Case Report

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Wolcott–Rallison syndrome: late-onset diabetes, multiple epiphyseal dysplasia, and acute liver failure – a case report

https://doi.org/10.1515/jpem-2025-0116
Received March 2, 2025; accepted May 12, 2025;
published online May 26, 2025

Abstract

Objectives: Wolcott–Rallison syndrome (WRS) is an autosomal recessive multisystemic genetic disorder caused by homozygous mutation in the eukaryotic translation initiation factor 2 alpha kinase 3 gene. It typically presents with neonatal onset insulin-dependent diabetes. Here, we report a 14-year-old male patient with WRS who presented with late-onset diabetes mellitus.

Case presentation: A 14-year-old male patient presented with acute liver failure secondary to acute gastroenteritis. On physical examination, signs of chronic malnutrition and muscle atrophy in the extremities were evident, accompanied by a waddling gait. Infectious, autoimmune, and metabolic diseases were excluded. Liver tests improved within 3 weeks with supportive treatment. Direct radiographs were consistent with multiple epiphyseal dysplasia. High blood glucose levels were observed at follow-up in the intensive care unit. At the 4-month follow-up, HbA1c increased to 55 mmol/mol (7.2 %) and basal insulin treatment was started at a dose of 0.4U/kg/day. Glycemic control was achieved after 6 months.

Conclusions: Diabetes typically manifests within the first 6 months of life, with a median age of 2.5 months, and has been observed in all patients with WRS reported in the literature. Our case is an interesting WRS patient whose diabetes started at the age of 14 years with a novel mutation.

Keywords: Wolcott–Rallison syndrome; acute liver failure; type 1 diabetes mellitus

Background

Wolcott–Rallison Syndrome (WRS) is an autosomal recessive multisystemic genetic disorder caused by a homozygous mutation in the eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3) gene. It typically presents with neonatal onset insulin-dependent diabetes. Other phenotypic features include epiphyseal dysplasia, recurrent acute

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liver failure (ALF), growth retardation, developmental delay, seizures, ataxia, renal failure, renal tubular acidosis, hypothyroidism, exocrine pancreatic insufficiency (EPI), neutropenia, cardiac malformations, pulmonary hypoplasia, skin anomalies, dysmorphic face, and changes in tooth color. Here, we report a 14-year-old male patient with WRS who presented with late-onset diabetes mellitus (DM) [1–3].

Case presentation

A 14-year-old male patient (Figure 1), presented with fever, diarrhea, vomiting, and abdominal pain. The patient was referred to our center with a diagnosis of acute viral gastroenteritis, acute liver, and renal failure based on the laboratory investigations (Table 1). The patient had no history of toxic exposure. He was always growth retarded compared to his peers. He had a waddling gait at the age of 2–3 years and lost the ability to walk at 5 years. A review of the patient's medical history revealed multiple visits to healthcare centers. During these visits, growth retardation and nonspecific skeletal abnormalities were noted; however, no advanced imaging, genetic, or metabolic evaluations were performed. His liver enzyme levels and blood glucose levels (BGL) were within normal limits. Family history was unremarkable except for consanguinity (first cousin marriage). The patient had 3 healthy siblings and there was no similar patient in the family. His body weight, height, body mass index, and head circumference z-scores were −5.3, −5.4, −3.4, and −2.24, respectively. Physical examination was normal except for marked muscle atrophy in the extremities.

Infectious, autoimmune, endocrine, and metabolic diseases were excluded. Except for grade-1 echogenicity enhancement in the liver parenchyma, hepatobiliary and portal Doppler ultrasonography, echocardiography, and ophthalmic examination were normal. Plasma exchange was performed a total of 4 times. Liver tests improved within 3 weeks and renal function tests improved within 48 h with supportive treatment. Liver biopsy showed severe canalicular cholestasis, ductular reaction, mild portal and lobular inflammation, and portoportal mild bridging fibrosis.

Table 1: Laboratory results on admission.

	Results	References
Urea	96 (mg/dL)	10–38 (mg/dL)
Creatinine	2.5 (mg/dL)	0.7–1.2 (mg/dL)
Alanine aminotransferase	1,560 (U/L)	0–50 (U/L)
Aspartate aminotransferase	2,768 (U/L)	0–50 (U/L)
Total bilirubin	7.6 (mg/dL)	0.1–1.2 (mg/dL)
Direct bilirubin	6.9 (mg/dL)	0–0.3 (mg/dL)
Ammonia	206 (μmol/L)	16–60 (μmol/L)
Prothrombin time	66 s	9.4–12.5 s
INR	5.7	0.85–1.12

INR, international normalized ratio.

