

## Permanent neonatal diabetes mellitus in a young Ukrainian child

Przetrwala cukrzyca noworodkowa u dziecka z Ukrainy

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### Abstract

Diabetes mellitus is a chronic metabolic disease with the manifestation possible in any period of life. The incidence of diabetes is rising around the world, and studies show that children are at an increasing risk of developing the disease. Type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, although less than 10% of children suffer from type 2 diabetes. Over the last few decades, inherited monogenic forms of DM were discovered and studied. An extremely rare form of diabetes (less than 1-2% of all diabetes in young people), with neonatal diabetes as a subset, and is usually suspected if a child is diagnosed with diabetes at less than 6 months of age. We present the first case reported in Ukraine of a child diagnosed with permanent neonatal diabetes resulting from a EIF2AK3 gene missense mutation of exon 15 (Wolcott-Rallison Syndrome). Despite low incidence of the permanent neonatal diabetes, this diagnosis should be considered in infants with persistent hyperglycaemia requiring insulin therapy.

### Key words:

Wolcott-Rallison Syndrome, neonatal diabetes

### Streszczenie

Cukrzyca jest przewlekłą chorobą metaboliczną, która może się ujawnić w każdym okresie życia. Na całym świecie obserwuje się wzrost zachorowalności, a badania wykazują, że ryzyko tej choroby wzrasta także u dzieci. U dzieci i młodzieży ponad 90% przypadków to cukrzyca typu 1, jakkolwiek mniej niż 10% dzieci dotkniętych jest cukrzycą typu 2. W ostatnich latach rozwinęły się badania nad cukrzycami monogenowymi. Są to jednak wyjątkowo rzadkie formy cukrzycy (mniej niż 1–2% wszystkich przypadków cukrzycy u młodych ludzi), z cukrzycą noworodkową, którą należy podejrzewać w przypadku rozpoznania cukrzycy u dziecka poniżej 6 miesięcy życia. Prezentujemy pierwszy przypadek dziecka z Ukrainy z rozpoznaną przetrwałą cukrzycą noworodkową z powodu mutacji w eksonie 15 genu EIF2AK3 (Zespół Wolcott-Rallison). Rozpoznanie zespołu Wolcott-Rallison jako przyczyny przetrwałej cukrzycy noworodkowej należy rozważyć w przypadku hiperglikemii wymagającej podawania insuliny u niemowląt.

### Słowa kluczowe:

zespół Wolcott-Rallison, przetrwała cukrzyca noworodkowa, dziecko

### Introduction

Diabetes mellitus is a chronic metabolic disease with manifestations possible in any period of life. The incidence of diabetes is rising around the world, and studies show that children are at an increasing risk of developing the disease. Type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, although less than 10% of children suffer from type 2 diabetes. Over the last few decades, inherited monogenic forms of DM were discovered and studied. It is an extremely rare form of diabetes (less than 1–2% of all diabetes in young

people), with neonatal diabetes as a subset, and is usually suspected if a child is diagnosed with diabetes at less than 6 months of age. About one in half a million children all over the world are diagnosed with neonatal diabetes at birth or a few weeks after [1].

Neonatal diabetes mellitus (NDM) was first described by doctor Kitselle in 1852, when his child presented with severe hyperglycemia at birth. From different studies scientists have concluded that this form of diabetes results from mutations that occur on the surface of pancreatic beta cells. These can be KCNJ11, ABCC8, FOXP3, IBEX, GCK, EIF2AK3 etc. [2].

Clinically two subgroups of NDM are recognised: transient and permanent. Transient NDM resolves at a median of 12 weeks but as many as 50% of cases will ultimately relapse. The majority of patients with transient NDM have an abnormality of imprinting of the *ZAC* and *HYMAI* genes on chromosome 6q. Permanent NDM requires an ongoing insulin treatment when diagnosed. The commonest, but not the only one known cause of permanent NDM are mutations in the *KCNJ11* gene encoding the Kir6.2 subunit of the  $\beta$ -cell KATP channel [1].

Due to the octamer structure of the pancreatic beta cell, the KATP channels, which regulate insulin release, are affected by mutations in either the *SUR1* (*ABCC8*) or *KCNJ11* (Kir6.2) that will result in insufficient insulin release and an increased calcium influx. In case of Wolcott-Rallison Syndrome the affected protein will be the eukaryotic translation initiation factor alpha kinase 3 (*EIF2AK3*), also known as PKR endoplasmic reticulum kinase. It is an autosomal recessive mutation which usually shows its first signs at the age of 3 months.

