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### ***Short Communication***

## **L-2-Hydroxyglutaric aciduria and lactic acidosis**

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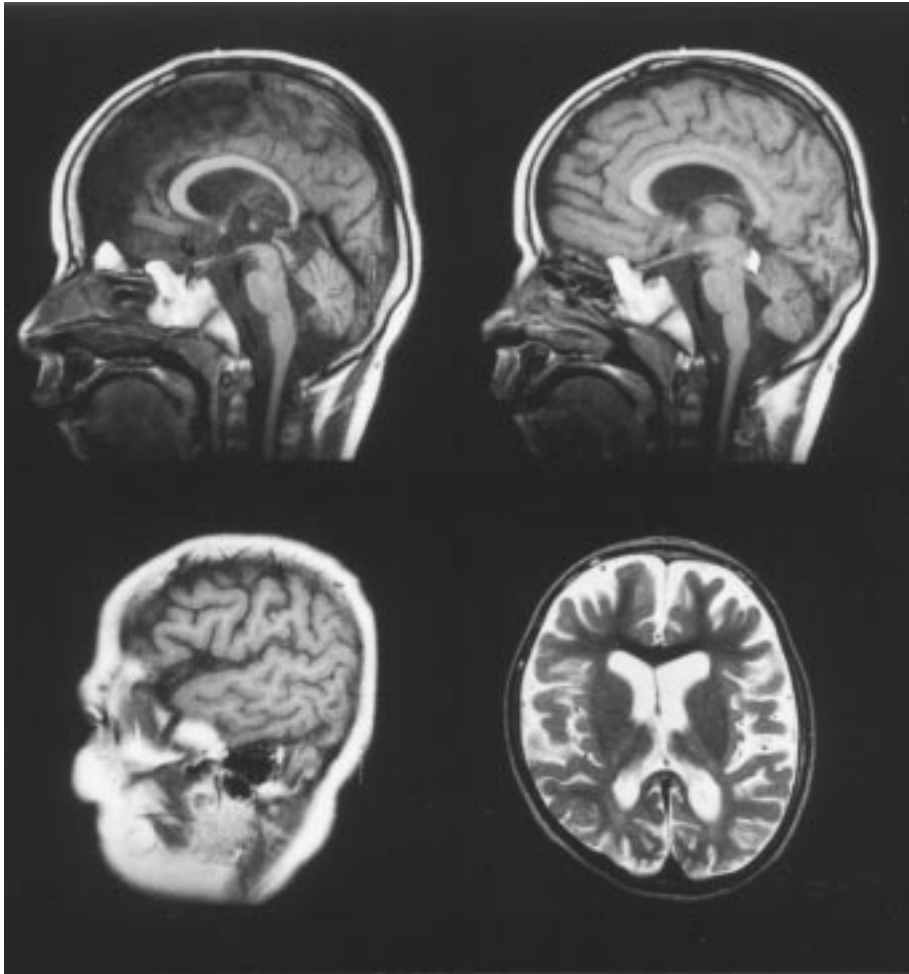
We present a case of L-2-hydroxyglutaric aciduria (McKusick 236792) different from the common profile of L-2-hydroxyglutaric aciduria (Duran et al 1980; Barth et al 1992, 1993; Larnaout et al 1994; Topçu et al 1996) with respect to the age of clinical onset, severity of symptoms, presence of excess lactic acid in plasma and CSF, and absence of L-2-hydroxyglutaric acid elevation in the CSF.

### **CASE REPORT**

The patient is the only male child born to healthy consanguineous parents (first cousins) of Turkish descent. He had full-term normal birth, weight 2730 g. He had seizures with onset at the first day of life. Initially unexplained mild metabolic acidosis (pH 7.24, base excess  $-10$  mmol/L) was found with hypoglycaemia/hypocalcaemia excluded. Severe developmental delay was noted in the first months with minimal head control and ocular pursuit as maximum achievements. At 3.5 years he had tetraparesis, diminished head control and dystonic posturing of the arms, minimal ocular pursuit, normal fundoscopic examination. Microcephaly was found: at 15 months  $-4$  SD and at 3.5 years,  $-6$  SD. Length was  $-1$  SD at 2.5 years. Feeding problems required continuous gavage feeding, followed by gastrostomy. Visual evoked potentials (flash) at 2.5 years produced normal latencies and amplitudes; electroencephalography at 3.5 years showed multifocal epileptogenic activity. Motor nerve conduction velocities of peroneal and median nerves were normal. Magnetic resonance imaging (MRI) of the brain showed (sub)cortical and cerebellar atrophy with no significant white matter involvement. A small lipoma was found in the arachnoid space overlying the right half of the mesencephalic tectum (Figure 1).

