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Short Communication

Pyruvate dehydrogenase E1α deficiency in a family: Different clinical presentation in two siblings

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The pyruvate dehydrogenase (PDH) complex (PDHc) is responsible for the irreversible conversion of pyruvate to acetyl-CoA. PDHc is a multienzyme complex consisting of three catalytic subunits, pyruvate decarboxylase (E1), dihydrolipoamide acetyltransferase (E2), dihydrolipoamide dehydrogenase (E3), and two regulatory subunits, E1 kinase and phospho-E1 phosphatase. An abnormal E1α subunit, whose gene is located on the X chromosome, is the most frequent cause of PDH deficiency. The clinical presentation of a PDH-E1α deficiency (McKusick 312170) is variable.

We have analysed a family with a mutation (36 bp insertion in exon 10) in the PDH-E1α gene in which the male member had a different and less severe clinical picture than his affected sister.

PATIENT DATA

Patient 1 is a 3-year-old boy born after an uneventful pregnancy. His parents are unrelated and have normal intelligence. His initial development showed a general hypotonia. From the age of 3 months he had several episodes of ptosis lasting 1–2 days. These episodes became more frequent between 15 and 17 months of age and were associated with swallowing disturbances and hypotonia, paralysis of lateral gaze and tachypnoea. A metabolic acidosis was found. Lactate was 3.8 mmol/L in the fasted state and 5.3 mmol/L in the fed state. Lactate/pyruvate (L/P) ratio remained normal between 13 and 18. Creatine kinase and serum glucose were normal. Analysis of amino acids revealed an increase of alanine and of the urinary organic acids a severe lactic aciduria. A PDH deficiency was suspected. The boy was treated with thiamine and lipoic acid and was finally put on a ketogenic diet, which improved his clinical status. The episodes became less frequent. He walked at the

age of 2 years. On neurological examination at 3 years he has no ptosis or ophthalmoplegia. His reflexes are hyporeactive. There is no ataxia. His general development is mildly delayed. He has had two episodes of acute ataxia with weakness since the age of 2 years. MRI of the brain demonstrated bilaterial pallidal lesions and demyelinating pons lesions.

Patient 2 is the younger sister, also born after an uneventful pregnancy. From birth she presented with severe hypotonia and dysmorphia. She had microcephaly, hypertelorism, low-set ears, long philtrum, microretrognathia and bilaterial unipalmar folds. She developed a spastic quadriplegia with areflexia and severe mental retardation by the age of 10 months.

She did not have metabolic acidosis; plasma lactate and pyruvate were normal, but CSF lactate was 3.5 mmol/L (normal < 2). On MRI of the brain there was cortical atrophy and hypoplasia of corpus callosum.

MOLECULAR STUDIES

Since in both patients a PDH-E1α deficiency was suspected, we proceeded directly with the analysis of the cDNA of the PDH-E1α gene, using RT-PCR (Lissens et al 1996). Epstein–Bar virus-transformed lymphocytes were available for study from both patients and their mother. The male patient was studied first and showed aberrant SSCP fragments E (primers PDS3 and PDS4) and F (primers PDS5 and PDS6), indicating that a mutation was present in the overlap region between both fragments and defined by primers PDS4 and PDS5, both contained in exon 10. Sequencing in both directions of a PCR-amplified fragment from genomic DNA with intronic primers on both sides of exon 10 (PDH 10i5 and PDH 10i3; Bonne et al 1993) revealed that the patient was carrying a duplication of 36 bp of bases 1074 to 1109 starting after cDNA position 1109. The presence of this duplication was confirmed in the sister and the mother by genomic sequencing of the same exon 10 fragment. To assess differential expression of the normal and the mutated PDH-E1α alleles in the females, RT-PCR was conducted with primers PDS3 and PDS6, and the resulting fragments were run on a 12% polyacrylamide gel. In normal individuals this results in a cDNA fragment of 457 bp. As expected from the previous results, the male patient showed only a fragment of 493 bp (457 bp + 36 bp). The cDNA fragments of his sister showed predominantly a fragment of 493 bp and a faint band of 457 bp, while in his mother both bands were almost equally represented. To estimate quantitatively the proportion of both bands in the females, genomic fragments of exon 10 of both females, where both fragments are equally present, were run. The sister was found to have mutated and normal fragments in a 95 : 5 proportion and the mother 50 : 50.

DISCUSSION

PDH-E1α deficiency has been characterized on a molecular basis in a large number of cases. At least 52 different mutations have been described, most seen only in one member of the family. Only once has the same mutation been found in both sexes

(Chun et al 1995). All other mutations are specific for one sex; certain mutations in females might be lethal in males. On the other hand, certain mutations in boys never seem to lead to symptoms in the carrier mothers.

The clinical picture in boys can be a severe neonatal lactic acidosis, associated with mutations in regulatory domains such as the phosphorylation sites and concentrated in exons 7, 10 and 11 (Robinson 1995). Another frequent clinical picture is a Leigh encephalopathy, which is slowly progressive as seen in patient 1. In this boy, energy deficit is present in all cells but predominantly in the energy-demanding areas such as basal ganglia and muscle. This is in contrast with his sister, who has almost the same amount of mutated cDNA but has no systemic lactic acidosis. The absence of metabolic acidosis could be explained by an inactivation of the mutated X chromosome in liver and muscle. However the more severe brain presentation leading to microcephaly and mental retardation can be explained neither by the mutation nor by a skewed X-inactivation pattern. The mother, in contrast, carrying the same mutation but only expressing it in 50%, is asymptomatic.

The clinical picture described has been seen in several girls with PDH deficiency. The prenatal energy deficit in the brain leads towards early onset of symptoms associated with cortical atrophy. It is possible that minor forms in girls are missed when X-inactivation patterns are different (Brown 1992).

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