Propionyl coenzyme A carboxylase deficiency presenting as non-ketotic hyperglycinaemia

Summary A 4-month-old girl presented with myoclonic seizures and an electroencephalogram showing hypsarrhythmia. Hyperglycinaemia and a cerebrospinal fluid to plasma glycine ratio of 0.2 suggested the diagnosis of non-ketotic hyperglycinaemia. Propionic acid and methyl citric acid were present in the urine, and propionyl coenzyme A carboxylase was deficient in leucocytes and fibroblasts. The ketotic and non-ketotic hyperglycinaemias cannot be differentiated by CSF: plasma glycine ratios.

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Hyperglycinaemic syndromes in children may assume either ketotic or non-ketotic forms. Children with non-ketotic hyperglycinaemia frequently exhibit myoclonic seizures and an absence of voluntary muscle movement. Although few survive the recurrent acute crises in infancy, those who do usually become spastic and profoundly delayed developmentally. On the other hand, ketotic hyperglycinaemia is clinically characterised by intermittent attacks of ketoacidosis and hyperammonaemia, which may cause vomiting, hypotonia, and lethargy, progressing to coma or ultimately death in the neonatal period. The glycine cleavage system, which converts glycine to serine, is deficient in the cerebral tissue of children with non-ketotic hyperglycinaemia. Raised brain glycine content and a cerebrospinal fluid glycine to plasma glycine ratio exceeding 0.03, in conjunction with clinical differences, was proposed as a discriminator of non-ketotic from ketotic hyperglycinaemia.2-4 Ketotic hyperglycinaemia is the consequence of deficient propionyl coenzyme A carboxylase, methylmalonyl coenzyme A mutase, β-ketothiolase, or isovaleryl coenzyme A dehydrogenase activity, none of which appears to affect CSF glycine concentration.

Case report

A 4-month-old girl was referred to us with the classical features of non-ketotic hyperglycinaemia, including excessive glycinuria, myoclonic seizures with a typical hypsarrhythmic electroencephalographic pattern, and a CSF-to-plasma glycine concentration of 0.2. However, despite the absence of ketoacidosis and hyperammonaemia, she was found to have propionic acidemia and deficient propionyl coenzyme A carboxylase activity. Seizure activity stopped one week after the introduction of ACTH gel therapy and her electroencephalogram reverted to a normal pattern. During the severe illness, plasma glycine was 1154 μmol/l (normal 175 to 296), propionate, 153 μmol/l (normal <3), and caprylate, 100 μmol/l (normal <3). The cerebrospinal fluid glycine was 213 μmol/l (normal 3-10). On gas chromatography/mass spectroscopy raised concentrations of 3-hydroxypropionate, fumarate, p-hydroxyphenylacetate, and methyl citrate were evident in the urine. Propionyl coenzyme A carboxylase activity was deficient in leucocytes and cultured skin fibroblasts (5 and 35 pmol/min/mg protein, respectively, compared with the corresponding normal activities of 349 ± 51 and 863 ± 102 pmol/min/mg protein). The fibroblast cell line was assigned to the pcc BC complementation group and was shown to be unresponsive to biotin. The patient’s disorder was managed by dietary protein restriction.
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(1.0 g protein/kg/day). At 9 months of age, after several weeks of poor feeding, she developed ketoacidosis for the first time. She had another severe episode of acidosis at 11 months of age which was complicated by staphylococcal sepsis and dietary protein deficiency. She has persistently refused to eat, necessitating gavage feeding. Her growth retardation was severe, but has improved during the last year so that now her weight is at the 50th centile for her age, as is her height at the 50th centile for a 21-month-old. There has been some developmental delay.

Discussion

Some reported patients have presented clinically with features of ketotic hyperglycinaemia with deficient glycine cleavage activity. One patient with hypotonicity and respiratory depression accompanied by hyperglycinuria, propionic acidemia, and hyperammonemia, all suggesting ketotic hyperglycinaemia resulting from PCC deficiency, was found to have normal propionyl coenzyme A carboxylase activity, but deficient glycine cleavage activity. Several other patients with glycine cleavage deficiency have had hyperglycinaemia, ketoadidosis, hyperammonemia, propionic acidemia, and deficient propionyl coenzyme A carboxylase activity in their fibroblasts.

Our patient, on the other hand,initially manifested findings consistent with non-ketotic hyperglycinaemia but in fact had propionyl coenzyme A carboxylase deficiency. She shows further that neither the initial clinical presentation nor the ratio of CSF to plasma glycine concentrations can be used reliably to differentiate between the types of hyperglycinaemia. Moreover, it is possible that some non-ketotic hyperglycinaemias are reflections of additional genetic heterogeneity in the propionyl CoA carboxylase deficiencies. Alternatively, non-ketotic hyperglycinaemia may simply represent a secondary inhibition of the glycine cleavage system by abnormal metabolites which accumulate in propionyl coenzyme A carboxylase deficiency.

Regardless of the aetiology of hyperglycinaemia, the correct diagnosis and differentiation between the types of hyperglycinaemia is therapeutically important. Since most patients with the ketotic forms respond to restricted protein diets and occasionally to pharmacological doses of vitamins, whereas patients who never develop ketotic forms do not respond to dietary manipulation but may respond to strychnine therapy, it is essential to exclude the various ketotic hyperglycinaemic enzyme deficiencies by examination of the urine and plasma for organic acid metabolites or, more definitively, by measurement of enzyme activity directly in the tissues of affected subjects.

References

6 Wolf B, Hsia YE, Rosenberg LE. Biochemical differences between mutant propionyl-CoA carboxylases from two complementation groups. Am J Hum Genet 1978;30:455-64.

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