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CASE REPORT

Clinical, biochemical, magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (^{1}H MRS) findings in a fourth case of combined D- and L-2 hydroxyglutaric aciduria

M.-H. Read[1], C. Bonamy[2], D. Laloum[2], F. Belloy[3], J. M. Constans[3], B. Guillois[2], M.-L. Kottler[1], N. M. Verhoeven[4] and C. Jakobs[4]*

[1]Departement Genetique et Reproduction, [2]Neonatalogie, [3]Departement de radiologie, Centre hospitalier universitaire, Caen, France; [4]Metabolic Unit of the Department of Clinical Chemistry, VU University Medical Center, Amsterdam, The Netherlands
*Correspondence: Departement Genetique et Reproduction, avenue Clémenceau, Centre Hospitalier Universitaire, 14033 Caen, France. E-mail: read-mh@chu-caen.fr

Summary: We report the fourth case of combined D- and L-2-hydroxyglutaric aciduria presenting with neonatal encephalopathy and subependymal cysts.

Two distinct disorders with elevated urinary excretion of 2-hydroxyglutaric acid (2HG) were described: L-2-hydroxyglutaric aciduria and D-2-hydroxyglutaric aciduria (van der Knaap et al 1999). A third variant was suspected as three patients with combined D- and L-2hydroxyglutaric aciduria were described (Muntau et al 2000).

This female patient was born at term, eutrophic, to a healthy mother. Her parents were caucasian and nonconsanguineous. Apgar scores were 7, 9, 10 at respectively 1, 5 and 10 min. A few hours after birth, she presented with seizures, which were controlled by phenobarbital. In view of recurrence of seizures, she was admitted to a university hospital on day 6. Electroencephalography showed signs of diffuse cerebral disturbance with generalized paroxystic abnormalities. She displayed a severe, rapidly deteriorating neonatal encephalopathy, with muscular hypotonia, poor eye contact and some abnormal movements of the upper limbs. She died at the age of 1 month.

Ultrasound and MRI showed enlarged lateral ventricles and subarachnoid spaces, the presence of subependymal germinolytic cysts and a very thin corpus callosum. Moreover, we noted seriously reduced white matter and abnormal gyration with lack of opercularization of sylvian fissures.

In vivo ^{1}H MRS of the left striatum, including cyst, showed low lactate and alanine and a significant decrease in *N*-acetylaspartate/creatine ratio. However, these changes are not dramatic in view of age and clinical severity. There was an increase in choline/creatine ratio, suggesting inflammation and/or demyelination.

Haemogram, serum electrolytes, blood glucose, lactic acid, ammonia and aminotransferase were normal, as well as plasma and CSF amino acids. The pattern of plasma acylcarnitines was normal as well as that of respiratory chain enzyme complexes measured on a fresh muscle biopsy.

Table 1 D- and L-2 hydroxyglutaric acid (D-2HG and L-2HG) values

Metabolite	*Sample*	*Unit*	*1st determination 9 days old*	*2nd determination 1 month old*	*Normal range*
D-2HG	Urine	mmol/mol creatinine	162	306	2.8–17
	Plasma	μmol/L	1.80	4.6	0.28–0.93
L-2HG	Urine	mmol/mol creatinine	127	152	1.3–18.9
	Plasma	μmol/L	1.91	1.7	0.45–1.04

Urine organic acids revealed a moderate increase in 2HG together with a slight increase in ethylmalonic and fumaric acids and normal 2-oxoglutaric acid. Quantification of the D- and L-stereoisomers of 2HG showed moderate increases of both stereoisomers (Gibson et al 1993). The increase in the D form was more pronounced at the second determination (Table 1).

A few months later, the mother became pregnant again. Amniotic fluid was analysed (at week 16 of gestation) by stable-isotope dilution GC-MS: both L-2HG and D-2HG were normal. MRI at 29 weeks of gestation did not reveal any abnormality and a male baby was born at term. His clinical state was normal, except for the absence of an ear, which was unexplained. The level of 2HG in the urine of this boy was checked twice and stayed within the normal range.

Biochemically and clinically, our patient resembles patients reported previously (Muntau et al 2000) and it is notable that *in vivo* magnetic resonance spectroscopy does not show important oxidative deficit or tissular disturbance.

This case emphazises the importance of careful organic acid examination in unexplained neonatal encephalopathy, especially if cerebral cysts are observed.

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