Antenatal and Postnatal Brain Magnetic Resonance Imaging in Muscle-Eye-Brain Disease

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Background: Muscle-eye-brain disease (MEB) is a rare autosomal recessive disorder characterized by congenital muscular dystrophy, structural eye abnormalities, and type II lissencephaly. Previous reports of brain abnormalities on magnetic resonance images (MRIs) in MEB have been in children older than 1 year.

Objective: To describe serial antenatal and postnatal brain MRIs in a child with MEB.

Design: Case report.

Patient: We report a 2-year-old white boy with genetically confirmed MEB. Antenatal MRIs at 25 and 35 weeks' gestation showed posterior ventriculomegaly but no cortical dysplasia. A postnatal brain MRI at age 1 week showed frontal cortical dysplasia and abnormal signal intensity within the frontal white matter. A brain MRI at 8 months showed bilateral frontoparietal polymicrogyria. All images demonstrated flattening of the pons and mild hypoplasia of the inferior vermis. The child had no weakness, and muscle involvement was only suspected when the serum creatine kinase level was found to be elevated at age 8 months.

Conclusion: Cortical dysplasia in MEB may not be evident until several postnatal months; therefore, if MEB is suspected, brain MRI performed in the first few months of life should be interpreted with caution.

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Report of a Case

The patient is the only son of healthy non-consanguineous parents of Anglo-Irish descent. He has 4 half siblings, all unaf-
fected by MEB, though 3 of them have autism or Asperger syndrome. A paternal uncle also has autism. Ventriculomegaly was documented by antenatal ultrasonography at 20 weeks' gestation and confirmed by fetal MRI at 25 weeks' gestation. Ventricular dilatation was most marked in the posterior lateral ventricles (Figure 1A). The third ventricle was also dilated and the fourth, prominent (Figure 1B). The inferior vermis appeared mildly hypoplastic (Figure 1B). Cortical folding was slightly delayed with minimal infolding of the central sulcus (Figure 1B). Fetal MRI 10 weeks later showed that cortical folding had increased. The lateral ventricles remained dilated, the pons flattened, and the vermis mildly hypoplastic (Figure 2 A and B).

The patient was born at 38 weeks' gestation by Cesarean section for breech presentation. No resuscitation was required. Birth weight and head circumference were in the 25th centile. Routine examination findings in the postnatal ward were normal.

At 1 week, he was feeding well but had suboptimal visual attention and poor quality of movements. Brain MRI confirmed the previous findings and also showed dilatation of the anterior horns of the lateral ventricles. The cerebellar hemispheres appeared small and

Figure 1. T2-weighted fetal magnetic resonance images at 25 weeks' gestation. A, Transverse plane at the level of the basal ganglia. There is bilateral ventriculomegaly and a smooth cortical surface. B, Sagittal plane. There is a hypoplastic vermis, and the pons may be slightly flattened. There is minimal folding in the region of the central sulcus (arrow).

Figure 2. T2-weighted fetal magnetic resonance images at 35 weeks' gestation. A, Transverse plane at the level of the basal ganglia. Ventricles remain dilated. There has been some maturation of cortical folding. There are bands of low signal intensity within the frontal white matter consistent with migrating cells (arrow). B, Transverse plane at the level of the posterior fossa. The vermis appears hypoplastic.
the cerebellar cortex dysplastic (Figure 3A). The frontal cortex was less folded than expected, and the frontal white matter showed abnormal long T1 and T2 (Figure 3B).

At 2 months, feeding difficulties were noticed. He had just started to smile. He had full conjugate eye movements, although visual following was limited. He had antigravity limb movements but reduced head and axial tone and a mild increase in limb tone. These features persisted at 7 months when Griffith neurodevelopmental testing gave an age equivalent of 4 to 4.5 months.

Brain MRI at 8 months showed obvious cortical dysplasia with areas of polymicrogyria in the frontal, frontoparietal, and anterior temporal lobes. There was abnormal low signal intensity (decreased T2) in the white matter, suggesting disordered myelination and possible areas of ectopic neurons. The pons was flattened, and the vermis remained hypoplastic. There was more marked ventricular dilation but no pachygyria or midline anomalies (Figure 4). Ophthalmological investigations revealed severe myopia (~12 diopters).

His serum creatine kinase level was elevated at 1567 U/L (normal, <200 U/L). Electroencephalography (at age 13 months) and peroneal nerve conduction velocity results were normal.

