

Long-Term Evolution of Patients with the Wolcott Rallison Syndrome: Case Series of 4 Patients and Review of Literatures

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Authors' contributions

This work was carried out in collaboration between both authors. Authors NEH and ZI contributed to the drafting, literature search, proof reading and finalization of the write up of this case. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Introduction: Wolcott-Rallison syndrome is a rare autosomal recessive disorder characterized by neonatal diabetes in consanguineous families. associated with liver dysfunction, epiphyseal dysplasia, and. growth retardation. It is caused by mutations in the gene encoding eukaryotic translation initiation factor 2 α kinase 3 (EIF2AK3). We report a long-term evolution of 4 patients with Wolcott Rallison syndrome.

Keywords: Neonatal Diabetes; Wolcott-Rallison; long-term evolution.

1. INTRODUCTION

Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive multisystem disorder due to homozygous mutations in *EIF2AK3* (PERK), the

gene encoding the eukaryotic translation initiation factor-2 α kinase 3 [1].

Its cardinal clinical manifestations as initially described by CD Wolcott and ML Rallison

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include non-autoimmune permanent early-onset diabetes mellitus and multiple epiphyseal dysplasia [2].

Other clinical features that show variability between WRS cases include mental retardation, hepatic and kidney dysfunction, cardiac abnormalities, exocrine pancreatic dysfunction, and neutropenia.

The prognosis is poor, and WRS patients generally die at a young age.

Here, we report the long term evolution of wolcott-Rallison syndrome in four children of our study and comparatively review of the literature.

2. CASE REPORTS

2.1 Patient 1

The first case a female infant, is born in october 1994 from consanguineous parents with birth weight of 3 kg, positive family history of diabetes mellitus (DM) : aunt and grand mother with type 2 diabetes. the patient has been followed since the age of 4 months for neonatal diabetes diagnosed on a history of polyuropolydipsic syndrome, she was initially treated by mixed insulin, she was hospitalized several times before the age of 12 years for ketoacid decompensation and hypoglycaemia, at the age of walking, she had difficulty walking with a waddling step. In 2004, the patient suffered an orthopedically treatment for left tibia fracture.

In 2006, she was hospitalized for unbalanced diabetes under a conventional regime (rapid insulin and NPH), the clinical examination found a patient with good psychomotor development with a waddling gait, a genu valgum, flat feet in valgus, an equinism of the left foot, toe overlap, left knee deviated inward with limited mobility. the laboratory test showed microcytic hypochromic anemia, normal hepatic and thyroid functions , and a disturbed phosphocalcic balance.

Radiologically, the x-ray of the pelvis found a coxofemoral joint change, with flattening of the femoral heads, verticalization of the acetabular roofs and shortening of the femoral necks and a slender aspect of the ilio and ischio pubic branches. X-ray of the knees found flattening of the tibial endplates with dysplasia of the epiphyses and extensive diffuse bone demineralization with pinching of the space. bone

age was 11 years according to the Atlas of pyle and greulich and cortico diaphyseal index at 0.36. Abdominal and pancreatic ultrasound is without abnormality.

The genetic study was in favor of a wolcott rallison syndrome, confirmed by the revelation of a gene mutation EIF2AK3, homozygous in our patient and heterozygous in her parents, and her two brothers.

Our patient is currently 27 years old, seen regularly in consultation, with good psychomotor development, weight loss at -4DS, without puberty delay. she had frequent minor and major nocturnal hypoglycaemia, Hba1c varies between 6.9% and 8.7%, she does not go into ketosis, under treatment for osteoporosis: actonel 35mg: 1/2 tab / week, calcium: 500mg / day, Vitamin D: 1 vial / 6 months, iron: 1 tablet / day Our patient presented with chronic renal failure with creatinine clearance at 65 / min / 1.73 m2, with a follow-up renal ultrasound which showed well-differentiated kidneys, and left kidney of reduced size.

Currently he had a Chronic renal failure not on dialysis.

2.2 Patient 2

The second case a female infant is born in july 2005 ,issued from consanguineous parents with birth weight of 2800 g, negative family history of diabetes mellitus (DM). At 6 months of age , she was hospitalized for unbalanced diabetes with dehydration treated by progressive rehydration and insulin therapy. the laboratory test showed normal hepatic, renal and thyroid functions, autoimmunity test was negative.

Radiologically, the x-ray of the bone and the abdominal ultrasound were normal.

The genetic study was in favor of a wolcott rallison syndrome, confirmed by the revelation of the mutation c.449delA of a gene EIF2AK3, homozygous in our patient and heterozygous in her parents.

The patient had 5 episodes of hepatocellular insufficiency respectively at the 9, 18, 21, 29 and 32 months, with very important cytolysis and cholestatic jaundice with negative hepatic serology, the hepatic biopsy made at 3 years showed a micronodular cirrhosis. At 4 years of age she presented with a delay in psychomotor

acquisitions and language, and ataxic walking, At 6 years of age, she presented with peripheral hypothyroidism treated by levothyrox, cervical ultrasound was normal. At 8 years of age, she presented with clonic seizures, treated by phenobarbital, the electroencephalogram and the cerebral tomodensitometry were normal.

Currently he had mental retardation and developmental delay.

2.3 Patient 3

This male patient is born in January 2013, issued from consanguineous parents with birth weight of 2900 g, positive family history of diabetes mellitus (DM): grand mother with type 2 diabetes.

At 2 months of age, he was hospitalized for inaugural diabetes secondary to polyuropolydipsia with vomiting, treated by conventional insulin therapy at a dose of 0.7 IU/kg/day.

