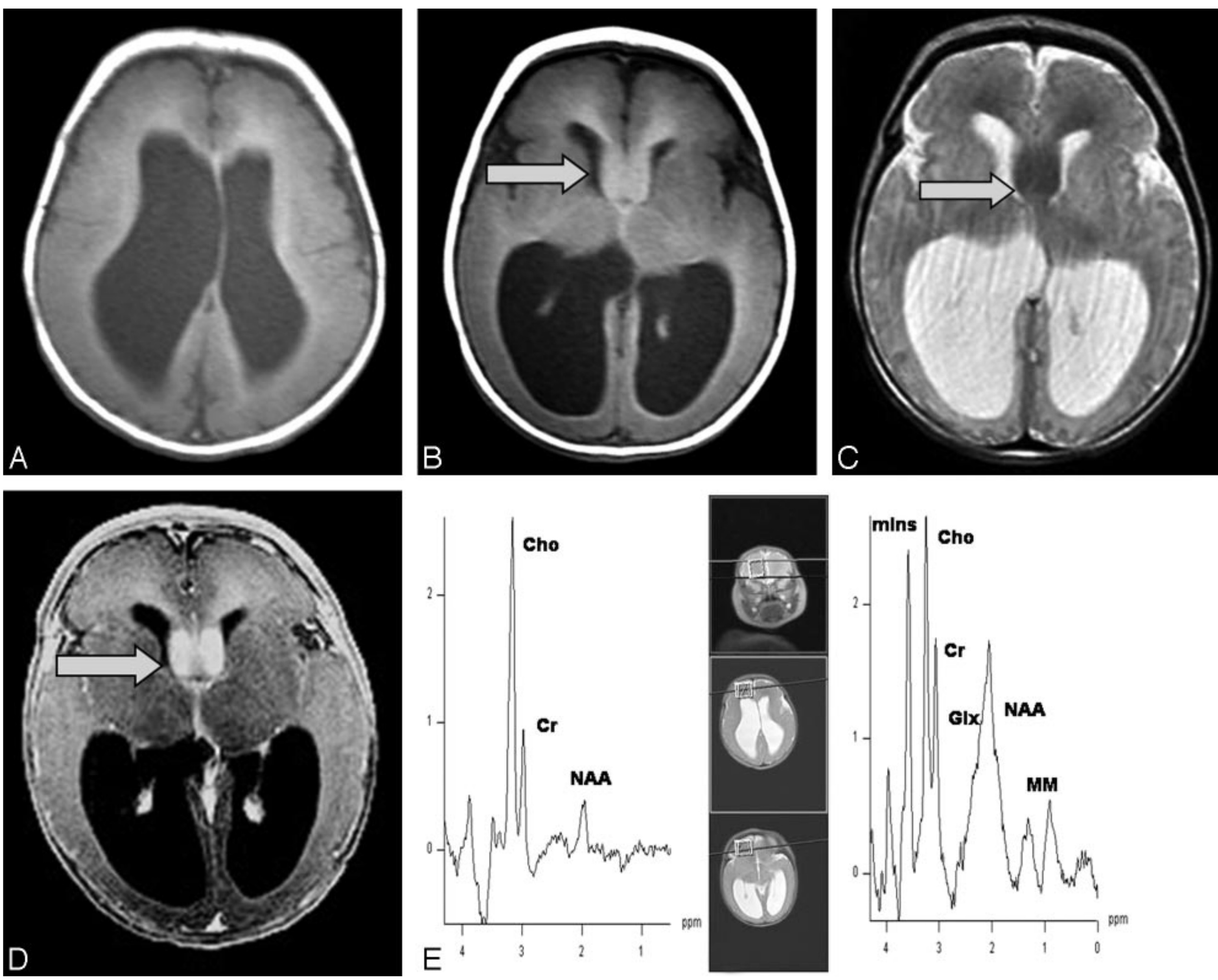

Fig 3. Neonatal MR imaging at 2 days of age. *A* and *B*, A typical hyperintense periventricular rim (*A*) is seen on the T1-weighted image (more clearly than in the prenatal images), with swollen frontal white matter and fornices (*B*, *arrow*). *C*, Corresponding abnormally hypointense signal intensity (*arrow*) is seen on the T2-weighted image. *D*, There is significant enhancement of the swollen fornices (*arrow*) following contrast administration. *E*, MR spectroscopy of the frontal white matter demonstrates abnormally low levels of *N*-acetylaspartate (NAA) and high levels of myo-inositol (mIns). Cho indicates choline; Cr, creatine; MM, macromolecules; Glx, glutamine/glutamate.

ependymal astrocytes.[2] On histopathologic study, astrocytes containing Rosenthal fibers are seen to surround and disrupt the ependyma of the aqueduct, resulting in obstructive hydrocephalus. The cerebellum, fornix, optic nerves, chiasm, and optic tracts may also contain these fibers, a nonspecific finding believed to represent a reaction to metabolic stress.[5] A characteristic histologic feature, mainly in the infantile form of AD, is a nearly complete absence of myelin sheaths, which is most pronounced in the frontal white matter.[6] MR imaging can diagnose AD with considerable accuracy. Five MR imaging criteria were defined by van der Knaap et al[7] for this purpose; 4 of the 5 criteria must be met for an MR imaging–based diagnosis of the condition.

Early MR imaging studies[8] reported in infantile AD were signal-intensity abnormalities and some swelling of the frontal white matter and basal ganglia, a periventricular rim of low signal intensity on T2-weighted images and high-signal intensity on T1-weighted images, and areas of signal-intensity abnormality in the brain stem. Postcontrast enhancement may be found in the ventricular lining, periventricular rim, parts of the frontal white matter, caudate nucleus, thalamus, dentate nucleus, parts of the midbrain, fornix, and optic chiasm. The characteristic periventricular rim of low signal intensity on T2-weighted and high signal intensity on T1-weighted images has been reported to be related to an extreme attenuation of Rosenthal fibers in the periventricular white matter.[2,7] The neonatal MR imaging examinations performed in our patient fulfilled all the diagnostic MR imaging criteria.

Until recently, the diagnosis of AD could only be established by the histologic finding of Rosenthal fibers in brain specimens. Mutations in the *GFAP* gene have been found in patients with pathologically proved AD.[5,8,9] *GFAP* mutations result in a dominant gain in the function of the protein that exerts a toxic effect on astrocyte function. In most cases, the mutation appears to occur de novo, being absent in both parents.[10]

MR imaging is now routinely and widely used in fetal neuroimaging and has proved to be valuable in the detection of many cerebral lesions, either genetically determined or acquired in utero.[11] Unfortunately, the sensitivity of fetal MR imaging in assessing diffuse white matter abnormalities is still poor.[12] Imaging diagnosis of rare metabolic diseases in utero is also highly challenging; hence, they are mainly detected in the neonatal period.[13] In our patient, the associated findings of hydrocephalus and abnormal white matter could have suggested AD, and the suggested diagnosis would have been supported by the swelling of several anterior structures, including the fornices and optic chiasm. The diagnosis would have been confirmed by molecular studies of deoxyribonucleic acid extracted from fetal cells. Unfortunately, late recognition of these prenatal abnormalities precludes adequate genetic counseling in most cases.

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