Wolcott-Rallison syndrome is a rare disease characterized by insulin-dependent diabetes mellitus (DM) and usually diabetic ketoacidosis (DKA) in the first 6 months of life. However, 2 rare cases with later presentation at 14 and 30 months old have been reported.1,2 Cardinal manifestations are neonatal DM, multiple skeletal dysplasia, hepatomegaly, and acute liver failure. Other manifestations include renal and pancreatic failure, neuromotor dysfunction, microcephaly, epilepsy (in severe cases),5,4 cerebral complications of DKA, severe hypoglycemia, central hypothyroidism,5 neutropenia,6,7 and dermal and dental manifestations.8 Renal failure in these patients is usually associated with liver failure.

Wolcott-Rallison syndrome is a rare autosomal recessive disease due to mutation in the gene encoding eukaryotic translation initiation factor 2a kinase 3 (EIF2AK3) or PKR-like endoplasmic reticulum kinase (PERK).9–11 Wolcott-Rallison syndrome should be considered in all patients with permanent neonatal DM and skeletal dysplasia with or without acute liver failure. Because most of the manifestations are present in older ages, any infant with DM before 6 months old in populations with high prevalence of neonatal DM should be evaluated for probable skeletal dysplasia or mineralization defects. Growth failure and short stature are often clinically presented after 1 year old. Because of different presentations of the disease in the different ages, lack of skeletal dysplasia or liver failure does not rule out the syndrome.12 and

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even a 32-year-old patient and many others older than 2.5 years without skeletal dysplasia have been reported with positive EIF2AK3 mutation.

CASE REPORTS

Case 1

The first case was a 7-month-old male infant from Iran (Khoozestan province), Arab race, delivered through cesarean section from relative parents with birth weight of 3 kg, normal prenatal and natal period, and both breastfed and formula fed, at 40 days old in workups for screening diabetes mellitus (DM) (because of positive family history of DM). Blood sugar was 328, so DM was diagnosed, and since that time, he was on NPH insulin 2.5 units every day.

In physical examination, his weight percentile was 70; his length and head circumference percentile was 85; his ophthalmologic examination was normal. There was no hepatosplenomegaly or skeletal anomaly, abdominopelvic sonography was normal, and there was no history of seizure. Laboratory workups showed fasting insulin of 4.5 mIU/L (reference range, 2–25 mIU/L), C peptide of 1.95 ng/mL, and urine analysis: specific gravity 1007 glucose: 3+, blood sugar was 328. Other tests including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, prothrombin time (PT), partial thromboplastin time (PTT), albumin, blood urea nitrogen (BUN), creatinine, electrolytes, calcium, phosphorous, and complete blood count differentials were reported as normal.

The patient had a sister who had developed DKA at 2 months, so she was admitted in the pediatric intensive care unit (PICU) and then was on NPH 2 units in the morning and 1 unit in the afternoon; then, at 4 years old, because of repeated attacks of hypoglycemia and hyperglycemia, insulin had been changed to 2 to 3 units Aspart (Novorapid) insulin before each meal and 5 units (Lantus) Glargine insulin before sleeping time. At 5.5 years old, the patient had developed severe DKA following upper respiratory tract infection and again was admitted in the PICU. There, she showed increased BUN, creatinine, PT, INR, PTT, aspartate aminotransferase, and aminotransferase but unfortunately had died. There was family history of DM type 1 in his cousin who was admitted because of DKA at 2.5 years old and also family history of DM type 2 in his aunt, uncle, and grandmother; none of them started before their 20 years of age.

In genetic study of this family (the infant and his parents), exon: N/M_004836, EIF2AK3: E524fs:1570_1573 del:c were reported. We identified 1 deleterious, novel, homozygous, frame shift deletion in EIF2AK3 gene. The mutation was not reported before; therefore, it was classified as a variation of unknown significant. Because of the pattern of the parents, the inheritance was AR.

Case 2

The second case was a 1.5-month-old male infant from Iran (Jahrom, Fars state), the first and only child of the family, product of normal vaginal delivery from distant relative parents, with normal prenatal and natal period, with birth weight of 2.5 kg, length of 46 cm, head circumference of 32 cm, formula fed; due to febrile status epilepticus, he had been admitted in the PICU, and he had hyperglycemia and metabolic acidosis and was managed as DKA. Electroencephalogram was normal.

