Muscle-eye-brain disease (MEB) is a rare autosomal recessive disorder characterized by congenital muscular dystrophy, structural eye abnormalities, and type II lissencephaly. Associated features are abnormal white matter, flattened brainstem, cerebellar hypoplasia, and ventriculomegaly. Patients with MEB usually have muscle weakness and hypotonia at birth or in the first few months after birth. Few patients achieve independent ambulation. The most common ocular features are severe myopia and retinal hypoplasia, and other abnormalities such as cataract or glaucoma may occur. Most have severe mental retardation, absent speech, and epilepsy. The recently identified MEB gene (POMGnTI) encodes the glycosyltransferase O-linked mannose β-1,2-N-acetylglucosaminyltransferase 1. Following the identification of the gene defect, there has been evidence that the clinical spectrum and distribution of MEB is broader than previously recognized. The combination of muscle involvement and cortical dysplasia also occurs in Fukuyama type congenital muscular dystrophy and Walker-Warburg syndrome, the genes for which also encode putative glycosyltransferase enzymes. Although MEB is generally milder than Walker-Warburg syndrome, there is significant clinical and neuroradiological overlap. More recently, our group reported structural brain involvement in patients with mutations in 2 other putative glycosyltransferases, the FKRP gene and the Large gene, responsible for the forms of congenital muscular dystrophy referred to as MDC1C and MDC1D, respectively.

We report serial antenatal and postnatal brain magnetic resonance images (MRIs) in a 2-year-old white boy with a genetically confirmed diagnosis of MEB. To our knowledge, this is the first report describing early brain MRI findings in MEB.

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 2A 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).](image1)

![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.](image2)
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 VIA4-1 (Upstate biotechnologies, Charlottesville, Va, following the manufacturer’s instructions) and IIH6 (gift of K. Campbell, PhD), directed against different glycosylated epitopes of α-dys-

Figure 3. T2-weighted early postnatal magnetic resonance images at 39 weeks’ gestation. A, Transverse plane at the level of the posterior fossa. The fourth ventricle remains dilated, and the pons is flattened (arrow). Cerebellar hemispheres appear small, and the cerebellar cortical sulcation appears abnormal. B, Transverse plane at the level of the basal ganglia. There is ventricular dilation, now involving the anterior horns of the lateral ventricles. There is abnormal increased signal intensity within the frontal white matter (arrow). The frontal cortex looks immature with shallow sulci.

Figure 4. T2-weighted late postnatal magnetic resonance image at 8 months of age. Transverse plane. There is widespread bilateral polymicrogyria involving the frontal and parietal lobes. White matter is reduced in volume with abnormally high signal intensity. Areas of lower signal intensity, mainly within the periventricular white matter (arrow), may represent heterotopic cells.
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).

Sequencing 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-
ing of the entire coding region as described by Brock-
ington et al. At age 2 years, both the boy’s weight and head cir-
cumference 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 move-
ments was slow and poor because of the pyramidal in-
volve ment. There were mild contractures of the knees and ankles bilaterally, and tendon reflexes were brisk. His severe myopia was partially corrected with glasses. He babbed but had no recognizable words.

Muscle-eye-brain disease was initially described in Finn-
ish patients, but it is now clear that the distribution of
the disease is wider than originally thought. 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 dis-
covery of high serum creatine kinase levels, which were measured when his cortical dysplasia was recognized. These findings support our previous suggestion that se-
rum creatine kinase levels should be determined in pa-
tients with cortical dysplasia, and this is especially valid if the pattern of brain involvement suggests a cobble-stone lissencephaly. Muscle biopsy results showed dys-
trophic features with reduced immunolabeling of α-dys-
troglycan. 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 de-
tected on ultrasound. This was more marked posteri-
orly, as is often observed in MEB, 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. A second fetal MRI at 35 weeks’ gestation still did not show any obvious ab-
normality of cortical maturation. While severe lissen-
cephaly, such as that observed in Walker-Warburg syn-
drome, can easily be seen on fetal MRIs, more discrete polymicrogyria may not be recognized. Both prenatal MRIs showed vermis hypoplasia and, in retrospect, flat-
tening 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 ob-
vious and was only fully recognized on the MRI per-
formed at age 8 months, when widespread polymicro-
gyria affecting the frontal, frontoparietal, and anterior temporal lobes was apparent. The white matter also had abnormal signal intensity. While other authors have re-
ported similar brain changes of cortical dysplasia, cer-
ebellar atrophy, flattened pons, and ventricular dilata-
tion in MEB, none have examined patients younger than 1 year; thus, the age at which these abnormalities be-

**COMMENT**

In addition, the presence of polymicrogyria has been reported most frequently in Fukuyama type congenital muscular dystrophy. This case therefore illustrates the evolution of the polymicrogyria in MEB, which may not become evi-

dent until several months postnatally. α-Dystroglycan has been implicated in central nervous system develop-
ment. Defects of cortical layering, brain morphogenesis, and basement membrane expression, resulting in overmigration of neurons beyond the pia mater as ob-
served in type II lissencephaly, have been documented in the Large mouse, which has abnormal glycosyla-
tion of α-dystroglycan because of a mutation in the gene encoding a putative glycosyltransferase. Also, mutated in MDC1D. Targeted deletion of dystroglycan in mouse brain results in similar defects. Hypoglycosyla-
tion of α-dystroglycan may underlie the observed cen-
tral nervous system defects in MEB. The cortical mi-
gration defect, however, may not be obvious in the first few months of life, and this should be taken into ac-
count when assessing children with suspected MEB.

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