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Case Report

A recurrent case of pyruvate dehydrogenase complex deficiency

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ABSTRACT

Pyruvate dehydrogenase complex deficiency is an inherited inborn error of metabolism causing lactic acidosis and several neurological symptoms. Its incidence and prevalence are not known. Here we report about a child with global developmental delay, central hypotonia and dyskinesia. Sanger sequencing was done and found to have homozygous nonsense mutation in exon 4 of PDHX gene causing lactic acidosis. In the next pregnancy selective Sanger variant analysis was carried out and the fetus was also found to be affected with the same genetic defect. Hence medical termination of Pregnancy was carried out. We conclude that early selective genetic testing will prevent further affected births.

Keywords: Pyruvate dehydrogenase, Lactic acidosis, Prenatal diagnosis

INTRODUCTION

The human mitochondrial matrix has the enzyme called pyruvate dehydrogenase complex. The irreversible oxidative decarboxylation of pyruvate to acetyl CoA is carried out by this enzyme complex. This complex comprises of three catalytic subunits, E1, E2, E3, two regulatory subunits, E1 kinase and E1 phosphatase and a component, E3 binding protein (E3BP). E3BP is encoded by the PDHX gene (MIM#608769) located on the chromosome 11p13, which extends over 86.7 kb with 11 widely spaced small exons.[1] In a normal metabolic cycle, energy is obtained by breaking down of carbohydrates by certain enzymes called the pyruvate dehydrogenase complex. When carbohydrates are broken down, pyruvate is obtained. This pyruvate is converted into acetyl-CoA by the enzyme pyruvate dehydrogenase. When there is decreased levels of this complex, the pyruvate builds up in the body and gets converted into lactic acid. Lactic acid thus accumulates causing lactic acidemia, leading to various neurological problems.[2] Those children with pyruvate dehydrogenase complex deficiency (PDCD) have fewer enzymes when compared to those without the disorder. These children are less able to break down carbohydrate and sugars into energy.[3] Although it's been more than 40 years since its first description of the disease, the incidence and prevalence remain unknown. We reported a recurrent case of Pyruvate dehydrogenase complex deficiency in the index child as well as in the fetus.

CASE REPORT

Here we present 23 years old female, with third degree consanguineous marriage, conceived spontaneously and delivered a female baby through Preterm LSCS done in view of IUGR with oligohydramnios. After delivery, baby was found to have features like depressed nasal bridge, antimongoloid slant, frontal bossing. As the child was growing, the child was found to have global developmental delay, central hypotonia and dyskinesia. Child was evaluated and MRI brain done (Figure 1, 2) and was found to have dysgenesis of corpus callosum. Sanger sequencing for the child was carried out and was found to have homozygous nonsense variation in exon 4 of PDHX gene, causing lactic acidemia due to PDX1

deficiency with autosomal recessive type of inheritance. Parents were also evaluated for the same and were found to be have heterozygous variation of the same, indicating that the parents are asymptomatic heterozygous carriers. Parents were counselled about the chances of the next child being affected. They were counselled to undergo genetic testing in the subsequent pregnancy.

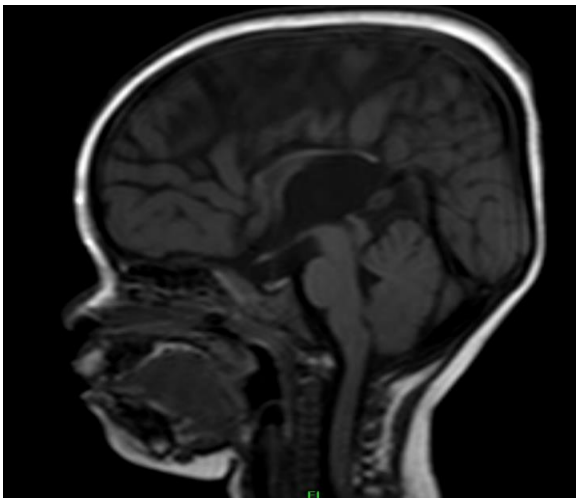

Figure 1: Thinned out corpus callosum.