### **METHODS**

Enzyme activities were determined in deep-frozen biopsies. L-2-Hydroxyglutaric acid dehydrogenase was determined as described (Jansen and Wander 1993).



**Figure 1** MRI at 3.5 years. *Left and right upper frames:* sagittal T1-weighted sections: mild cerebellar atrophy, normally myelinated corpus callosum and a small lipoma-like structure overlying the right half of the mesencephalon (right upper frame). *Bottom left:* sagittal T1-weighted section showing atrophy of perisylvian cortex, with normal subcortical myelination. *Bottom right:* axial T2-weighted section: widened lateral ventricles and neocortical atrophy; almost normal myelin pattern and normal basal ganglia

D-2-Hydroxyglutaric acid dehydrogenase was determined as described (Wanders and Mooyer 1995). Respiratory chain complexes, pyruvate dehydrogenase, 2-ketoglutarate dehydrogenase and marker enzymes in liver and muscle were determined as described (Maaswinkel-Mooij et al 1996).

## RESULTS AND DISCUSSION

CSF lactic acid values were 3.16, 4.10 and 2.56 mmol/L. Random plasma values

**Table 1** 2-Hydroxyglutaric acid in body fluids

	Chirality	2-Hydroxyglutaric acid concentration	
		Patient	Control values (range)
Urine (mmol/mol creatinine):	L	136	1.3–18.9
	D	14	2.8–17.0
Plasma ( $\mu\text{mol/L}$ )	L	4.11	0.45–1.04
	D	0.37	0.28–0.93
CSF ( $\mu\text{mol/L}$ )	L	0.87	0.25–2.34
	D	0.18	0.07–0.34

were 1.26 and 1.68 mmol/L, after an overnight fast 4.92 mmol/L and one hour after a meal 2.72 mmol/L. Lactate/pyruvate ratios were  $\geq 20$  in plasma and CSF.

GC-MS of the urine revealed increased levels of lactic acid, 2-hydroxyglutaric acid, and the citric acid intermediates succinic acid, fumaric acid and 2-ketoglutaric acid. Analysis of 2-hydroxyglutaric acid in urine and plasma revealed that the L-form but not the D-form was increased, whereas no elevation of 2-hydroxyglutaric acid was found in the CSF (Table 1).

Activities of respiratory chain complexes I–V were determined in liver and muscle biopsies with normal results. Activities of pyruvate dehydrogenase complex and 2-ketoglutarate dehydrogenase were also normal in liver and muscle. L-2-Hydroxyglutaric acid dehydrogenase and D-2-hydroxyglutaric acid dehydrogenase activities were measured in a liver biopsy specimen as previously described with the following results (nmol/min per mg): L-2-hydroxyglutaric acid dehydrogenase 81 (controls 11.0–14.8), D-2-hydroxyglutaric acid dehydrogenase 36 (controls 8.0–12.3).

Symptoms in this patient were dominated by severe neurological dysfunction and dystrophy. The normal concentration of L-2-hydroxyglutaric acid in the CSF indicates that this compound cannot be the cause of the brain damage. Moreover, the increased activities of both L-2-hydroxyglutaric acid dehydrogenase and D-2-hydroxyglutaric acid dehydrogenase in liver indicate that the increased production of L-2-hydroxyglutaric acid may represent a secondary route, rather than the primary substrate of the missing enzyme activity. Differences between the present case and earlier descriptions of L-2-hydroxyglutaric aciduria are the presence of neonatal seizures and neocortical atrophy, and the absence of subcortical white matter and basal ganglia involvement (MRI). Additionally, our patient had elevated lactate in blood and CSF but no increase in CSF 2-hydroxyglutarate.

A single case of L-2-hydroxyglutaric aciduria described by Chen and colleagues (1996) in a neonate with fatal disease bears similarities to our case in various regards, including neonatal seizures, lactic acidosis and destructive changes in the cerebral hemispheres and cerebellum at autopsy. L-2-Hydroxyglutaric acid was not determined in CSF. Because of the early death of the patient described by Chen and colleagues (1996) we feel that comparison of the neuropathological findings with the MRI findings of our case at a later age is not possible. Otherwise, similarities are suggestive of the same disease.

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