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SHORT COMMUNICATION

Primary hypothyroidism and nipple hypoplasia in a girl with Wolcott–Rallison syndrome

Anita Špehar Uroić · Vjosa Mulliqi Kotori · Nataša Rojnić Putarek · Vesna Kušec · Miroslav Dumić

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Abstract Wolcott–Rallison syndrome (WRS), caused by mutation in the EIF2AK3 gene encoding the PERK enzyme, is the most common cause of permanent neonatal diabetes mellitus (PNDM) in consanguineous families and isolated populations. Besides PNDM, it also includes skeletal abnormalities, liver and renal dysfunction, and other inconsistently present features. We present two siblings, who are WRS patients, and are Albanians from Kosovo born to unrelated parents. The older sister presented with PNDM, exocrine pancreatic insufficiency, short stature, microcephaly, normocytic anemia, delay in speech development, skeletal abnormalities, primary hypothyroidism, and hypoplastic nipples. Sequencing of the EIF2AK3 gene identified a homozygous mutation R902X in exon 13. The younger brother was diagnosed with PNDM and died from hepatic failure suggesting that he has been suffering from WRS as well. Including one previously reported patient from Kosovo carrying the same homozygous mutation, there are three WRS patients from this very small, ethnically homogenous region suggesting founder effect in this population. Conclusion: We postulate that thyroid hypoplasia with primary subclinical hypothyroidism already reported in two WRS patients and nipple hypoplasia could also be the phenotypic reflection of the mutation of pleiotropic EIF2AK3 gene in secretory cells.

Keywords Wolcott–Rallison syndrome · EIF2AK3 · Primary hypothyroidism · Nipple hypoplasia

A. Špehar Uroić (✉)
Department of Pediatrics, University Hospital Centre Zagreb, Kišpatićeva 12, Zagreb 10000, Croatia
e-mail: anspehar@gmail.com

V. Mulliqi Kotori
Pediatric Clinic Department of Endocrinology, University Clinical Center Kosovo, Prishtina 10000, Kosovo

N. Rojnić Putarek · M. Dumić
School of Medicine, Department of Pediatrics, University Hospital Center Zagreb, Zagreb 10000, Croatia

V. Kušec
School of Medicine, Clinical Institute of Laboratory Diagnostic, University Hospital Center Zagreb, Zagreb 10000, Croatia

Introduction

Walcott–Rallison syndrome (WRS, OMIM 226980) is a rare autosomal recessive disorder characterized by permanent neonatal diabetes mellitus (PNDM) and spondyloepiphyseal dysplasia [6, 8]. It also includes growth retardation, liver, and/or kidney dysfunction [1] and other, inconsistently present clinical features.

WRS is caused by mutations in the *EIF2AK3* gene [2] encoding the eukaryotic translation initiation factor 2 alpha kinase-3, also known as PERK. PERK is localized in the endoplasmatic reticulum and seems to be important for the control of pancreatic beta cell differentiation, proliferation, and postnatal glucose homeostasis [10]. Mutations in the *EIF2AK3* gene, which is highly expressed in both beta cells and bone tissue but also in a number of other actively secreting cells, result in failure to downregulate translation under stress conditions [9], accumulation of unfolded proteins, and finally cell loss. Resulting diminished functional mass of affected tissue could explain a number of WRS features.

WRS is the most common genetic condition causing PNDM in consanguineous families and should be thought of in patients with PNDM coming from isolated populations and countries with frequent inbreeding [4], especially if they develop epiphyseal dysplasia or additional clinical signs.

Herein, we present two WRS patients, who are siblings, Albanians from Kosovo. Molecular analysis of the *EIF2AK3* gene in an older sister identified a homozygous R902X mutation in exon 13. The younger brother was diagnosed with

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PNDM and died due to fulminant hepatic failure suggesting that he has been suffering from WRS as well.

We postulate that thyroid hypoplasia with consecutive subclinical primary hypothyroidism and perhaps hypoplastic nipples observed in older sister are consequences of insufficient PERK activity in thyroid and breast tissue.