Between January 2000 and August 2013 in the Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK genetic testing was conducted in 1020 patients (571 boys, 449 girls). This large, international, cohort study included patients with neonatal diabetes diagnosed with diabetes before 6 months of age who were referred from 79 countries [3]. Mutations by comprehensive genetic testing, including Sanger sequencing, 6q24 methylation analysis, and targeted next-generation sequencing of all known neonatal diabetes genes we identified. Mutations in the potassium channel genes were the most common cause ( $n=390$ ) of neonatal diabetes, but were identified less frequently in consanguineous families. In patients with genetically diagnosed Wolcott-Rallison syndrome, 23 (88%) of 26 patients tested within 3 months from the diagnosis had an isolated diabetes, compared with three (17%) of 18 patients referred later ( $>4$  years;  $p<0.0001$ ), in whom skeletal and liver involvement was common.

We present the first case reported from Ukraine of a child diagnosed with permanent NDM resulting from a *EIF2AK3* gene missense mutation of exon 15 (Wolcott-Rallison Syndrome). Confirmation of the gene mutation *EIF2AK3* presence in our patient was done by the laboratory of Exeter University, UK.

A diabetic boy was admitted for usual check up to the Endocrinology Department of Ternopil Regional Childrens' Hospital.

From anamnesis: he is full-term child from second physiological pregnancy and delivery, birth weight 2,500 g. Neonatal period was usual. Family history is unremarkable. In the age of 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 NDM had been diagnosed. General condition of the child quickly improved due to the 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 which confirmed the clinical diagnosis of Wolcott-Rallison syndrome.

The analysis of all other known neonatal diabetes genes did not identify a pathogenic mutation.

The child grew and developed properly on a regular basis-bolus insulin therapy in a 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 the boy was hospitalized in the intensive care unit due to a grave general condition: fever, intoxication, lethargy, anorexia, jaundice, generalized edema, hepatomegaly, oliguria, acholic stool. A 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 the urine analyses. HbA1c was 8.6%. Hepatomegaly, portions of free liquid in abdominal and pericardial cavity, hydrocephaly were revealed at the 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.

The mother complained of lameness of left leg in the child, which had become more intensive and persistent during the previous months. The x-ray examination confirmed the hypoplasia of the left hip joint. Bone dysplasia is one of the typical signs of Wolcott-Rallison Syndrome. The child was discharged from the hospital in a satisfactory condition.

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

## Discussion

Most of all mutations at NDM are normally caused by intrauterine growth restriction, meaning these mutations usually occur during the first trimester. Early signs and symptoms in these infants include low weight, hyperglycemia, seizures, developmental delay and abnormal cognitive function. In the case of Wolcott-Rallison Syndrome, the children also do present with above stated signs but their distinctive features are osteopenia, bone dysplasia and, in most cases, a series of hepatic failures and splenomegaly. Although skeletal dysplasia is a main feature, it is usually noticed in patients in the period from 3 to 6 years old.

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 [5]. It associates permanent neonatal or early-childhood insulin-dependent diabetes and epiphyseal dysplasia. Other clinical features that show variability among WRS cases include mental retardation, hepatic and kidney dysfunction, cardiac abnormalities, exocrine pancreatic dysfunction, and neutropenia. Data on the epidemiology of WRS are limited, and

the latest literature review on the subject suggested that less than 60 of WRS cases were reported worldwide [5–7]. However, the condition has been recently found to be the commonest genetic cause of PNDM in consanguineous families and in the Arab population [8].

In our case we could not find any confirmation of consanguineous marriage. Our patients were found to be homozygous for a novel *EIF2AK3* missense mutation p.G1010V has not been reported previously. But it is likely to be pathogenic since this glycine residue is highly conserved across species and a different mutation at this codon, p. G1010D has been identified by this laboratory in 2 patients with Wolcott-Rallison syndrome.

There are only few case reports of the Wolcott-Rallison syndrome in which the clinical presentation includes recurrent infections, renal insufficiency, neutropenia, growth and developmental retardation, osteopenia, multiple epiphyseal dysplasia, and exocrine pancreas insufficiency as common features [5,9]. Episodes of Acute Liver Failure are typical for this syndrome.

Another specific feature of Wolcott-Rallison syndrome is bone dysplasia [5]. The multiple epiphyseal dysplasia associated with WRS characteristically affects the long bones, pelvis and vertebrae. Osteoporosis has also been described in association with WRS in some patients [10].

Genetic counselling, molecular analysis and sequencing, electrophysiological analysis and antenatal history can help in confirmation of the right diagnosis. Patients need management

with insulin and appropriate treatment for other associated conditions. Early genetic verification of the syndrome can be useful for individualized medical support of the patients and preventing early mortality by providing multiorgan transplantation, for example [11].

## Conclusion

WRS 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.

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Patient's consent for publication has been granted

Contribution of authors must be listed on a separate form.

The authors contributed equally to this article. They read and approved the final version of the manuscript.

The authors declare that they have no competing interests

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