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# Wolcott-Rallison syndrome: a case series of three patients

Zespół Wolcotta-Rallisona: seria trzech przypadków

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**Abstract**

**Introduction:** Neonatal diabetes is a rare disease with incidence estimated at 1 in 300,000 to 1 in 400,000 live births. Walcott-Rallison syndrome has been identified as the most common cause of permanent neonatal diabetes in consanguineous families caused by mutations in eukaryotic translation initiation factor 2-α kinase 3 (EIF2AK3), characterized by permanent neonatal diabetes associated with liver dysfunction, multiple epiphyseal dysplasia, and developmental delay. We herein report 3 cases of genetically proven Wolcott-Rallison syndrome with variable phenotype presentation.

**Case series:** All cases presented with high glucose levels and were treated with insulin. EIF2AK3 homozygous mutation was identified in all 3 on genetic analysis. Initial screening testing for associated comorbidities was normal, including X-ray examination, which did not show any signs of epiphyseal dysplasia in all cases. Case 2 and case 3 were both lost to follow-up and were later found to have expired at the ages of 18 months and 2 years, respectively, due to liver failure associated with intercurrent respiratory illness in hospitals in their native towns. Case one is now 2 years old on regular follow-up in paediatric Endocrine and neurology clinics and doing well so far.

**Conclusions:** Morbidity, as well as mortality, is high among children with WRS neonatal diabetes. It is crucial to screen for gene mutation in patients with diabetes diagnosed before 6 months. Close therapeutic monitoring is recommended in WRS because of the risk of acute episodes of hypoglycaemia and ketoacidosis.

**Key words:**

Wolcott-Rallison syndrome (WRS), permanent neonatal diabetes mellitus (PNDM), skeletal dysplasia, liver failure.

## Introduction

Wolcott-Rallison syndrome (WRS, OMIM 226980) is a rare autosomal recessive disorder characterized by early-onset diabetes mellitus, liver failure, and skeletal abnormalities (spondyloepiphyseal dysplasia). Other disorders include growth retardation, renal dysfunction, hypothyroidism, exocrine pancreas insufficiency, neutropaenia intellectual deficit, and recurrent infections [1, 2]. In addition, WRS has been reported in countries where the incidence of marriage between first cousins is high [1]. Mutations in the eukaryotic translation initiation factor 2 kinase 3 (EIF2AK3) are responsible for this disorder at chromosome 2p12. EIF2AK3, also known as PKR-like ER kinase (PERK), is an endoplasmic reticulum (ER) transmembrane protein. It is activated by the accumulation of unfolded proteins in the endoplasmic reticulum lumen during stress, resulting in phosphorylation of the -subunit of the eukaryotic initiation factor 2 at residue Ser51 down-regulation of protein synthesis [2, 3]. We herein report 3 cases of genetically proven WRS.

## Case 1

A boy aged 2 years and 5 months presented for the first time via a clinic to our hospital, diagnosed with neonatal diabetes. At the age of 2 months, he was admitted to his local hospital due to lethargy and respiratory distress; a workup revealed high sugar and acidosis. His sugars were controlled with basal-bolus insulin after receiving treatment for diabetic ketoacidosis (DKA).

His parents have a consanguineous marriage. In the birth history, the mother was G4P3+ 0 and had no history of gestational diabetes. Although his 2 siblings died, one at the age of 6 months due to aspiration pneumonia, and the second at the age of 3 months due to a similar illness (high blood sugar and respiratory distress). Unfortunately, the diagnosis of the siblings was not established. The child had a history of fits for which he received Levetiracetam and Phenobarbitone, which continued for one year.

On examination: active alert baby, weight 7.5 kg (< 3rd centile), height 77.5 cm (< 3rd centile), and systemic examination was unremarkable. Laboratory revealed $HbA_{1c}$ 11.1%, celiac workup was negative, Na 135 mmol/l, K 4.7 mmol/l, Cl 101 mmol/l, Bic 13.6 mmol/l, Hb 13 g/dl, and haematocrit 40%. Liver function test showed total bilirubin 0.3 mg/dl, GGT 7U/l, SGPT 21 U/l, AP 299 U/l, SGOT 31 U/l, and TSH 1.6 mIU/l. Urine ketones +4 and CRP 0.39 mg/dl. Due to uncontrolled sugars, NPH (neutral protamine Hagedorn) insulin was started for blood sugar control. Furthermore, genetic testing was sent after obtaining informed consent from the parents.



