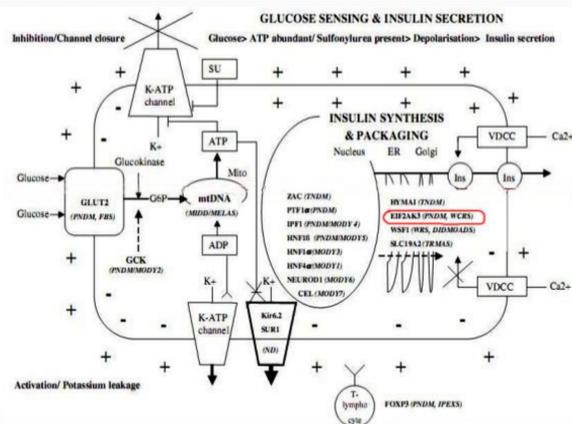




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Introduction

Monogenic diabetes mellitus (DM) is extremely rare form of the disease (less than 1-2% of all diabetes in young people), with neonatal diabetes as a subset, and is usually suspected if it's diagnosed at less than 6 months of child's age. About one in half a million children all over the world are diagnosed with neonatal diabetes at birth or a few weeks after. Clinically two subgroups of neonatal DM are recognised: transient and permanent. Transient neonatal DM resolves at a median of 12 weeks but as many as 50% of cases will ultimately relapse. Permanent neonatal DM requires ongoing insulin treatment when diagnosed. The majority of patients with transient neonatal DM have an abnormality of imprinting of the ZAC and HYMAI genes on chromosome 6q. Permanent neonatal DM requires ongoing insulin treatment when diagnosed. The commonest known cause of permanent DM are mutations in the *KCNJ11* gene encoding the Kir6.2 subunit of the β -cell K ATP channel but not alone (fig).



We present the first case reported in Ukraine of a child diagnosed with permanent neonatal DM resulting from a eukaryotic translation initiation factor alpha kinase 3 (EIF2KA3) gene missense mutation of exon 15 (Wolcott-Rallison Syndrome). It's an autosomal recessive mutation which usually shows its first signs at the age of 3 months.

Case presentation

A 1 years 10 mo old boy was referred to endocrinologist of Ternopil Regional Children's Hospital for further management as he had been on insulin therapy for last 1 year and 8 months.

From anamnesis: he's full-term child from second physiological pregnancy and delivery, birth weight 2500 g. Neonatal period was usual. Family history is unremarkable. In age 6 weeks he was hospitalized due to moderate dehydration and intoxication syndromes without vomiting or diarrhea. Capillary blood glucose was 22 mmol/l (N=3,3-5,5) [396 mg/dl], Hb1Ac = 9.662 % (N = 4,8-5,9), C-peptide = 0,27 ng/ml, (N = 0,9-7,10) and manifestation of neonatal DM had been diagnosed. General condition of the child quickly improved due to combined insulin therapy.

By genetic DNA analysis of parents and child blood novel EIF2AK3 gene missense mutation of exon 15 was revealed by Sanger sequencing, that confirm the clinical diagnosis of Wolcott Rallison syndrome. Analysis of all other known neonatal diabetes genes did not identify a pathogenic mutation.

Confirmation of the gene mutation EIF2AK3 presence in our patient was done by the laboratory of Exeter University, United Kingdom.

Child grew and developed properly on regular basis-bolus insulin therapy in daily dose of 0,36 U/kg body weight. The course of diabetes was stable, glycosylated hemoglobin per year observation was 8,2-8,5%.

In the age of 1 year boy was hospitalized to intensive care unit due to grave general condition: fever, intoxication, lethargy, anorexia, jaundice, generalized edema, hepatomegaly, oliguria, acholic stool. Blood test revealed: mild hypochromic anemia, hypoproteinemia, normal urea and creatinine level, high transaminases, hyperbilirubinemia, hypokaliemia. Hepatitis markers were negative. Glucose and ketone bodies were absent in urine analyses. HbA1c was 8,6%. Hepatomegaly, portions of free liquid in abdominal and pericardial cavity, hydrocephaly were revealed at ultrasound examination. Based on these signs and symptoms acute liver failure was diagnosed.

After the intensive care for a month with insulin therapy, parenteral nutrition, repeated blood transfusions, albumin infusion, detoxification therapy, forced diuresis, correction of electrolyte balance, the child's condition improved.

Mother had complained of lameness of left leg in child which becomes more intensive and persistent during the last months. By x-ray examination hypoplasia of the left hip joint was confirmed. Bone dysplasia is one of the typical sign of Wolcott-Rallison Syndrome. Child was discharged from the hospital in satisfactory condition.

In the age of two years child was hospitalized with acute respiratory infection and sudden aggressive development of liver failure which was fatal to the child despite of intensive care.

Discussion

Wolcott-Rallison syndrome is an extremely rare condition worldwide. It was named after Drs Wolcott and Rallison, who first described this syndrome in three affected siblings. It associates permanent neonatal or early-childhood insulin-dependent diabetes and epiphyseal dysplasia. Other clinical features that show variability among Wolcott-Rallison Syndrome cases include mental retardation, hepatic and kidney dysfunction, cardiac abnormalities, exocrine pancreatic dysfunction, and neutropenia. Data on the epidemiology of Wolcott-Rallison Syndrome are limited, and the latest literature review on the subject suggested that less than 60 of WRS cases were reported worldwide. However, the condition has been recently found to be the commonest genetic cause of permanent neonatal DM in consanguineous families and in the Arab population.

Conclusion

Wolcott-Rallison Syndrome should be suspected in any infant who presents with permanent neonatal diabetes associated with episodes of acute liver failure. Molecular genetic testing confirms the diagnosis. Early diagnostics is recommended in order to ensure rapid intervention for episodes of hepatic failure, which is the most life threatening complication.