

**CASE REPORT**

**WOLCOTT-RALLISON SYNDROME - A CASE REPORT**

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**Abstract**

Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive disorder. It is characterized by neonatal/ early onset non-autoimmune insulin dependent diabetes (permanent neonatal diabetes mellitus-PNDM) associated with spondyloepiphyseal dysplasia, tendency to skeletal fractures and growth retardation. We report a child with features of WRS, born to consanguineous parents and with an older sister having similar clinical features.

**Keywords:** Wolcott-Rallison syndrome (WRS), permanent neonatal diabetes mellitus (PNDM), consanguinity, skeletal dysplasia, liver failure, neutropaenia

**Introduction**

Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive disorder. It is characterized by neonatal/early onset non-autoimmune insulin dependent diabetes (permanent neonatal diabetes mellitus-PNDM) associated with spondyloepiphyseal dysplasia, tendency to skeletal fractures and growth retardation.<sup>1</sup> WRS is now suggested as the most frequent cause of PNDM in children who are born to consanguineous parents.<sup>2,3</sup> Here we report a child with features of WRS, born to consanguineous parents and with similar clinical features found in his sister.

**Case report**

A 3-year-and-3-month old boy was admitted with painful swelling of bilateral knees of 10 days duration. It was not associated with fever, skin rashes, restricted movements and other joint involvement.

He was the youngest child of second degree consanguineous parents. There were no antenatal complications and polyhydroamnios was not noted. He was born at term with a weight of 2.925 Kg at a local hospital. At birth he was found to have a high imperforated anus and underwent colostomy on the first day of life without any post-operative complications.



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At 2-months of age he was noted to have hyperglycaemia with positive urine sugar when admitted with a respiratory tract infection. This episode was managed as diabetic ketoacidosis and he was subsequently discharged on mixtard insulin with a diagnosis of diabetes mellitus. At 4-months of age he was treated for bronchopneumonia with intravenous (IV) antibiotics and at 10-months of age he was managed for bilateral otitis media. At 1 ½-years of age he developed two episodes of hypoglycaemic convulsions. He underwent reversal of colostomy at 1 ½-years of age, without any post operative complications.

His elder sister was diagnosed as having type 1 diabetes mellitus (T1DM) at 2 months of age, when she presented with features of diabetic ketoacidosis. She had also developed frequent lower respiratory tract infections needing hospital admissions. At 4-years of age she died presumably due to acute liver failure though records of this event were not available. He had an elder brother who was healthy and there were no other significant illnesses in the family including diabetes.

On examination his height was 87 cm (below 3<sup>rd</sup> centile) and weight was 12 kg (below 10<sup>th</sup> centile). He was an active and playful boy with no dysmorphic features. Both knee joints were swollen but no effusions were noted. They had normal range of movements, were non-tender with no erythema or warmth. The systemic examination was normal. There was no hepatomegaly. His genitalia were normal and development was appropriate for the age.

His investigations revealed anaemia with neutropenia. Bone profile revealed slightly elevated serum alkaline phosphatase, calcium levels and phosphate levels. Both liver and renal function tests were essentially normal. Ultrasound scan of the abdomen was normal with no organomegaly. X-rays of the hands and

long bones revealed features of an epiphyseal dysplasia. Thyroid function tests were normal.

Review of his sister's medical records found that she had recurrent episodes of infections and neutropenia. Changes seen in X-rays of hands of both children were similar.

## **Discussion**

Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive disorder. It is categorised by neonatal/early onset non-autoimmune insulin dependent diabetes (permanent neonatal diabetes mellitus-PNDM) linked with spondyloepiphyseal dysplasia, tendency to skeletal fractures secondary to osteopaenia, osteoporosis and growth retardation.<sup>1</sup> WRS is now suggested as the most frequent cause of PNDM in children who are born to consanguineous parents.<sup>1, 2</sup> PNDM is a very rare clinical condition which is defined as diabetes within the first 6 months of life, which does not remit.<sup>3</sup> WRS is caused by mutation in the eukaryotic translation initiation factor 2 $\alpha$ kinase (EIF2AK3) gene.<sup>1</sup> This gene regulates protein synthesis by phosphorylating the  $\alpha$ -subunit of the eukaryotic initiation factor-2 in the endoplasmic reticulum and is specially required in the insulin-secreting  $\beta$ -cells during foetal life and the early neonatal period.<sup>4</sup>