High BGLs were observed fasting BGL between 129 and 174 mg/dL (normal range: 74–100 mg/dL), postprandial BGLs were between 198 and 214 mg/dL (normal range; <200 mg/dL) after follow-up in the intensive care unit. Tests for hyperglycemia showed simultaneous BGL 132 mg/dL; C-peptide: 2.8 ng/mL (normal range: 0.5–2 ng/mL); insulin: 8.8 μU/mL (normal range: 4–23 μU/mL); and HbA1c: 40 mmol/mol (normal range: 15–38 mmol/mol) [5.8 % (normal range: 3.5–5.6 %)]. Diabetes autoantibodies were negative. Oral glucose tolerance test revealed, BGL 213 mg/dL (normal range; <140 mg/dL) at minute 120. At the 4-month follow-up, HbA1c level increased to 55 mmol/mol (7.2 %) and basal insulin treatment was started at a dose of 0.4U/kg/day. After 6 months, the glycemic control was obtained. HbA1c values at 3-month intervals were 55 mmol/mol (7.2 %) and 53 mmol/mol (7.0 %), respectively. The dose of basal insulin treatment was increased to 0.45 U/kg/day. At the 12-month and last follow-up, fasting BGL was 148 mg/dL and C-peptide was 1.35 ng/mL. Fecal elastase level, checked for EPI was normal.

Initially, the patient exhibited anemia (8.6 g/dl), lymphopenia (0.7×10^9/L), and thrombocytopenia (57×10^9/L); neutrophil count was within the normal range. Vitamin B12,

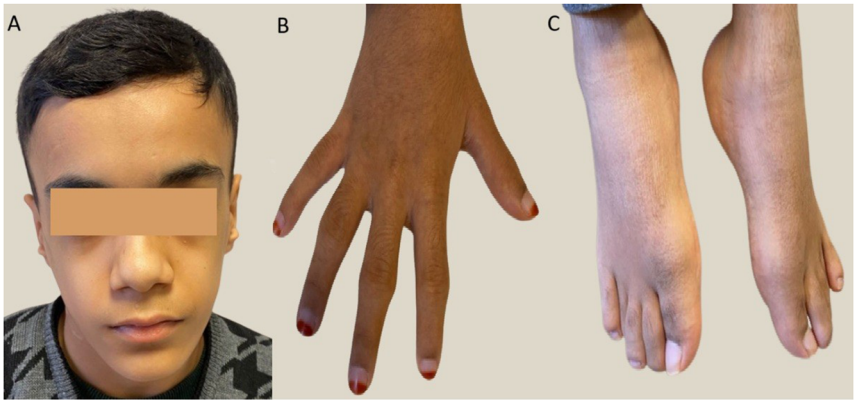


Figure 1: Facial appearance (A), hands (B), and feet (C) of the patient.

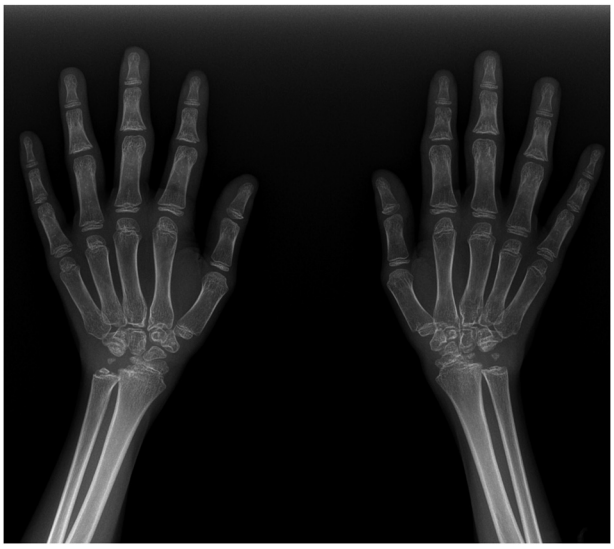


Figure 2: Bilateral hand X-rays show metaphyseal irregularities of the distal radius and ulna, small and deformed epiphyses, irregular carpal bones, and delayed bone age.

folic acid, and ferritin levels were within the normal ranges, and bone marrow evaluation was also normal. With regard to myelodysplastic syndrome, no evidence of monosomy 7, trisomy 8 or 7q deletion was found. Lymphopenia and thrombocytopenia showed improvement, but anemia persisted. The patient was diagnosed with anemia of chronic disease.

