Wolcott-Rallison syndrome (WRS), a Rare Pediatric Case Report

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Keywords: WRS, skeletal dysplasia, EIF2AK3 mutations.

DOI: 10.37978/tijfs.v7i1.397

Submitted: October 25, 2023
Accepted: December 15,2023
Published Online: March 29, 2024

How to cite this: khurshied et al., 2024. Wolcott-Rallison syndrome (WRS), A rare Paediatric case report Int J Front Sci, 7, 1.

Significance:
Walcott-Rallison syndrome is a very rare disease and physicians found in difficult to diagnose and manage this disease. This case report is a clinical presentation with literature review so, it may help physicians to have a background knowledge and management options in mind which will help in diagnosis and hence treatment of patient.

Abstract

Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive, neonatal or infancy onset disease that is non-autoimmune insulin-dependent diabetes and is associated with skeletal dysplasia and liver failure. It results in the death of the patient, mainly due to multi-organ failure. Less than 60 cases have been described in the literature so far. Here, we present a very rare case of WRS, which was diagnosed by genetic testing for EIF2AK3 mutations with typical findings of the disease, except skeletal dysplasia, which eventually died due to multi-organ failure. To the best of our knowledge, this is the first case report of WRS in Pakistan.

Introduction:

Wolcott-Rallison syndrome (WRS), an autosomal recessive disease, is characterized by neonatal/early-onset non-autoimmune insulin-dependent diabetes associated with skeletal dysplasia, growth retardation, liver failure and other variable multi-systemic clinical manifestations. It is a very rare disease, and fewer than 60 cases have been described in the literature so far, and are found to be more frequent in populations where consanguineous marriages are common, such as the Middle East, North Africa, Pakistan, and Turkey. Although it is a very rare disease and very few cases have been reported so far, it is still considered the most prevalent cause of Permanent Neonatal Diabetes Mellitus (PNDM) in families with consanguineous marriages (1). The two well-recognized clinical features of this disease are neonatal/early onset diabetes and multiple epiphyseal dysplasia. Third, hepatic dysfunction manifests as elevated hepatic enzyme levels, liver enlargement, and recurrent acute liver failure, which are characteristic features of this syndrome. It presents with acute severe Diabetic ketoacidosis (2). Wolcott-Rallison syndrome is an autosomal recessive multi-systemic disorder due to biallelic mutations in EIF2AK3, this gene encodes the eukaryotic translation initiation factor-2α kinase. This could be commonly homozygous in consanguineous marriages and rarely compound heterozygous in non-consanguineous marriages (3). This transmembrane enzyme, which is also called protein kinase RNA (PKR) like endoplasmic reticulum kinase (PERK) or pancreatic eIF-2alpha kinase, is found in the endoplasmic reticulum and is activated by the accumulation of unfolded proteins in the endoplasmic reticulum during stress, resulting in phosphorylation of the α-subunit of eukaryotic initiation factor 2 at residue Ser51, thus decreasing protein synthesis (4). Failure of PERK activity results in cell death via apoptosis in many tissues (5). The increased expression of EIF2AK3 in both β-cells and bone tissue results in the development of early onset diabetes mellitus and skeletal abnormalities in virtually all patients with WRS; hence, their association is important in diagnosing this disease (6). Mutations in EIF2AK3 disrupt the expression and function of PERK, which blocks β cell development and impairs gluconeogenesis. PERK is highly expressed in the nucleus of pancreatic β-cells and bone tissues, which comprise the major sites involved in WRS and are used for its diagnosis. EIF2AK3 is expressed at lower levels in the liver and kidney, which leads to liver and kidney dysfunction or even liver failure (7). The prognosis for WRS is poor. Patients typically succumb to hepatic and renal failure at an early age; however, the gene is expressed at even lower levels in several other tissues, which determines several other inconsistently present features. Most patients ultimately develop hepatic failure (8).

Case Report:

The patient, a male baby, was born by spontaneous vaginal delivery at the 39th week of gestation, with a birth weight of 3100 g. At 8 months of age, his blood sugar levels started to increase with symptoms of jaundice, generalized edema, anemia, and multiple emergency room (ER) visits with diabetic ketoacidosis. The child was diagnosed with early onset diabetes at eight months of age. After regular follow-ups and multiple organ involvement, a syndrome was suspected, and multiple investigations were performed. WRS was eventually assumed due to diabetes, liver disease, kidney disease, anemia, and growth retardation. Skeletal dysplasia was the only feature of WRS, yet it did not manifest. After obtaining written informed consent from the parents, sequencing analysis of the patient's sample was sent to one of the laboratories in the United Kingdom. A targeted gene

panel of Sanger sequencing of the coding and flanking intron regions was ordered, and a missense mutation was found in EIF2AK3. The patient was diagnosed with WRS and management was initiated accordingly. The patient received insulin and supportive treatment, with good glucose control. The patient had normal developmental milestones. His family history revealed that his parents were first-degree cousins and that he was a third-born child. His two elder brothers died at 2.5 months and 17 days of age, respectively, with more or less the same complaints. At 22 months of age, the patient's health progressively began to deteriorate. The child's condition became critical, and he went into a state of multiorgan failure and eventually died. The table below shows the examination and laboratory findings of the patient during his stay in the Pediatric ICU (PICU) for 5 days before he expired.