Case report

Patient 1

The older sister was born at term after an uncomplicated pregnancy from healthy unrelated parents, Albanians from Kosovo, as their first child. Birth weight was 2,200 g (−2.26 SD) and birth length was 47 cm (−1.72 SD). She was diagnosed with diabetes mellitus at the age of 10 days (blood glucose (BG) level 22 mmol/L, glucosuria, and mild ketonuria) and insulin therapy was introduced. Islet cell antibodies, insulin antibodies, and glutamic acid decarboxylase antibodies tests were negative. HLA genotyping did not reveal type 1 diabetes susceptibility loci (HLA-A*02,*24; B*38,*44; DRB1*13,*16). At the age of 7 months, her stool became frequent and greasy. Concentration of chloride in sweat was 20 mmol/L, making cystic fibrosis unlikely. At the age of 5 years, subclinical primary hypothyroidism was diagnosed: thyroid stimulating hormone (TSH), 19 mU/L (normal range, 0.4–4.2); T3, 1.5 nmol/L (normal range, 1.3–2.5); T4, 74 nmol/L (normal range, 70.0–165.0), thyroid peroxidase antibodies, and thyroglobulin autoantibodies were negative. Echosonography showed a normal echostructure of a smaller-for-age thyroid gland. L-thyroxin (25 μg/day) therapy was introduced. A neonatal screening test for hypothyroidism is not performed in Kosovo, so we cannot know since when our patient has had primary hypothyroidism. Except for some delay in speech development, her psychoneurological development was normal.

At the age of 7 years, the girl was admitted to our department. Her body weight was 12.4 kg (−3.63 SD), height was 97 cm (−4.38 SD), and head circumference was 46 cm (−2.83 SD for height). Hypoplastic nipples were noticed (Fig. 1). There were no apparent skeletal deformities. Laboratory tests revealed mild normocytic anemia (Hb, 107 g/L (normal range, 109–138); Htc, 0.31 (normal range, 0.32–0.40); MCV, 80.0 fL (normal range, 73.8–98.4)) and were consistent with subclinical primary hypothyroidism (TSH, 8.7 mU/L, normal levels of T3 and T4 (T3, 2.4 nmol/L; T4, 117.4 nmol/L)), although she was already taking L-thyroxin therapy. The C-peptide level was undetectably low. Low levels of serum lipase (3 U/L; normal range, 13–60 U/L) and pancreatic elastase in stool (<15 μg/g; normal range, >200μg/g) indicated exocrine pancreatic insufficiency and pancreatic enzyme replacement was introduced. There were no signs of liver dysfunction. Glycemic control was poor (HbAlc, 10.3 %; normal range, <6 %). A CT scan of the abdomen revealed hypoplastic pancreatic head and uncinate, with no signs of the trunk and the tail of the pancreas and normal morphology of other internal organs. A CT scan and MRI of the brain gave normal findings. A skeletal X-ray showed signs of bone dysplasia: a poorly developed core in the distal epiphysis of the radius (normal for a 1-year-old child) and lunate (normal for a 4-year-old child), sclerotic capitate bone, sclerotic and dysplastic both femur heads, delayed ossification of the bones of the feet with fragmented first metatarsal bone on the left foot, and sclerotic lateral part of the epiphysis of left tibia. The spine was normal.

The molecular genetic analysis of the *EIF2AK3* gene revealed that the patient 1 is a carrier of homozygous nonsense mutation (c.2704C>T) in exon 13, resulting in the premature termination codon (R902X). The parents are both heterozygous for the same mutation.