Direct radiographs revealed characteristic skeletal abnormalities (Figures 2–5). Bone mineral densitometry revealed low z-score (–1.01 SDS) for lumbal vertebra according to age and gender, and vitamin D and calcium treatment was initiated due to low vitamin D and high parathyroid hormone levels.

Brain MRI exhibited normal findings, except for atrophic alterations in both cerebellar hemispheres and the vermis, which were more pronounced in the superior regions. Electroencephalogram yielded normal results. Muscle enzymes and deep tendon reflexes were normal; ENMG showed no evidence of peripheral neuropathy.

A whole exome sequencing (WES) analysis identified a novel homozygous missense variant of unknown significance, EIF2AK3:c.797T>G (p.Leu266Arg). For a missense variant, computational prediction tools unanimously support a deleterious effect on the gene (REVELscore: 0,8; AlphaMissense score: 0.986; SIFT: 0). There was no observation for this variant in gnomAD (Exome) or Turkish Variome. Besides this novel homozygous variant was predicted to likely pathogenic according to following ACMG guideline criteria: Patient's phenotype or family history is highly specific for a disease with a single genetic etiology (PP4) and the segregation analysis was performed for the parents and the heterozygous state of the same variant was confirmed; for recessive disorders, detected in trans with a pathogenic variant, or in a homozygous or compound heterozygous state in affected cases (PM3).

Since no secondary point or structural variant anomalies were detected in WES analysis that could explain the clinic, except for the homozygous variant in EIF2AK3, Wolcott–Rallison syndrome was clinically confirmed molecularly in the patient.



Figure 3: Pelvic radiograph demonstrates bilateral coxa vara deformity, short and thickened femoral necks, and deformed femoral heads.



Figure 4: Knee radiograph shows osteopenia, with small, irregular, and dysplastic tibial epiphyses and lateral femoral condyles.

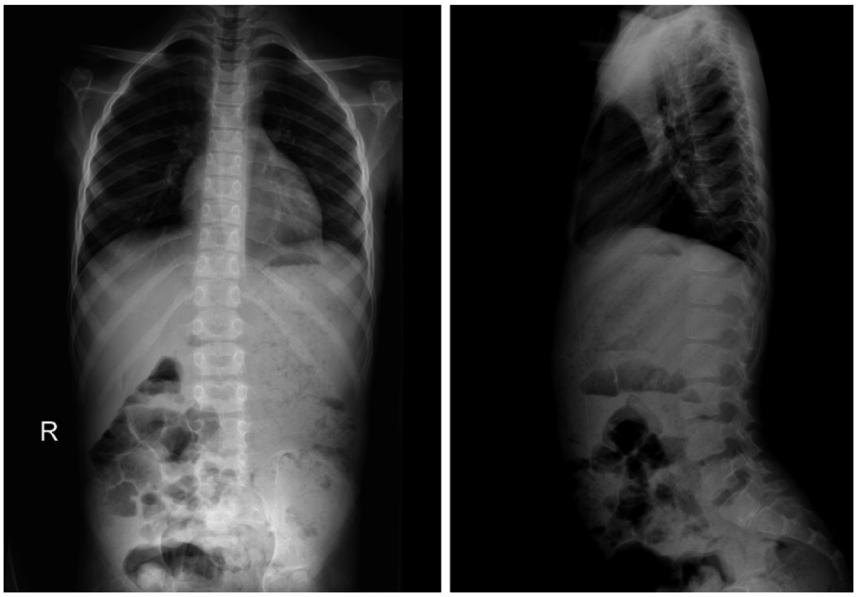


Figure 5: Anteroposterior and lateral spine radiographs show normal imaging findings.

Discussion

This case highlights the variable clinical presentation of WRS and emphasizes the importance of genetic testing in diagnosis. Most reported cases are from the Middle East and North Africa, where consanguineous marriages are common.

In WRS, diabetes typically begins within the first 6 months of life (median age: 2.5 months) and has been reported in all cases. It is the leading cause of neonatal diabetes in consanguineous populations. The condition is nonautoimmune, lifelong, and marked by severe beta-cell destruction. Most patients present with diabetic ketoacidosis [1].

The genetic basis of WRS was first described in 2004. Defects in protein translation steps result in an inappropriate insulin response, which affects blood glucose regulation. Apoptosis-related genes further contribute to the clinical features [2].

