Successful prenatal molecular diagnosis of Carbamyl Phosphate Syntetase I deficiency in two at risk pregnancies.

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SHORT REPORT

Successful prenatal molecular diagnosis of carbamyl-phosphate synthetase I deficiency in two at-risk pregnancies

S. Funghini, A. Morrone, E. Pasquini, E. Zammarchi and M. A. Donati*

Metabolic and Muscular Disease Unit, Department of Pediatrics, University of Florence, Florence, Italy
*Correspondence: Metabolic and Muscular Disease Unit, Department of Pediatrics, University of Florence, Meyer Children's Hospital, Via L. Giordano 13, Florence, Italy. E-mail: malmetab@unifi.it

Summary: We report the two first prenatal diagnoses in an Italian family with a proband affected by neonatal carbamyl-phosphate synthetase I deficiency in which molecular analysis identified V457G and Q810R amino acid substitutions. We performed a prenatal diagnosis on genomic DNA isolated from chorionic villus and amniotic fluid samples collected at 13 weeks of gestation. In the first pregnacy, the fetus was compound heterozygous for the mutations and termination of pregnancy was elected. The genetic lesions were also confirmed on genomic DNA isolated from the fetus's liver and skin fibroblasts. A few months later, we performed a second prenatal diagnosis in this family. The second fetus was heterozygous for the wild-type alleles. The pregnancy was continued and a girl was born at 41 weeks of gestation. We have confirmed the wild-type state on the baby's DNA.

Carbamyl-phosphate synthetase I (CPS I) deficiency (CPSD: McKusick 237300) is a rare autosomal recessive urea cycle disorder characterized mainly by hyperammonaemia. The highly tissue-specific CPS I enzyme is located in the mitochondrial matrix of hepatocytes and epithelial cells of intestinal mucosa. CPSD is a inborn error of metabolism with a poor prognosis.

Prenatal diagnosis, in an at-risk pregnancy for CPSD, was attempted by enzymatic assay in fetal liver biopsy performed at 18–21 weeks of gestation (Kamoun et al 1995; Murotsuki et al 1994; Piceni Sereni et al 1988; Yoshino et al 1997). This method may give an ambiguous result (Yoshino et al 1997) or diagnostic error (Kamoun et al 1995). An incorrect enzymatic assay leading to a misdiagnosis could occur owing to contamination by a blood clot or to the heterozygosity of the fetus. Fetal liver biopsy implies a greater risk of complications such as bleeding during the biopsy causing hepatic necrosis. This method is an invasive procedure compared to chorionic villus samples (CVS) and/or amniocentesis. Recently prenatal diagnostic procedures based on molecular genetics have been introduced for many diseases. Until recently, CPS I was rarely investigated genetically because of the complex and unknown genomic organization. The determination of the organization of the CPS I gene (Funghini et al 2003; Haberle et al 2003) and the knowledge that CPS I genetic lesions can also be detected in nonspecific tissue make it possible to perform prenatal molecular

diagnosis once the proband's genetic lesions are known, by amplifying and sequencing chorionic villus/amniotic fluid fetal DNA.

Up to now only very few molecular prenatal diagnoses of CPS I have been reported (Aoshima et al 2001; Finckh et al 1998; Haberle and Koch 2004). We performed two prenatal molecular diagnosis on genomic DNA isolated from CVS and amniotic fluid collected at 13 weeks of gestation in an Italian family. The proband was affected by neonatal-onset CPS I deficiency in which molecular analysis of CPS I cDNA and genomic DNA identified V457G and Q810R amino acid substitutions (Funghini et al 2003). The first fetus was compound heterozygous for the amino acid substitutions detected on the proband's genomic DNA and the pregnancy was interrupted. The genetic lesions were also confirmed on genomic DNA extracted from the fetus's liver and skin fibroblasts. Some months later, a second prenatal diagnosis was performed in the same family. The fetus was unaffected and a girl was born.

In contrast to prenatal enzymatic diagnosis of CPS I deficiency by fetal liver biopsy, prenatal molecular diagnosis is less invasive and more certain. Prenatal molecular diagnosis is performed at 11–12 weeks of gestation on genomic DNA isolated from CVS or at 14–16 weeks of gestation on genomic DNA isolated from amniocytes. In contrast, enzymatic assay in a fetal liver biopsy is performed relatively late in pregnancy. An abortion performed at 11–13 weeks is less invasive and less psychologically harmful than one at 18–22 weeks of gestation.

The prenatal enzymatic liver biopsy method can be used successfully to assess prenatal diagnosis only when direct mutation analysis is impossible or no other tissue is suitable for biochemical assay.

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