The laboratory test showed hyperglycemia in 6,2 g/l, the glycosylated hemoglobin in 11%, initially with normal renal, hepatic and thyroid functions, autoimmunity test was negative.

Radiologically, the x-ray of the bone was normal, the pelvic abdominal ultrasound was normal except cryptorchidism.

The genetic study was in favor of a Wolcott Rallison syndrome, confirmed by the revelation of the gene mutation EIF2AK3, homozygous in our patient.

At 2 years of age, he presented with a delay in walking.

Died in 2015 by fulminant hepatitis installed in a brutal way at the age of 26 months.

2.4 Patient 4

The Fourth patient is a male born in January 2006, issued from consanguineous parents with birth weight of 2850 g, positive family history of diabetes mellitus (DM): father with type 2 diabetes.

At the age of 40 days, he was hospitalized for inaugural diabetes treated by insulin therapy.

At 1 year of age, he presented a developmental delay with mental retardation and epiphyseal retardation. The clinical examination found a patient with a genu valgum and flat feet in valgus. The laboratory test showed normal renal and hepatic functions. Radiologically, the x-ray showed a bone dysplasia, the pelvic abdominal ultrasound was normal. The genetic study was in favor of a Wolcott Rallison syndrome, confirmed by the revelation of the gene mutation EIF2AK3. Currently he does not walk.



Image 1. Genu valgum, flat feet in valgus, equinization of the left foot, overlapping of the toes



Image 2. Bilateral dysplasia severe of both hips with coxa plana



Image 3. Flattening of tibial platters with dysplasia of the epiphysis and important diffuse bone demineralization

Table 1. Clinical features and current evolution of the four cases in our study

Patient ID	sex	Age at diagnostic	Current age	Consanguineous family	Family history	Epiphyseal dysplasia	Mental retardation/developmental delay	Current evolution
Case 1	F	4 months	27 years	Yes	Yes	Yes	No	-Chronic renal failure
Case 2	F	6 months	16 years	Yes	No	No	Yes	- Mental retardation
Case 3	M	2 months	Died at 2 years of age	Yes	Yes	No	Yes	- Developmental delay Died by fulminant hepatitis
Case 4	M	1 month	15 years	Yes	Yes	Yes	Yes	- Mental retardation -Inability to walk

3. DISCUSSION

WRS is a rare complex genetic disorder caused by mutations in *EIF2AK3* (PERK) gene and is characterized by neonatal diabetes, liver disease, pancreatic exocrine insufficiency and epiphyseal dysplasia. Here, we present the long term evolution of wolcott-Rallison syndrome in four children of our study and we will compare them with the data from the literature.

Many cases of Wolcott-Rallison syndrome die before a complete clinical presentation of the disease appears.

Cases of Wolcott-Rallison syndrome can develop variable clinical phenotypes starting at different time points after the initial diabetes diagnosis, causing many cases to be either misdiagnosed or undiagnosed. The most common implications

Table 2. Comparative table of the long-term evolution of WRS between our study and the literature

Series	Number of cases	Number of death	Cause of death	Age of death	Number of complications	Type of complications
Alena [6]	11	3	-Multiple organ failure -Cause unclear (died at home) -Cerebral oedema	-7months -5 years -9 years	-	-
Samaneh [7]	7	0	-	-6 years -9 years -9 years -10 years -2 years -2 years -6,5 years	7	-Microcephaly, hypotonia, absence of head control, leukodistrophy, liver disease, renal disease, seizure, skeletal anomalies, Intellectual disability
Dias [8]	4	2	-Acute liver failure.	-12 years -15 years	2	-Myelopathy -Seizures
Jahnavi et al. [9]	8	3	NR	-2,5 years -3 years -3,5 years	5	-Global developmental Delay -Severe growth retardation
Our Study	4	1	-Fulminant hepatitis	-3 years	3	- Epiphyseal dysplasia - Mental retardation - - Developmental delay

include skeletal dysplasia and liver failure which is the most deadly feature of the disease. To prepare for the right clinical intervention and management of the disease, a timely diagnosis is critical. [3].

Today, prognosis of WRS is poor and most patients die at a young age before long-term complications of diabetes become clinically evident [4,5]. However, earlier recognition of WRS and increased awareness of additional features, particularly liver failure, may improve the care of children with WRS and lead to prolonged survival. Given their relatively poor metabolic control and young age at diabetes onset, these patients may have a high risk of developing long-term complications of diabetes (5).

We reported the long term evolution of four new cases of Wolcott-Rallison syndrome, one of them is died at the age of 3 years by fulminant hepatitis. The average age of death in the most recent study of Alena's (6) in 2020 was 4,9 years.

While in samaneh's study [7] was 6,3 years , in the Dias's study [8] was 13,5 years , and in the study of jahnnavy [9] was 3 years.

The main cause of death in the different series was the multiple organ failure specifically liver failure.

The main complications was neurological as Myelopathy, Seizures, intellectual disability, Microcephaly, hypotonia, and mental retardation, in the other hand we have the multisystemic disorder as liver disease, renal disease, Global developmental delay, Epiphyseal dysplasia. (Table 2).

5. CONCLUSION

WRS is known to have a poor prognosis. In the present study we report a long term evolution for four patients with WRS.

Our study reported the highest life expectancy at 27 years with good prognosis compared to data in the literature.

The interest is to establish that correct therapeutic management of patients with WRS can guarantee a better quality of life with fewer complications.

CONSENT

Informed verbal consent was taken from the parents of all children.

ETHICAL APPROVAL

The Ethics Committee has been informed that the study is about the evaluation of parent's knowledge about fever.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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