PERK is crucial for the development and function of pancreatic beta cells. Its deficiency leads to dysfunction due to cellular damage. Anchored to the endoplasmic reticulum, PERK acts as a stress sensor. When misfolded proteins accumulate, it activates and phosphorylates eIF2α. This reduces protein synthesis, increases chaperone production, and facilitates degradation of misfolded proteins in the cytosol [3].

A clear correlation between genotype and phenotype has not been established in WRS. Even siblings who are carriers of the same mutation can exhibit disparate clinical manifestations. This may be attributed to intragenic sequence variations, modifier genes, epigenetic alterations, and environmental factors.

The mutation identified in this case is a missense mutation, which has not been documented before. The patient developed diabetes at the age of 14 years, which was not accompanied by diabetic ketoacidosis and there was no evidence of EPI. Although functional studies were not conducted, it is postulated that the late onset and mild course of DM in the patient may be attributable to a restricted reduction in protein function [4].

Insulin is the only treatment for WRS, and glycemic control is often challenging. In contrast, our patient achieved stable control with long-acting insulin alone, likely due to older age and preserved insulin secretion.

In all 13 cases of WRS reported from Turkey, diabetes developed within the first 4 months of life. Five of these patients died during the neonatal period. Excluding the three patients who died in the very early phase, liver involvement – most commonly acute liver failure – along with epiphyseal dysplasia and growth retardation were observed in the remaining cases. Endocrine system involvement included hypothyroidism in a few patients and hypoaldosteronism in one. Additionally, seizures were reported in two patients [5–10]. While our patient shares common features with previously reported Turkish cases – such as acute liver failure, growth retardation, and epiphyseal dysplasia – he is notably distinguished by the late onset of diabetes and a relatively milder clinical course.

Other clinical features of WRS may not be apparent until the infant is 2 years old. Multiple epiphyseal dysplasia, which was also observed in our patient, is a common manifestation of WRS. Especially long bones, vertebrae and pelvis are affected. Bone mineralization is also abnormal, short stature is one of the typical findings, and subluxation of the femoral heads is a

common complication. Clinically, difficulty in walking or running is common, as in our case, and there is a waddling gait associated with stiff hips and limited abduction [3].

Liver dysfunction, such as elevated liver enzymes, hepatomegaly, and recurrent ALF, is a prevalent and characteristic finding of WRS. Attacks may resolve spontaneously or lead to severe complications. They are often triggered by infections and may result in chronic liver disease [1, 3]. In our patient, ALF occurred after acute gastroenteritis and resolved with supportive care, with no recurrence over 12 months. As in our case, renal dysfunction has also been reported alongside hepatic involvement [3].

One limitation of this study is the lack of functional validation for the newly identified EIF2AK3 variant. Although late-onset, mild diabetes suggests limited functional loss, this remains uncertain. Therefore, further functional studies are needed to better understand the pathogenicity and clinical significance of this novel variant.

In conclusion, we report for the first time the late-onset DM in WRS. This case report aimed to increase the awareness of WRS about the features and the importance of close follow-up of the affected cases.

Learning points

- WRS is a rare autosomal recessive disorder caused by a homozygous mutation in the EIF2AK3 gene.
- Diabetes typically begins within the first 6 months of life (median age: 2.5 months).
- Key features include epiphyseal dysplasia, acute liver failure, growth retardation, and multisystem involvement.

What is new?

- This is the first WRS case with diabetes onset at age 14, showing it is not confined to early infancy.
- A novel homozygous EIF2AK3 variant (c.797T>G; p.Leu266Arg) was identified and classified as likely pathogenic, contributing to the genetic spectrum of WRS.
- The patient presented with a mild metabolic phenotype and no history of diabetic ketoacidosis.
- Glycemic control was achieved with basal insulin alone, unlike the typically challenging insulin management in WRS.
- WRS should be considered in patients with growth delay, skeletal dysplasia, and liver involvement – even without neonatal diabetes.

Research ethics: The authors declare that the research presented in this manuscript adheres to the ethical principles. All procedures involving human participants were conducted in accordance with the ethical standards of the Ankara University Faculty of Medicine, Ankara, Türkiye and the Declaration of Helsinki (1964), as revised in 2013. IRB is not applicable.

Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Use of Large Language Models, AI and Machine Learning Tools: None declared.

Conflict of interest: All other authors state no conflict of interest.

Research funding: None declared.

Data availability: Not applicable.

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