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Wolcott-Rallison syndrome was confirmed on genetic testing, which revealed homozygous for a frameshift mutation (c.1213-1214del) and P. Lys405fs (p. k405fs) mutation in exons 7 of the *E1F2AK3* gene (Table I). In addition, both parents had a heterozygous mutation for EIF2AK3 (c.1213-1214del), which is consistent with an autosomal recessive form of neonatal diabetes mellitus WRS.

On the subsequent visit a skeletal survey was performed, which was normal. The parents were counselled in detail regarding the prognosis of this disease. He has been followed at our clinic and has persistent issues of poor growth; however, no other abnormality has been observed.

## Case 2

A girl aged one month and 20 days presented at our paediatric emergency unit with complaints of fever, polyuria, polydipsia, and respiratory distress. On examination, she was dull, dehydrated, drowsy, and in respiratory distress, with a height of 52 cm ($10^{th}$ centile), and a weight of 5.2 kg ($10^{th}$ centile).

Initial venous blood gas revealed: pH 7.25, 18 $CO_2$ mmHg, –10.7 base deficit mmol/l, bicarbonate 11.6 mmol/l, sodium 134 mmol/l, potassium 4.7 mmol/l, Ca 9.8 mmg/dl, mg 2.3 ng/dl, BUN 20 mg/dl, Cr 0.9 mg/dl, glucose 1198 mg/dl, $HbA_{1c}$ 12%, C-peptide 1.4 ng/ml, insulin 7.6 $\mu$U/ml, and phosphorus 6.6 mg/dl. Urinalysis demonstrated 4+ sugars and 3+ ketones, indicating a diagnosis of diabetic ketoacidosis.

DKA management was started according to the standard protocol. The patient had 2 episodes of seizures in ER, aborted by antiepileptics. Subsequently, acidosis and ketonuria resolved within 36 hours of hospital admission.

Subcutaneous insulin, glargine, and regular insulin were started for sugar control. Regarding birth history, the baby born to consanguineous parents' mother was G3P2, with a history of one sibling death at the $28^{th}$ day of life due to respiratory distress – the cause of death was not established. After obtaining informed consent from parents, genetic samples were taken and sent to the Exeter laboratory. In subsequent follow-ups, the genetic testing confirmed the patient had a homozygosity for a nonsense mutation (c.3087delC) and P. Leu1030X (p.L1030X) mutation in exons 16 of the *E1F2AK3* gene (Table I).

The skeletal survey was negative for skeletal dysplasia, and the patient was discharged home 9 days after hospital admission. The patient is followed as an outpatient by our paediatric endocrinologist. Unfortunately, samples from parents could not be sent because they did not visit the clinic after discharge. Unfortunately, she died due to liver failure following an intercurrent illness in her home town.

## Case 3

A 7.5-month-old boy was referred from another province, diagnosed with neonatal diabetes at the age of 6 months after a DKA episode. His initial sugar level was 438 mg/dl. The baby was discharged on oral tablets (prescribed by the general physician in his home town) and presented at our centre for further management due to persistent uncontrolled sugars.

He was the product of a consanguineous parent, born full term to a G3P2 mother via vaginal delivery. There was a history of one sibling's death at the age of 2.5 months due to pneumonia; he also had a history of documented raised blood sugar 1000 mg/dl, but unfortunately, the baby died before the diagnosis was established. In addition, there is a history of a 34-week preterm baby who died on the first day of life due to meconium aspiration. On examination, the baby was active alert, with a height of 67 cm ($10^{th}$ centile), and a weight of 7.1 kg ($25^{th}$ centile). The rest of the systemic examination was routine. The NPH was started to control blood sugars, and the skeletal survey was normal – laboratory investigation revealed Hb 8.5 mg/dl, HCT 26%, TSH 2.9 $\mu$IU/ml, $HbA_{1c}$ 9%, and normal liver function testing. Genetic testing was suggestive of homozygosity for a frameshift mutation (c.2039_2040del) and a mutation of P. (Thr680fs) in exons 13 of the *E1F2AK3* gene, which is probably consistent with an autosomal recessive form of neonatal diabetes mellitus WRS (Table I). Unfortunately, the patient expired in his home town due to liver failure following an intercurrent illness.