Other features of WRS include central hypothyroidism, hepatic dysfunction in the form of frequent episodes of acute liver failure<sup>1</sup>, central nervous system abnormalities (CNS), cardio respiratory defects, intellectual deficit, neutropenia, recurrent infections<sup>1</sup> and hypothalamic-pituitary dysfunction.<sup>5</sup> Skeletal abnormalities reported in WRS include epiphyseal-metaphyseal dysplasia, osteoporosis, osteopenia, thoraco-lumbar

kyphosis, beaked thoracic and lumbar vertebrae, spina bifida, and bowing of the femora<sup>5</sup>. Skeletal dysplasia is diagnosed within the first year or two of life.<sup>1</sup> CNS abnormalities include cerebellar cortical dysplasia, cerebral atrophy and pachygyria.<sup>5</sup> Significant hypoplasia of the pancreas with prominent islets of Langerhans is an important finding in WRS.

WRS should be considered in any infant presenting with PNDM concomitant with skeletal dysplasia and/or episodes of acute liver failure. The clinical diagnosis of WRS is confirmed by the identification of mutation in EIF2AK3 gene. Timely diagnosis is essential, with the intention of prompt treatment of acute liver failure, which is the most lethal complication. Genetic counselling and antenatal diagnosis should be offered to parents of a WRS child with confirmed EIF2AK3 gene mutation.<sup>1</sup>

In the management of WRS, diabetes should be managed closely with an insulin pump especially during the first months of life to avoid acute episodes of hypoglycaemia and ketoacidosis.<sup>1</sup> Interventions under general anaesthesia (GA) should be avoided whenever possible because GA increases the risk of acute exacerbations as these patients are predominantly sensitive to anaesthetics.<sup>1</sup> Any drug or vaccine, which is not strictly indicated should be restricted due to the risk of triggering secondary liver and/or renal failure. Prognosis is poor and most children die at a young age.

Our child was born to consanguineous parents and he was diagnosed as having diabetes when he was 2 months old. He had evidence of recurrent infections and neutropenia was noted on some occasions. His long bone X-rays revealed epiphyseal dysplasia. His liver functions remained within the normal limits and liver echogenicity was normal in ultra sound

scan. He showed evidence of growth retardation in the form of short stature. This clinical picture was thus highly suggestive of WRS but, unfortunately, we could not confirm it genetically due to the limited availability of resources in our country.

His sister was also diagnosed as having diabetes at 2 months of age. She had frequent lower respiratory tract infections and died following possible acute liver failure. Her X-rays also revealed features of epiphyseal dysplasia. These features of WRS in the sister also supports the diagnosis of WRS in the boy.

## References

1. Cécile Julier and Marc Nicolino. Wolcott-Rallison syndrome. [Orphanet Journal of Rare Diseases](https://doi.org/10.1186/1750-1172-5-29). 2010;5(1):29. <https://doi.org/10.1186/1750-1172-5-29>
2. Rubio-Cabezas O, Patch AM, Minton JA, Flanagan SE, Edghill EL, Hussain K, Balafrej A, Deeb A, Buchanan CR, Jefferson IG, Hattersley AT, Ellard S. Wolcott-Rallison syndrome is the most common genetic cause of permanent neonatal diabetes in consanguineous families. *J Clin Endocrinol Metab*. 2009;94:4162–4170. <https://doi.org/10.1210/jc.2009-1137>
3. Slingerland AS, Shields BM, Flanagan SE, Bruining GJ, Noordam K, Gach A, Mlynarski W, Malecki MT, Hattersley AT, Ellard S. Referral rates for diagnostic testing support an incidence of permanent neonatal diabetes in three European countries of at least 1 in 260,000 live births. *Diabetologia*. 2009;52:1683–1685. <https://doi.org/10.1007/s00125-009-1416-6>

4. Bignon-Laubert A, Lang-Muritano M, Vaccaro T, Schoenle EJ. Loss of kinase activity in a patient with Wolcott-Rallison syndrome caused by a novel mutation in the EIF2AK3 gene. *Diabetes*. 2002;51:2301–2305. <https://doi.org/10.2337/diabetes.51.7.2301>
5. Iyer S, Korada M, Rainbow L, Kirk J, Brown RM, Shaw N, Barrett TG. Wolcott-Rallison syndrome: a clinical and genetic study of three children, novel mutation in EIF2AK3 and review of the literature. *Acta Paediatr*. 2004;93:1195–1201. <https://doi.org/10.1080/08035250410029362>