The results of muscle biopsy performed at age 16 months showed dystrophic changes. Immunohistochemical studies revealed a significant reduction of α-dystroglycan labeling with antibodies VI4-1 (Upstate biotechnology, Charlottesville, Va, following the manufacturer’s instructions) and IHH6 (gift of K. Campbell, PhD), directed against different glycosylated epitopes of α-dys-
troglycan, and a mild reduction with an antibody (gift of S. Kroger, PhD) that recognizes the core protein (Figure 5). There was normal labeling of β-dystroglycan and other sarcolemmal and extracellular matrix proteins with the exception of laminin-α2 chain, which was slightly reduced in some fibers. Immunoblot analysis of skeletal muscle protein extract showed a virtual absence of polypeptide bands corresponding to β-dystroglycan but normal labeling of α-dystroglycan (Figure 6).

Sequence of the entire coding region of the POMGnTI gene identified a novel heterozygous missense mutation in 1 allele, a 1373G->C, resulting in an Asp427His, which was inherited from his mother, and a single-nucleotide insertion 542insT creating a frameshift at amino acid 150. This second mutation was inherited from his healthy father; the missense mutation was excluded from 94 healthy controls. FKRP gene mutations were excluded as well following direct sequenc-

Figure 5. Indirect immunofluorescence results of frozen muscle sections incubated with antibodies to α-dystroglycan. Scale bars: left panel, 130 µm; right panel, 60 µm. Brightness and contrast minimally modified using Adobe Photoshop (Microsoft, Redmond, Wash).
ing of the entire coding region as described by Brockington et al.  

At age 2 years, both the boy’s weight and head circumference were between the 3rd and 10th centile. He had prominent muscles, poor head control, and truncal hypotonia but was able to sit unsupported for a few minutes, to roll, and to bear weight on his legs if held. He had antigravity movements, but the quality of his movements was slow and poor because of the pyramidal involvement. There were mild contractures of the knees and ankles bilaterally, and tendon reflexes were brisk. His severe myopia was partially corrected with glasses. He babbled but had no recognizable words.

Muscle-eye-brain disease was initially described in Finnish patients, but it is now clear that the distribution of the disease is wider than originally thought. 1,3 This is the first report of MEB in a UK patient. Our patient is mildly affected when compared with most patients with MEB and in particular does not have overt muscle weakness. A neuromuscular disorder was suspected only on the discovery of high serum creatine kinase levels, which were measured when his cortical dysplasia was recognized. These findings support our previous suggestion that serum creatine kinase levels should be determined in patients with cortical dysplasia, 10 and this is especially valid if the pattern of brain involvement suggests a cobblestone lissencephaly. Muscle biopsy results showed dystrophic features with reduced immunolabeling of α-dystroglycan. This, together with his clinical features, led us to suspect a diagnosis of MEB, which was confirmed by finding homozygous mutations in the MEB gene, POMGnTI.

The initial MRI in our patient was performed at 25 weeks’ gestation and confirmed the ventriculomegaly detected on ultrasound. This was more marked posteriorly, as is often observed in MEB, 11 but such posterior dilatation is nonspecific. Cortical abnormalities may be difficult to identify at this early gestation, as the major sulci are only beginning to form. 12 A second fetal MRI at 35 weeks’ gestation still did not show any obvious abnormality of cortical maturation. While severe lissencephaly, such as that observed in Walker-Warburg syndrome, can easily be seen on fetal MRIs, more discrete polymicrogyria may not be recognized. 13 Both prenatal MRIs showed vermis hypoplasia and, in retrospect, flattening of the pons. A suggestion of abnormal folding in the frontoparietal cortex was noted for the first time on the early postnatal brain MRI obtained 1 week after birth. The pattern of polymicrogyria, however, was still not obvious and was only fully recognized on the MRI performed at age 8 months, when widespread polymicrogyria affecting the frontal, frontoparietal, and anterior temporal lobes was apparent. The white matter also had abnormal signal intensity. While other authors have reported similar brain changes of cortical dysplasia, cerebellar atrophy, flattened pons, and ventricular dilatation in MEB, none have examined patients younger than 1 year; thus, the age at which these abnormalities became apparent was not known. 1,11,14,15 In addition, the presence of polymicrogyria has been reported most frequently in Fukuyama type congenital muscular dystrophy. 14,15 This case therefore illustrates the evolution of the polymicrogyria in MEB, which may not become evident until several months postnatally. α-Dystroglycan has been implicated in central nervous system development. Defects of cortical layering, brain morphogenesis, and basement membrane expression, resulting in overmigration of neurons beyond the pia mater as observed in type II lissencephaly, have been documented in the Large 16 mouse, which has abnormal glycosylation of α-dystroglycan because of a mutation in the gene encoding a putative glycosyltransferase. Large, 16 also mutated in MDC1D. 17 Targeted deletion of dystroglycan in mouse brain results in similar defects. 17 Hypoglycosylation of α-dystroglycan may underlie the observed central nervous system defects in MEB. 18 The cortical migration defect, however, may not be obvious in the first few months of life, and this should be taken into account when assessing children with suspected MEB.

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