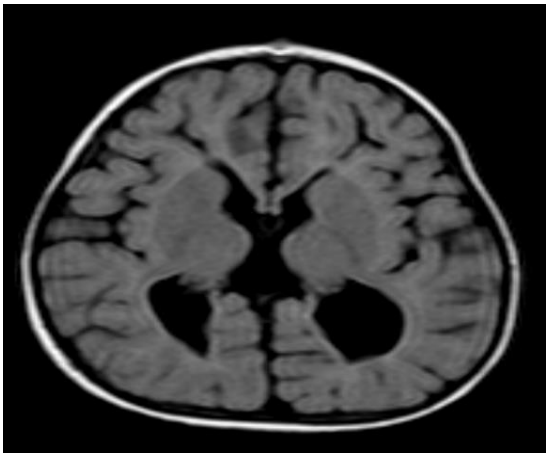

Figure 2: Colpocephaly.

Patient being pregnant now was subjected to chorionic villous sampling at 12 weeks of gestation and the samples taken were subjected to Prenatal sanger variant analysis [1 variant] (MGM 1483). The fetus was also found to have the same defect as the index child, homozygous nonsense variation in exon 4 of the PDHX gene. Parents wanted time to decide on the line of management. Early anomaly scan was done subsequently and the affected fetus was found to have partial agenesis of corpus callosum and abnormal facial profile. Since this child is at a risk being born with serious mental and physical abnormalities, under eugenic backgrounds medical termination of pregnancy was carried out (Figure 3). The fetus autopsy was not done since the parents refused.

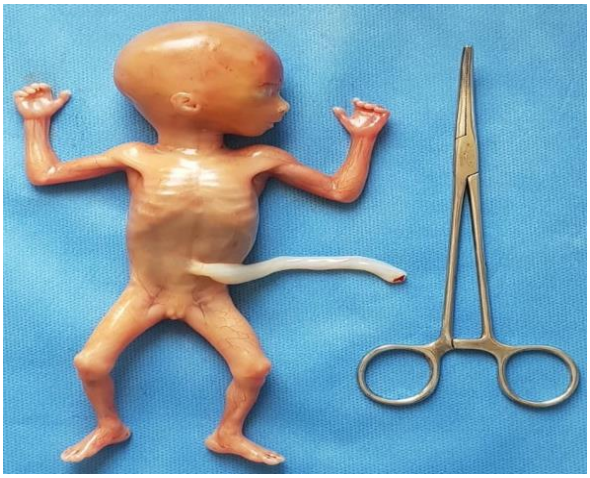

Figure 3: Post-abortal specimen.

DISCUSSION

PDCD is an inherited inborn error of metabolism. It is a major cause of primary lactic acidosis and neurodegenerative disease in infancy and childhood.[4] The PDHX gene encodes component X of the pyruvate dehydrogenase (PDH) complex. Component X binds to the E3 component of the PDH complex. Product of the PDX1 gene is E3 binding protein. The PDHX gene contains 11 exons.[5] Pyruvate dehydrogenase deficiency can have different inheritance patterns. It can have X-linked inheritance pattern, when it is caused by mutations in the PDHA1 gene. When caused by mutations in other genes, pyruvate dehydrogenase deficiency is inherited in an autosomal recessive pattern.[2] Meta-analysis studied by Patel et al states that, the most common clinical feature of Pyruvate dehydrogenase complex deficiency is neurodevelopmental delay and hypotonia and the most common structural abnormalities were ventriculomegaly, dysgenesis of corpus callosum.[6]

Tajir et al reviewed the clinical features of 26 patients with PDHX gene defect. The main clinical features are psychomotor developmental delay with mental retardation, hypotonia and lactic acidosis of variable degrees.[7] Our index patient also has similar features like global developmental delay, central hypotonia and dyskinesia and MR imaging showed dysgenesis of corpus callosum. Ramadan et al studied about 4 patients with E3BP deficiency with 13 other defined cases and he has found that half the mutations were splicing mutation, and the remainder was either frameshift or nonsense mutation.[8] In our case we have found nonsense mutation of the PDHX gene. Ivanov et al stated that both the sexes were equally affected.

Most common presenting complaints were vomiting, failure to thrive, hypotonia, apnoea/grunting, seizures, stupor and coma. In a small number of patients, delayed psychomotor development and/or seizures at the age of 3-6 months were also the reasons for seeking medical attention.[9]

CONCLUSION

PDHX defects are the second most common cause of congenital lactic acidosis. Early selective genetic counselling and testing will help prevent further affected births.

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