Patient 2

The brother who was 4 years younger was born after an uncomplicated pregnancy. His birth weight was 2,800 g

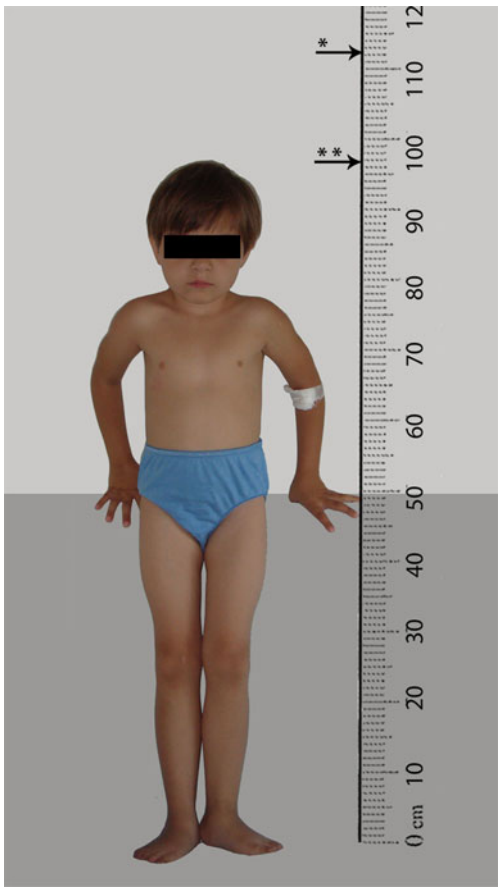

Fig. 1 Patient 1. Please note short stature (*5th percentile for patient's age and sex, **patient's height) and hypoplastic nipples

(−1.14 SD). He was diagnosed with diabetes at the age of 2 weeks (20 mmol/L BG, glucosuria, ketonuria, and 9.8 % HbA1c) and insulin therapy was started. According to scant data from the medical records, at the age of 6 months, he died from fulminant hepatic failure during an acute viral illness. Besides a high level of AST (up to 7,770 U/L; normal range, 14–55 U/L) and ALT (up to 3,200 U/L; normal range, 11–68 U/L), anemia was present (Hb, 94 g/L; Htc, 0.28). At that time, the diagnosis of WRS was not suspected and other tests (including genotyping) were not performed.

Discussion

Patient 1 presented with PNDM, exocrine pancreatic insufficiency, short stature, microcephaly, normocytic anemia, delay in speech development, skeletal abnormalities (visible only on X-ray), primary hypothyroidism, and hypoplastic nipples. The diagnosis of WRS was confirmed by molecular genetic analysis. Patient 2 was diagnosed with PNDM and died from hepatic failure suggesting that he has been suffering from WRS as well. WRS was recognized years after he died due to diagnosis of the disease in his sister. We believe that he had the same *EIF2AK3* gene mutation as his sister, considering that their parents are both heterozygous for the same mutation.

WRS is the most common genetic condition causing PNDM in isolated populations or countries in which consanguineous marriages are frequent [4]. Including the previously reported patient from Kosovo [4], there are at least three WRS patients coming from this small region counting 1.7 million inhabitants. Albanians, who make more than 90 % of the population in that country are rather closed and do not mix with other ethnic groups. The reported patient does not have consanguineous parents and carries the same homozygous mutation of *EIF2AK3* gene (R902X) as our patient, suggesting founder effect in this population.

It was shown that the PERK enzyme, which is malfunctioning in WRS, has an important regulatory role in secretory cells such as beta cells, pancreatic acinar cells [9], as well as in thyrocytes [7]. Primary hypothyroidism was already reported in two patients with WRS [3, 4]. We would like to support the suggestions of Ersoy at al. that primary hypothyroidism could be one of the symptoms of the disease. However, it seems that there is no genotype–phenotype correlation since the patient reported by Rubio-Cabezas, patient reported by Ersoy and our patient carry different *EIF2AK3* mutations [3, 4].

Hypoplastic nipples observed in patient 1 have not been reported in WRS patients yet and might suggest breast hypoplasia. Since PERK has been expressed in breast tissue as well [5], this could be a case of hypoplasia of another secretory organ. As very few WRS patients survived through adult life; information about breast development in these patients is missing.

Considering earlier diagnostic possibilities for WRS, which enable timely introduction of therapy and rapid intervention for life-threatening complication, we can expect longer patient survival and further discoveries of associated manifestations of this disease.

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Conflict of interest The authors have no conflicts of interest.

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