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Clinical Letter

Alteration of the Arcuate Fasciculus in Jacobsen Syndrome Shown by Diffusion Tensor Imaging

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Introduction

Jacobsen syndrome (JBS) is a rare genetic disorder due to chromosome 11q deletion with prevalence of 1:100,000 characterized by facial dysmorphism, multisystem involvement, developmental delay, and brain white matter abnormalities.[1,2] As the primary connection between Broca and Wernicke areas, the arcuate fasciculus (AF) is essential for normal language function and is considered part of the language pathway. We describe the longitudinal magnetic resonance imaging (MRI) changes of the brain in a child with JBS, magnetic resonance spectroscopy, and diffusion tensor imaging (DTI) findings showing alteration in white matter microstructural integrity and alteration in AF. These findings have not been previously reported.

Patient Description

Our patient presented at birth with respiratory distress, congenital heart disease, thrombocytopenia, vertebral anomalies, duodenal malrotation, facial dysmorphism including hypertelorism and ptosis, developmental delay, and hypotonia. Chromosomal microarray detected a *de novo* 11.06-Mb terminal chromosome 11q24.1-q25 deletion consistent with JBS. Brain MRI (Fig 1) on day 14 of life showed mild ventriculomegaly with scattered areas of subtle supratentorial white matter abnormality. A follow-up MRI, at age one year, showed diffusely increased T2/fluid-attenuated inversion recovery (FLAIR) signal intensity, involving almost the entire supratentorial white matter. Brain magnetic resonance spectroscopy, performed at this time, showed elevated choline and decreased *N*-acetyl aspartic acid (NAA) peaks without any lactate

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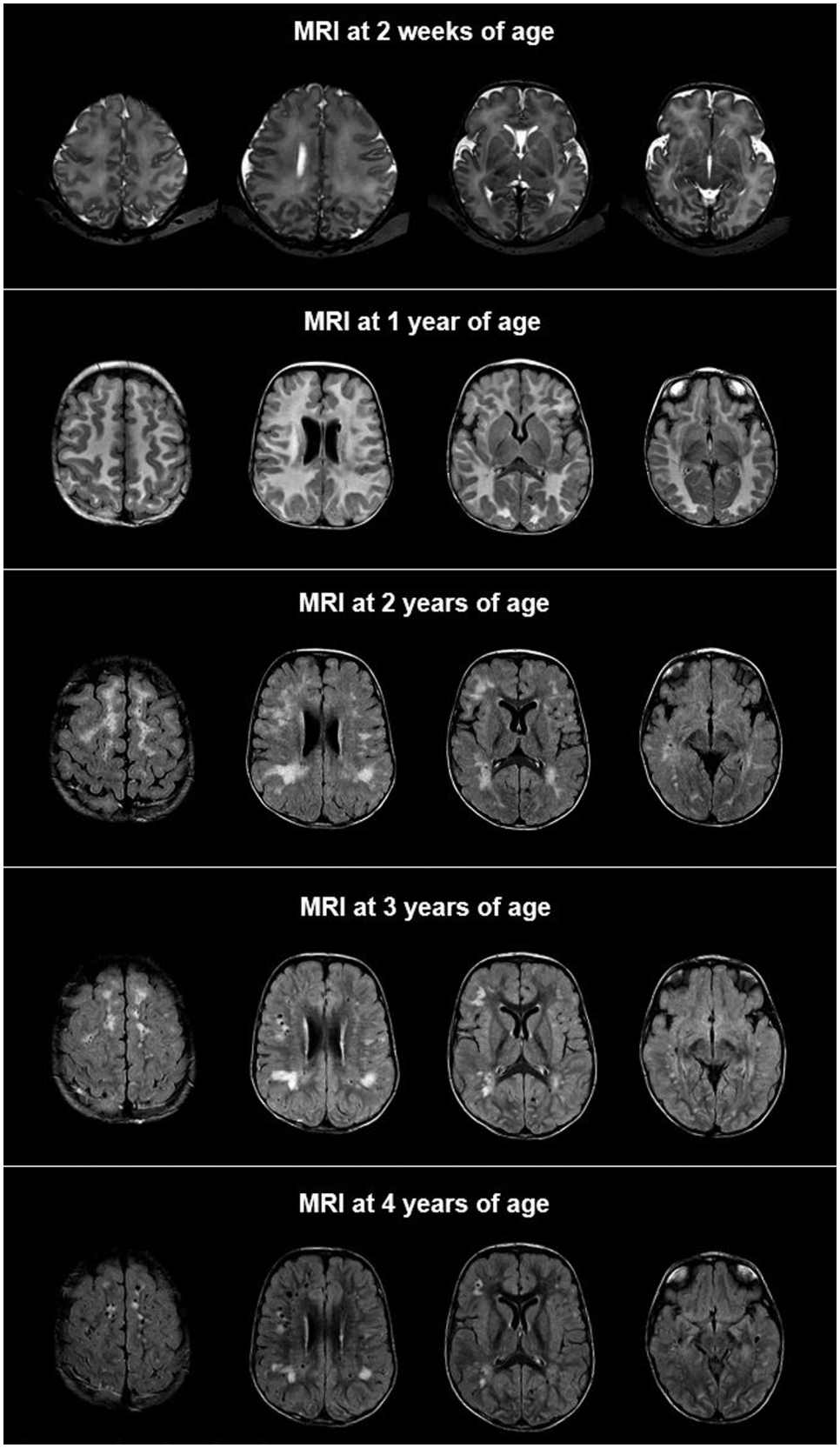