## Discussion

Wolcott-Rallison syndrome is the most common cause of neonatal diabetes in countries where consanguineous mar-

**Table I.** Genetic variant description of 3 cases

| Parameter | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Gene | *E1F2AK3* | *E1F2AK3* | *E1F2AK3* |
| Location | EXON 7 | EXON 16 | EXON 13 |
| DNA Description | c.1213-1214del | c.3087delC | c.2039_2040del |
| Protein Description | P. Lys405fs (p. k405fs) | P. Leu1030X (p.L1030X) | P. (Thr680fs) |
| Consequence | Frameshift | Nonsense | Frameshift |

riages are common [3]. In our case series, all 3 patients were born to consanguineous parents. Permanent neonatal diabetes is usually diagnosed before 6 months of age and frequently presented in DKA; all 3 patients presented first with insulin-dependent diabetes mellitus at a median age of 3 months (range: 1 month, 20 days to 6 months). In addition, all 3 were homozygous for *EIF2AK3* mutation. In one case, genetic findings of the parents were possible, and both were heterozygous for *EIF2AK3* mutation.

One of the typical manifestations of liver disease in WRS was intermittent hepatitis, usually precipitated by mild stress, but manifestations may vary between patients in their nature and severity. Acute fatal hepatic failure in these children is not uncommon [4]. In one study, Habeb *et al*. found that liver disease was the common feature identified in 85.7% of cases (24/28). The majority had at least one episode of acute hepatic failure, which was the cause of death in all deceased patients (13/28) [4]. In our case series, 2 babies died due to acute liver.

In WRS, the reported skeletal dysplasia findings included small and irregular epiphyses, flattened acetabula, enlarged metaphysis, and atlantoaxial subluxation; moreover, osteopaenia and fractures have also been reported. The expression of *EIF2AK3* in β-cells and bone tissue explains the development of early-onset diabetes mellitus and skeletal abnormalities. In previous studies, epiphyseal changes can be apparent radiologically as early as 6 months [5]. Unexpectedly, we could not identify any skeletal abnormalities in all 3 cases. Along with skeletal abnormalities, WRS has been reported to include developmental delay, mental retardation, or learning difficulties. We did not observe abnormal neurological development in any of the 3 patients. In the literature review, bone abnormalities and other associated findings would be identified later during follow-ups [3]. However, in our cases, 2 patients were lost to follow-up and were later found to have died of liver failure, whereas one patient is doing fine on subsequent follow-ups. Usually, most children develop acute liver failure with every intercurrent illness [6], which occurred in our 2 cases.In addition to these associated findings, there are other rare findings associated with WRS: e.g. Thornton *et al*., in the autopsy of a single 4-year-old WRS patient found arrhinencephaly, cerebellar cortical dysplasia in the brain, severe pancreatic hypoplasia with markedly abnormal pancreatic histology, laryngeal stenosis, pulmonary hypoplasia, enlarged heart with mitral valve dysplasia, and stenosis and other heart abnormalities [7]. Subsequently, a query for an association with hypothyroidism was raised in one case report [8].

This variability of the clinical manifestations observed in WRS remains unexplained [9]. Therefore, genetic counselling and antenatal diagnosis are recommended for parents of a WRS patient with confirmed *EIF2AK3* mutation. In addition to testing patients with a definite clinical diagnosis, *EIF2AK3* should be tested in patients with isolated neonatal diabetes diagnosed, to ensure rapid intervention for stress-induced episodes of hepatic failure, which is the most life-threatening complication.

## Conclusions

Wolcott-Rallison syndrome is the most common cause of permanent neonatal diabetes mellitus in consanguineous pedigrees and should be differentiated from other forms of neonatal or early insulin-dependent diabetes. Genetic counselling and antenatal diagnosis are recommended for parents of a WRS patient with confirmed *EIF2AK3* mutation. In addition to testing patients with a definite clinical diagnosis, *EIF2AK3* should be tested for in patients with isolated neonatal diabetes diagnosed, to ensure rapid intervention for stress-induced episodes of hepatic failure, which is the most life-threatening complication. Hence, screening is essential for predicting the development of additional features, optimal management, and improving patient outcomes.

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