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SHORT REPORT

D-2-Hydroxyglutaric aciduria with absence of corpus callosum and neonatal intracranial haemorrhage

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Summary: We report D-2-hydroxyglutaric aciduria in a neonate with intracranial haemorrhage and absence of the corpus callosum. D-2-hydroxyglutaric acid was confirmed by specific chiral derivatization gas chromatography–mass spectrometry. Absence of the corpus callosum and spontaneous neonatal intracranial haemorrhage should raise the suspicion for metabolic disease, and especially organic acidurias.

D-2-Hydroxyglutaric aciduria (McKusick 600721) is a rare genetic condition with a wide spectrum of phenotypes. The severe cases are characterized by encephalopathy of early infantile onset, seizures, hypotonia, cortical blindness and marked developmental delay; the mildest cases manifest only slight developmental delay (Nyhan et al 1995; van der Knapp et al 1999a,b). Some severely affected individuals had asymptomatic siblings whose urinary D-2-hydroxyglutaric acid excretion was elevated (van der Knapp et al 1999a,b). About 25 cases have been reported to date. Autosomal recessive inheritance is suspected based on observation of families with affected siblings. The enzymatic deficiency and metabolic pathway of these disorders have been hypothesized but have yet to be demonstrated. We report the first case of D-2-hydroxyglutaric aciduria presenting with neonatal intracranial haemorrhage and absence of corpus callosum.

The mother of the proband was a 31-year-old (gravida 10; parity 4; stillborn 1; spontaneous miscarriage 4) who had an incompetent cervix for which a cerclage was placed. Prenatal ultrasound at 30 weeks showed dilated cerebral ventricles and the absence of the corpus callosum. A karyotype performed on a fetal blood sample showed normal male, 46, XY. The proband, C.S., was born at 36 weeks of gestation by Caesarean section after premature rupture of the membranes. His birth weight was 2420 g (25th centile), length 48 cm (80th centile) and head circumference 33.0 cm (60th centile). His Apgar scores were 8 at 1 min and 9 at 5 min. Within 4 days after birth, cranial ultrasonography and computed tomography studies confirmed the absence of corpus callosum. The studies also demonstrated developing and progressing haemorrhage in subependymal, subdural, subarachnoid

and intraventricular space, as well as cerebral parenchyma. Diffused ischaemia, focal infarction and oedema in cerebral parenchyma occurred concurrently. Infectious encephalopathy was excluded. An extensive investigation for a possible coagulopathy was performed. The resulting values suggested a consumptive coagulopathy. Methylenetetrahydrofolate reductase (MTHFR) DNA assay revealed that C.S. is a carrier of variant 667C>T substitution. A follow-up computed tomography of the brain at $2\frac{1}{2}$ months of age showed dilatation of the occipital horns of the lateral ventricles and the third ventricle.

At 5 months of age, he presented to the hospital with generalized tonic-clonic seizures. These were controlled with phenobarbital. His development was delayed. Ophthalmological examination was normal. At this admission, brain magnetic resonance imaging showed moderate ventricular dilatation and a large fluid collection with a small haemorrhage in the interhemispheric fissure (Figure 1). His serum lactate, pyruvate and plasma quantitative amino acid profile showed normal levels. Quantitative urinary organic acid profile revealed mildly elevated glutaric acid at 44.23 μg/mg creatinine (normal 0.6–15.2) and massively elevated 2-hydroxyglutaric acid at 3716 mmol/mol creatinine. 2-Ketoglutaric acid was not elevated. The urine was further analysed by specific chiral derivatization gas chromatography–mass spectrometry (Gibson et al 1993) and showed D-2-hydroxyglutaric acid at 2234 mmol/mol creatinine (normal 2.8–17). The L-2-hydroxyglutaric acid was 10 mmol/mol creatinine (normal 1.3–18.9). At 16 month of age, his length was 84 cm (75th centile), weight 8.5 kg (<5th centile)

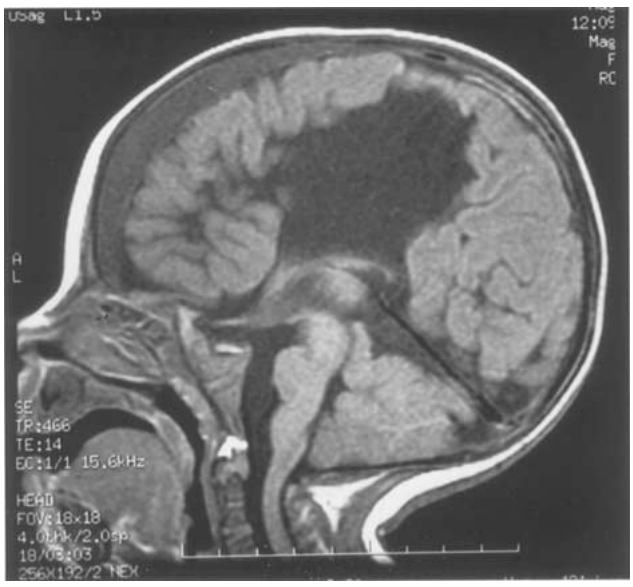

Figure 1 Magnetic resonance imaging (T1) of the brain of the patient at 5 months of age. Note the absence of corpus callosum and extra-axial fluid collection

and head circumference 46 cm (5th centile). His truncal muscle tone was low and deep tendon reflexes were brisk.

Owing to the position he adopted the skull was tall and asymmetrical. His face appeared elongated with epicanthal folds, flat nasal bridge, thick and tented upper lip, gum hypertrophy and high arched palate. He had two café-au-lait spots and a small umbilical hernia. The scrotum was small with an unusual dimple anteriorly in the midline. The right testis was in the inguinal canal and the left was undescended. His global development showed very little progress. C.S. is of African American/Native American/Caucasian descent. There was no consanguinity and no other family members were affected.

Two cases of D-2-hydroxyglutaric aciduria have been reported with thinning of the corpus callosum (Amiel et al 1999; Baker et al 1997). Individual cases with cerebral arterial infarction and aneurysms have also been reported (Eeg-Olofsson et al 2000; van der Knapp et al 1999a,b), the aetiology of which is unclear. The absence of corpus callosum and spontaneous neonatal intracranial haemorrhage should raise the suspicion of D-2-hydroxyglutaric aciduria.

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