FIGURE 1. Serial axial T2 fluid-attenuated inversion recovery magnetic resonance imaging showing diffuse bilateral supratentorial white matter abnormalities at birth, reaching its nadir and involving almost the entire supratentorial white matter around age one year and then gradually improving over years with development of prominent perivascular space.

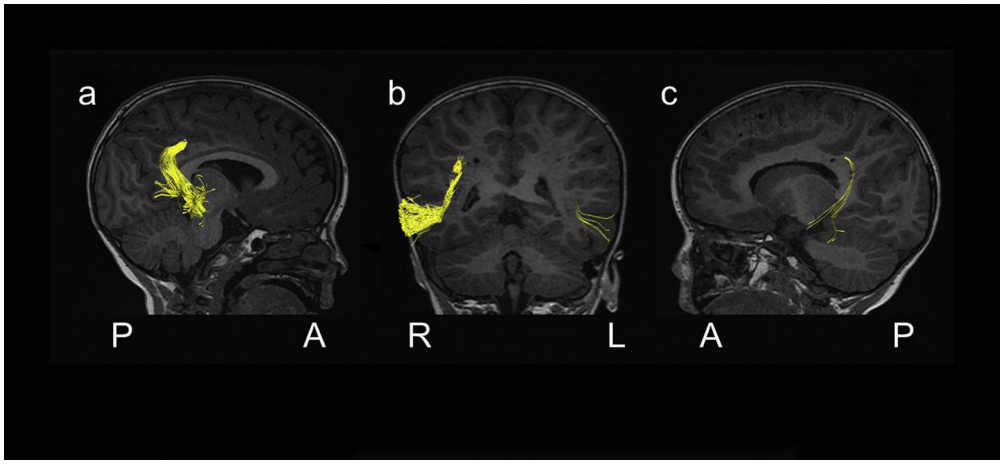

FIGURE 2. Diffusion tensor imaging tractography performed at age four years showed asymmetry of the posterior segments of the arcuate fasciculus (AF), right (A) more robust than left (C), with absence of the anterior segments bilaterally. (B) AF on the coronal view. The color version of this figure is available in the online edition.

peak. A repeat MRI, at age two years, showed some interval improvement in extensive white matter abnormality, particularly in the posterior quadrant, with an appearance resembling demyelination process, such as leukoencephalopathy. No signs of old hemorrhage were seen on susceptibility-weighted imaging (SWI). Subsequent MRIs, performed at ages three and four years, showed continued interval improvement in white matter signal abnormalities with interval development of prominent perivascular spaces bilaterally. DTI, performed at age four years, showed absence of identifiable anterior segments of the AF bilaterally, whereas the posterior segments were asymmetric, right more robust than left (Fig 2). Currently, although her motor milestones are appropriate, she continues to have speech delay, says two- to three-word phrases, but speech is not well understood.

Discussion

Our patient has all classic features of JBS, and the diagnosis was confirmed by chromosomal microarray. Chromosome 11q encompasses *HEPACAM* (hepatic and glial cell adhesion molecule), the second gene implicated in megalencephalic leukoencephalopathy with subcortical cysts (MLC), a leukodystrophy with diffuse white matter swelling, neurological deterioration, and *MLC1* mutation. *HEPACAM* mutation causes improving MLC phenotype. *MLC1* protein is present in astrocyte-astrocyte junctions and with *HEPACAM* forms a complex and regulates astrocytes' water-ion homeostasis.[3]

White matter abnormalities in JBS can be diffuse or multifocal and typically improve over time,[2] on routine MRI sequences. DTI noninvasively detects water movement within the white matter and can demonstrate microstructural changes in the myelin and axons not seen with conventional MRI. Indeed, although our patient's white matter signal abnormalities appear to be improving, DTI showed abnormal AF; absence of anterior segments and asymmetric posterior segments of bilaterally. The AF is a major association neuronal pathway, connecting the Broca and Wernicke areas, and is considered to be important in language development. DTI can show its developmental process and typically follows the sequence of posterior, anterior, and direct AF development, and by three to five years, both segments are usually developed,[4] which is not found in our case. Absence or abnormal development of AF has been reported in children with global developmental delay[5] and in children with polymicrogyria and language impairment.[6] Although our DTI findings are interesting and appear to be intuitive, some of the changes may be related to inherent limitations of the technique or may be transient, due to delayed myelination or white matter edema. Long-term follow-up study with larger sample size is required to make any definite or conclusive inference.

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