A RARE CASE OF A YOUNG INFANT WITH MONOGENIC DIABETES MELLITUS AND CENTRAL VENOUS SINUS THROMBOSIS

Paediatrics

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ABSTRACT

Diabetes mellitus is a metabolic disease characterised by chronically high glucose levels. Genetic factors have been implicated in the etiology following mutations in a single gene. An extremely rare form of diabetes mellitus is monogenic diabetes, a subset of which is permanent neonatal diabetes which is usually suspected in a child less than 6 months presenting with hyperglycaemia. We are reporting case of a 40 days old female child with an autosomal dominant *INS* gene mutation which results in permanent neonatal diabetes in infants requiring lifelong insulin therapy.

KEYWORDS

Summary

Neonatal diabetes mellitus is a rare disorder with an incidence of 1 in 2,60,000 live births. (1) Monogenic diabetes results from inheritance of mutation or mutation in a single gene which accounts for 1-5 % of all childhood diabetes. Neonatal diabetes mellitus and maturity onset diabetes mellitus are the two main forms of monogenic diabetes (1). The condition usually manifests within the first 6 months of life, and occasionally in second half of the first year with polyuria, dehydration and diabetic ketoacidosis. (2) The genetic defect involves mutation of genes involving the pancreatic B cell development, function, apoptosis and insulin molecule. (3)

Recent molecular analysis of neonatal diabetes mellitus identified at least 12 responsible genes: chromosome 6q24, *KCNJ11*, *ABCC8*, *INS*, *FOXP3*, *GCK*, *IPF1* which is also known as pancreatic and duodenal homeobox 1 (*PDX1*), *PTF1A*, *EIF2AK3*, *GLUT2*, *HNF1β*, and *GLIS3*. Defects on chromosome 6q24 (approximately 70%) and the *KCNJ11* mutation have been recognized as the major causes of transient neonatal diabetes mellitus and permanent neonatal diabetes mellitus respectively in Caucasians imprinting (3). Early diagnosis as well as early insulin therapy initiation prevents the metabolic catastrophe of ketoacidosis and development of chronic and irreversible complications. Neonatal diabetes is still area under research since there are many novel mutations still under study. Very few cases has been reported in literature of infantile diabetes mellitus presentation as ketoacidosis as well as central nervous system complication of thrombosis.

Case description :

A 40 days old female child was brought to the casualty with complaints of vomiting, drowsiness, increased abdominal movements and increased urine output since one day. Child was born of non consanguineous marriage. It was a full term, caesarean delivered normal child with birth weight of 2.4 kg without any previous history of NICU admission. There were no previous admission with similar complaints. There was no history of Diabetes Mellitus in the family. On admission, she had tachypnea with deep, rapid and laboured breathing pattern. Her blood sugar levels was >600 mg/dl, urine ketones were large and ABG suggested severe metabolic acidosis (pH-6.92, PO₂-126, PCO₂-10.5, hCO₃-4.6 with BE -28). Other systemic examination findings were within normal limits. Child was diagnosed to have diabetic ketoacidosis. Hence; child was given fluid bolus and was started Milwaukee regimen and insulin drip. Her acidosis got corrected sensorium improved within 48 hours of admission. Child was started on orogastric feeds and subcutaneous regular insulin. Eventually her regular insulin was omitted after 2 days and she was shifted on insulin lispro and glargine. On day two of admission child had one episode of generalized tonic clonic convulsion lasting for 30 sec resolved after inj midazolam without any prolonged postictal drowsiness or focal neurological deficit. Her ionic calcium levels were normal. This child had prolonged hyperglycemia which could have led to cerebral thrombosis as hyperglycemia is known to cause endothelial dysfunction, altered platelet activation and increased blood coagulability. Hence, CT brain was done. She was diagnosed to have

left transverse and sigmoid venous sinus thrombosis for which she was treated with low molecular weight heparin for 6 weeks. Her USG abdomen and 2DEcho was normal.

Fathers and mother's blood sugars were normal. There was no history of diabetes mellitus in the family. Parents as well as babies samples were sent for genetic testing. Child had heterozygous autosomal dominant variety of *INS* gene mutation on chromosome 11. Eventually child was discharged on oral breastfeeds and insulin without any focal neurological deficit.

DISCUSSION :

In permanent neonatal diabetes (PNDM), the most common genetic mutations seen are in *KCNJ11* and *ABCC8*, accounting for close to 50% of PNDM; *INS* gene mutations account for ~20% of PNDM, with mutations in other genes (such as *GCK* and *PDX1*) occurring less commonly. (4)

One study done by Nithya A on permanent neonatal diabetes mellitus due to *ABCC8* mutation on a two-month-old female baby, born to non consanguineous parents, was referred in view of diabetic ketoacidosis. Antenatal period was uneventful with no history of gestational diabetes mellitus. Family history was unremarkable except that maternal grandmother had diabetes. Her genetic study revealed a heterozygous missense mutation in exon 29 of *ABCC8*. (5)

N Catherine et al reported a rare case of permanent neonatal diabetes mellitus from east Africa in a term, caesarean delivered, small for gestation baby, who was admitted multiple times for neonatal sepsis. At 6 weeks, child presented with diabetic ketoacidosis. It is known to be a rare condition worldwide but should be suspected in low birth weight infants with persistent hyperglycaemia requiring insulin therapy. A missense mutation, p.R201C, on *KCNJ11* gene on the Kir6.2 subunit encoding for beta cell ATP-sensitive potassium channel was confirmed. Both his parents were found to be normal. Children with a *KCNJ11* gene mutation affecting the ATP-sensitive potassium channel in the pancreatic beta cell have an overall good prognosis with good glycaemic control attained with oral sulphonylurea therapy. (6)

A 65 day old baby from Iran was reported to have diabetes mellitus. His mother had a history of gestational diabetes and his second degree relatives had type II diabetes mellitus. He was born at 38 weeks of gestation with birth weight of 1800 g (< third percentile) and length 46 cm (< third percentile) and his USG revealed duodenal atresia with fatty liver and normal spleen and pancreas. He was diagnosed as having hyperglycaemia on 28th days. He was diagnosed as a syndromic case of NDM with mutation in *PDX1* gene. This was a novel homozygous mutation, p.Phe167Val, located on chromosome 13 (c.499 T>G). (7)

In our study it was observed that the child was born out of non-consanguineous marriage with no associated anomalies. This child also presented with diabetic ketoacidosis which is the most common presentation in all similar cases. There was no history of Diabetes

Mellitus in the family. Child was a full term baby who was appropriate for gestational age. Her genetic study revealed, there was a de novo INS gene mutation of autosomal dominant variety located on Chr11:g 2182053.

CONCLUSION :

Autosomal dominant type of INS gene mutation is a rare cause of permanent neonatal diabetes mellitus. Most common presentation is Diabetic Ketoacidosis. Child should be screened for associated congenital anomalies. Every child with early onset diabetes mellitus <1 yr should undergo genetic testing for adequate diagnosis and treatment. Those children with *KCNJ11* and *ABCC8* mutation respond to sulphonylureas. Children with INS mutation will require life long insulin therapy. An additional clinical feature worth noting in these cases includes HbA1c at diagnosis; alternative estimates of glycemic control, such as fructosamine or glycated albumin can also be used for diagnosis which were not measured in our patient.

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