CASE REPORT

Prenatal Diagnosis of Glycogen Storage Disorder Type III

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Among glycogen storage disorders, deficiency of glycogen debranching enzyme causes an incomplete glycogenolysis resulting in glycogen accumulation with abnormal structure in liver and muscle. This report describes a novel mutation in a family with glycogen storage disorder Type III in index child used in prenatal diagnosis in the fetus in second trimester.

Keywords: AGL gene mutation, Glycogen Storage Disorder Type III, Prenatal Diagnosis.

Debranching enzyme is required in complete breakdown of the glycogen molecule. Deficiency of debranching enzyme results in glycogen storage disorder (GSD) Type III. GSD III is panethnic, with an estimated incidence of 1 in 100 000(7). Type III is further subclassified into IIIa (liver and muscle form), IIIb (liver form), and IIIc (muscle form)(1-3). Clinically, this may manifest in childhood with hepatomegaly, liver dysfunction, failure to thrive, and fasting hypoglycemia, occasionally resulting in hypoglyce-mic seizures. Some develop weakness, hypotonia, gross-motor delay, and cardiomyopathy. So ascertainment of the exact subtype is essential in management.

CASE REPORT

A mother in her second gravida at 12 weeks presented with her previous seven year old girl child born of a third degree consanguineous marriage. She was referred for evaluation of suspected metabolic disorder in her child, the proband, and with view to explore the possibility of a prenatal diagnosis. The girl had an apparently normal perinatal and neonatal period with age appropriate milestones until five months when she developed an episode of respiratory infection. Hepatomegaly was docu-mented and a few episodes of hypoglycemic seizures were noted. Investigations revealed elevated liver enzymes SGOT-400 IU/L (0-45 IU/L), SGPT - 499 IU/L(0-45 IU/L), and serum alkaline phosphatase 1016 IU/L (100-644). Creatine phosphokinase was elevated 1539 (0-197 U/L). Blood pyruvate and lactate was within normal range and echocardiogram was normal. A tandem mass spectrometry screen, which included a screen for carnitine, amino acid and organic acid was within normal limits. Liver biopsy was reported to have features suggestive of glycogen storage disorder. She has had a fairly asymptomatic course from then until recently (at about 7 years of age) when she developed complains of distal weakness in her upper limbs. This was evidenced by difficulty in fine motor tasks as in writing and finger grip. On clinical examination, all anthropometric measurements were noted to be at fifth centile. Liver size was increased to 7cm below sub costal region. Neuromotor examination revealed mild weakness of distal muscle with normal deep tendon reflexes and muscle tone. Prenatal diagnosis was planned for GSD type III. Investigations comprised of sequencing the AGL gene which identified a homozygous insertion mutation (c.3110insT) (p.Lys1038GlufsX32) in Exon 25 in the proband. Lys (Lysine) is the first amino acid affected by this insertion, changing into Glu(Glutamate) and a stop at 32nd position downstream from this change resulting in frame shift mutation, thereby introducing a premature stop codon. Following this, both maternal and paternal

samples were sent and both were identified to be heterozygous carriers of the same mutation. As the mother was in the 16th week of gestation, prenatal testing by amniocentesis was performed and the DNA extracted were analyzed. Sequence analysis revealed the fetus was also homozygous for the same mutation as in the elder sibling and hence was found to be affected.

DISCUSSION

In a suspected case of GSD type III, ideally there are two steps in workup, first is the clinical, biochemical (enzyme analysis) and histopathological studies (liver and muscle) done as a preliminary step. The second is molecular confirmation of the index case. Chronic hepatomegaly, hypoglycemia, elevated liver enzymes and serum CPK levels, prompted us to suspect glycogen storage disorder initially. Further evidence from a normal echocardiogram, normal blood lactate and pyruvate and urine ketone were supportive in ruling out other metabolic conditions. The presence of liver involvement, recent onset of myopathy and a positive liver biopsy report, GSD Type IIIa was the most probable provisional diagnosis. Enzyme studies were not done in our case because in this a prenatal diagnosis warranted an earlier diagnosis. Moreover, it cannot be correlated with subsequent prenatal testing as in molecular analysis. It is understood that the AGL gene located on chromosome 1p21 codes for two enzymes namely, Amylo-1, 6-glucosidase and 1, 4-Alpha-glucotransferase(1,4). Mutations in AGL gene result in enzyme deficiency causing GSD Type III. Published reports have identified two mutations, 3964delT and IVS32-12A>G to represent more than 12% of the molecular defects among GSD IIIa (4). This clearly signifies the heterogeneous mutation types identified in this disorder. The mutation identified in this report, c.3110insT in AGL gene is reported for the first time in a GSD III family; the index child, the parents and in the fetus for prenatal diagnosis.

The mutation leads to frame shift and a stop codon; when retrospectively correlated with clinical phenotype and histopathology; it can be hypothesized that it is likely to be a pathogenic mutation in GSD Type IIIa. The couple underwent counseling when several issues including pregnancy decision were discussed. They chose to terminate the pregnancy subsequently.

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