At present, his weight was 6.5 kg (15th percentile), length was 59 cm (SD, 3 cm), and head circumference is 40.5 cm (third percentile). He has no hepatosplenomegaly, and his lung and heart sounds are normal. On birth, he had bilateral undescending testis, but now the left testis has descended and the right one is palpable in the inguinal canal. He has no neck holding yet, but he has good eye contact and social smiling. Laboratory data of the patient on admission in the PICU due to DKA were as follows: INR 2.26, PT 20.6 sec, PTT 26.3 sec, hemoglobin 7, mean corpuscular volume 100, BUN 40, creatinine 1.1, potassium 2.9, and sodium 162, and liver function test was normal. This is indicative of coagulopathy, which is justified by multiorgan involvement due to systemic inflammatory response syndrome, and also, the patient had acute tubular necrosis, all of which were managed through controlling the acute phase of the disease.

In the serum metabolic panel of Germany, false-positive result of 170 hydroxyprogesterone and false-negative result of thyroid-stimulating...
hormone was reported, and when repeated, both of them were normal. Also, adrenocorticotropic hormone and cortisol were normal. The urine metabolic panel of Germany was normal.

In the genetic study of this family, homozygous for EIF2AK3 mutation and p.Gln333 was reported.

DISCUSSION

Major manifestations of WRS are early onset (neonatal or infantile) of DM, skeletal dysplasia, bone mineralization defect, and liver failure. The variety of clinical manifestations of the disease was considerable in a way that even the clinical manifestations in the siblings of the first family with similar mutations were completely different. This is in the same line with the results of Habeb’s study in which no relationship was found between genotype and phenotype of 12 families under study. In the first family, the second patient’s disease first presented with DKA before 6 months old, but is still early for developing skeletal dysplasia as both patients were younger than 1 year (5 and 7 months old).

In a recent report of os odontoideum in 4 patients with WRS, it has been revealed that because of the atlantoaxial instability, the patients were subject to neurologic and respiratory system disorders. In addition to insulin-dependent DM, the most prevalent disorder in WRS, as found by Habeb, was nonautoimmune hepatitis, which was observed in 85.7% of the patients, leading to their death. Surprisingly, one of the mentioned patients controlled his diabetes and the hepatic manifestations after liver transplantation.

Our first case (the 7-month-old infant) has not still developed hepatic disorders (increase in hepatic aminotransferase, hepatomegaly, hepatic insufficiency), but in his sister, who died at 5.5 years of age due to diabetes type 1, increase in aminotransferase 5 times the normal level was observed as well as increase in BUN, creatinine, PTT, INR, and PT. However, in the second case, although we observed the primary presentation of coagulopathy, she never had an increase in liver aminotransferase. Also, in the follow-up, no hepatic disorder was observed. Tzakis et al reported that transplantations of liver, pancreas, and both kidneys in WRS patients have had promising results, leading to increase in the survival of patients with multiorgan damages.

The second case, who had DKA at 1.5 years of age, on admission to PICU presented with convulsion, reduced level of consciousness, electrolyte disorders including hypernatremia, hypocalcemia, and increased BUN and creatinine, indicative of acute renal tubular, which was then controlled by the treatment. However, the first case had acute renal failure when she was dying, although she had no problem in the initial screening.

With respect to the aforementioned points, evaluation and genetic study of infants with DM younger than 6 months, especially those who develop DKA and have positive family history of DM and abnormal liver or renal function tests, are important. In these patients, at least yearly evaluation of liver enzymes, renal function tests, and also routine screenings of diabetic patients such as thyroid function test and celiac are recommended.

Radiologic study and careful physical examination of patients after 1 year old would be helpful for evaluation of probable skeletal dysplasia because most of the patients do not have any skeletal dysplasia before 1 year old. Moreover, genetic study of the patients and their family (due to autosomal recessive pattern of inheritance in the first family), especially those who develop DM before 6 months old, could be helpful for early diagnosis and screening of complications and appropriate treatment.

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