L-2-hydroxyglutaric aciduria: normal L-2-hydroxyglutarate dehydrogenase activity in liver from two new patients

Wanders, R.J.A.; Vilarinho, L.; Hartung, H.P.; Hoffmann, G.F.; Mooijer, P.A.W.; Jansen, G.; Huijmans, J.G.M.; de Klerk, J.B.C.; ten Brink, H.J.; Jakobs, C.; Duran, M.

DOI
10.1023/A:1005355316599

Publication date
1997

Published in
Journal of inherited metabolic disease

J. Inher. Metab. Dis. 20 (1997) 725–726

SHORT REPORT

L-2-Hydroxyglutaric aciduria: Normal L-2-hydroxyglutarate dehydrogenase activity in liver from two new patients

R. J. A. Wanders[1,2*], *L. Vilarinho*[3], *H. P. Hartung*[4], *G. F. Hoffmann*[5], *P. A. W. Mooijer*[2], *G. A. Jansen*[2], *J. G. M. Huijmans*[6], *J. B. C. de Klerk*[7], *H. J. ten Brink*[8], *C. Jakobs*[8] *and M. Duran*[9]

University Hospital Amsterdam, Academic Medical Centre, Departments of [1]Pediatrics, [2]Clinical Chemistry, Amsterdam, The Netherlands; [3]Instituto de Genetica Medica, Porto, Portugal; [4]Department of Neurology, University of Würzburg, Germany; [5]Department of Neuropediatrics, University of Marburg, Germany; [6]Department of Clinical Genetics, Erasmus University Rotterdam, The Netherlands; [7]Sophia Children's Hospital, Rotterdam, The Netherlands; [8]Department of Clinical Chemistry, Free University Amsterdam, The Netherlands; [9]University Children's Hospital Het Wilhelmina Kinderziekenhuis, Utrecht, The Netherlands

*Correspondence: University Hospital Amsterdam, Department of Pediatrics, Emma Children's Hospital and Department of Clinical Chemistry, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

L-2-Hydroxyglutaric aciduria was first described in 1980 by Duran and coworkers (Duran et al 1980) and has now been identified in at least 40 patients. Affected individuals show a variable set of symptoms including ataxia, intention tremor and choreiform movements, seizures, speech and mental retardation with developmental regression in infancy or childhood (Barth et al 1992, 1993). Despite the considerable variability in the clinical course, all patients described so far were normal in the perinatal period, with onset of symptoms in early to mid childhood. Recently, however, a more severe form of L-2-hydroxyglutaric aciduria has been described in an infant which presented shortly after birth with hypotonia, apnoea and seizures, with death at 28 days of life (Chen et al 1996).

The underlying metabolic defect in L-2-hydroxyglutaric aciduria has remained an enigma through the years. We recently described the identification of an enzyme catalysing the NAD^+-dependent dehydrogenation of L-2-hydroxyglutarate, making it an obvious candidate for the enzyme defect in L-2-hydroxyglutaric aciduria (Jansen and Wanders, 1993). At that time no liver biopsy material was available for testing this hypothesis. We have now been able to measure the activity of this enzyme in liver biopsy specimens from two unrelated patients with established L-2-hydroxyglutaric aciduria.

The clinical characteristics of these patients are described below.

Patient 1 is a Portuguese girl born to consanguineous parents. At 5 months she had febrile seizures and at 8 months of age she presented generalized seizures and psychomotor retardation. She began to walk at 22 months of age but with frequent falls and unsteady gait. At 7 years there was no neurological motor abnormality. Her head circumference was above the 90th centile. EEG showed generalized epileptiform activity and CT showed bilateral symmetrical subcortical white matter changes. Urine analysis revealed the presence of L-2-hydroxyglutaric acid (1400 μmol/mmol creatinine). At 9 years of age cerebellar signs were evident with gait ataxia, whereas at 10 years there was

a fast neurological deterioration and in 1 month she became left hemiplegic. MRI revealed a right hemispheric tumour arising from the right thalamus that, on biopsy proved to be a low-grade astrocytoma. Cytogenic studies carried out on a biopsy sample of the tumor showed no chromosome abnormalities. The cerebral biopsy showed a normal cerebral cortex but severe alterations of the subcortical white matter with spongiosis and cystic cavitations. At this time hepatic and skin biopsies were taken. The tumour progressed rapidly and the child died 6 months later. Post-mortem examination was not performed. A sister from the index patient also has 2-hydroxyglutaric aciduria.

Patient 2 was born in 1952 and suffered from febrile seizures as a child. At the age of 10 he was recognized to have an abnormal gait and some slight dysarthria. Over the years, he developed a progressive spastic ataxic gait with truncal and limb ataxia and poor intellectual development. On examination in 1994 he was found to have a spastic ataxic gait, truncal and limb ataxia, dysmetria, intentional tremor, dystonic posturing, dysarthria, extensor plantar responses and dementia. His last mean IQ at the age of 44 was 58. His disease continues to show a slow downhill progression.

Measurement of L-2-hydroxyglutarate dehydrogenase activity in liver biopsy specimens from these patients gave the following results: 14.5 and 14.8nmol/min per mg protein in liver homogenates from patients 1 and 2, respectively, with normal values of 13.9 ± 3.6 (mean ± SD; range: 11.0 – 24.8 ($n = 5$)) (see Jansen and Wanders, 1993).

These results virtually exclude L-2-hydroxyglutarate dehydrogenase as the deficient enzyme in L-2-hydroxyglutaric aciduria. We are pursuing our efforts to try to identify the true enzyme defect in this disorder. A possibility we investigate at the moment is whether it is the CoA ester rather than the free acid that is actively metabolized.

REFERENCES

Barth PG, Hoffmann GF, Jaeken J, et al (1992) L-2-Hydroxyglutaric acidemia: a novel inherited neurometabolic disease. *Ann Neurol* **32:** 66 – 71.

Barth PG, Hoffmann GF, Jaeken J, et al (1993) L-2-Hydroxyglutaric acidemia: clinical and biochemical findings in 12 patients and preliminary report on L-2-hydroxyacid dehydrogenase. *J Inher Metab Dis* **16:** 753 – 761.

Chen E, Nyhan WL, Jakobs C, et al (1996) L-2-Hydroxyglutaric aciduria: neuropathological correlations and first report of severe neurodegenerative disease and neonatal death. *J Inher Metab Dis* **19:** 335 – 343.

Duran M, Kamerling JP, Bakker HD, van Gennip AH, Wadman SK (1980) L-2-Hydroxyglutaric aciduria: an inborn error of metabolism? *J Inher Metab Dis* **3:** 109 – 112.

Jansen GA, Wanders RJA (1993) L-2-Hydroxyglutarate dehydrogenase: identification of a novel enzyme activity in rat and human liver. Implications for L-2-hydroxyglutaric aciduria. *Biochim Biophys Acta* **1225:** 53 – 56.