Table 1: Examination findings of the patient during the 5-day PICU stay

EXAMINATION	RESULTS				
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
General look	Ill looking Irritable	Critical	Critical	Critical	Very critical
Edema	+	++	+	++	++
Pallor	+	+	+	+	+
Icterus	+	+	+	++	++
Tachypnea	No	Present	No	No	Severe
Bilateral chest auscultation	Normal Vesicular Breathing (NVB)	NVB	Harsh breathing	Crackles present	Crepitation
GCS	13/15	13/15	13/15	14/15	12/15
Blood pressure	>95th percentile	90th percentile	>99th percentile	<90th percentile	<50th percentile
Peripheries	Cold	Cold	Warm	Warm	Cold
Respiratory distress	No	No	No	Occasionally present	Severe
Urine output	Decreased	On peritoneal dialysis	On peritoneal dialysis	On peritoneal dialysis	On peritoneal dialysis
Capillary refill time	2 sec	4 sec	4 sec	4 sec	4sec

Discussion:

WRS was first reported in 1972, when three siblings had diabetes mellitus onset in infancy. Multiple epiphyseal dysplasias were present in two of the three patients. Other manifestations include demineralization of bones with multiple fractures, tooth discoloration, and skin abnormalities (2). WRS has a variable clinical course of WRS varies between studies. The age at diabetes onset, bone dysplasia, and recurrent hepatic failure, which are the most characteristic features, vary among different patients. Typically, the onset of diabetes occurs before the age of 6 months, and bone dysplasia is diagnosed before one or two years of age. In contrast, our patient had a relatively atypical presentation with a somewhat late onset of diabetes and absence of skeletal dysplasia. However, the age at onset has been reported to be up to 2.5 years in the literature (8).

During the aggravated stages of the disease, the patient initially had flu-like symptoms and fever; death occurred later from multi-organ failure with predominant liver and renal dysfunction, which was evident in our case (9). In the study by Senee et al. (8), 19 patients with WRS were followed until death, and it was found that only three lived over 10 years of age. Two cases have been reported in the literature that lived up to 35 years of age. No episodes of acute liver failure were reported in patients who survived until that age.

In a study by Fatani et al. (10), a 30-day-old girl with WRS born to consanguineous parents presented with chronic diarrhea and no skeletal deformities. She had microcytic anemia, liver impairment, and primary hypothyroidism, which led to septic shock, multiorgan failure, fulminant hepatic failure, and death. This scenario is similar to that in our case.

In the study by Habeb et al. (11), liver disease was found in 24 of 28 (85%) patients with WRS, similar to our case. Valérie Senée in his study (7) observed cases from twelve families and the coding region of the EIF2AK3 gene was assessed for possible mutations. In 11 of the 12 families, mutations were identified in EIF2AK3, as in our case, and all patients had diabetes and multisystem manifestations, similar to our study. In the study by Stoss et al. (6), all three siblings were involved, and this was similar to our findings where all the siblings of the patients were involved and all of them died, similar to our patient. In a study by Delépine et al. (3), patients with WRS ultimately developed hepatic, renal, and cardiovascular failure, similar to our patient, leading to his death.

Table 2: Laboratory findings of the patient during the 5-day PICU stay

INVESTIGATIONS	RESULTS				
	Day 1	Day 2	Day 3	Day 4	Day 5
Serum Urea (mmol/l)	38	35.2	27.5	17.2	13.1
Serum creatinine(umol/l)	433	414	344	290	248
BSR (mg/dl) Mean ± SD (2 hourly monitoring; Total measurements per day N= 12)	203 ± 45	416 ± 56	455 ± 123	423 ± 118	439 ± 152
Serum sodium(mmol/l)	127	136	144	135	136
Serum potassium(mmol/l)	3.9	4	4.6	5.1	4.9
Serum Albumin(g/l)	25	-	29	-	-
Serum total Bilirubin(umol/l)	117	-	45	-	32
Serum ALT(U/l)	1537	-	854	-	652
Serum Phosphate(mmol/l)	-	2.73	2.22	-	1.68
Ph. (ABGs)	-	7.3	-	7.31	7.09
Pco_2. (ABGs)(mmhg)	-	32	-	29	44
Po_2. (ABGs)(mmhg)	-	37	-	26	55
Bicarbonate. (ABGs) (mmol/l)	-	17	-	14	13
Oxygen saturation. (ABGs)	-	67.4	-	48	75
Hemoglobin(g/dl)	9.3	-	11.6	-	-
TLC(g/l)	13.9x10^9	-	8.8x10^9	-	16.4x10^9
Platelet count(g/l)	71x10^9	-	140x10^9	-	-
Urine ketone bodies	Not present	-	Not present	-	-

Conflict of interest: Authors do not have any conflict of interest to declare.

Disclosure: None

Human/Animal Rights: No human or animal rights are violated during this study.

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