Wolcott-Rallison Syndrome: A Case Report

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ABSTRACT

Wolcott-Rallison Syndrome is a rare autosomal recessive disease, characterized by neonatal diabetes associated with skeletal dysplasia and growth retardation; fewer than 60 cases have been reported in the literature, although Wolcott-Rallison Syndrome is the most common cause of neonatal diabetes in consanguineous parents. Here we present a case of Wolcott-Rallison Syndrome in a two year old male child born to consanguineous parents who was diagnosed to have neonatal diabetes, developmental delay, microcephaly, seizures, congenital heart disease and hypothyroidism. Genetic testing was sent for the patient and his parents to Molecular Genetics Laboratory - Peninsula Medical School - University of Exeter-UK. The result of the genetic testing reports a homozygous EIF2AK3 gene mutation in the patient and heterozygous mutation in both parents. The patient was screened for other features of Wolcott-Rallison Syndrome, including skeletal survey for skeletal dysplasia which was not present in early life and recognized later. The genetic testing for patients with neonatal diabetes is of great importance for definite diagnosis, detecting associated findings, complications and even treatment. It is mandatory for family planning.

Key words: Diabetes, Neonatal, Wolcott-Rallison Syndrome

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Introduction

Diabetes mellitus is the third most common chronic disease of childhood,[1-5] although neonatal diabetes which is diagnosed in the first six months of life is a rare disorder. Diabetes mellitus accounts for one case in 300,000 to 500,000 live births which is most probably of monogenic origin and thus candidate for genetic screening.[6] Table I[7] illustrates, and compares genetic causes of neonatal diabetes and their associated clinical features.

In the early 1970s, Wolcott and Rallison reported a novel recessive disorder in three siblings presenting with permanent neonatal diabetes mellitus, multiple epiphyseal dysplasia and growth retardation.[1,2,6,8-16]

One out of 13 patients in follow-up for neonatal diabetes in the endocrine clinic at Queen Rania Al Abdullah Hospital was found to have Wolcott-Rallison Syndrome (WRS) confirmed by genetic testing.

Case report

This two years old male child was born to consanguineous parents at term by normal vaginal delivery with a birth weight of 3.2 kg.

He was healthy till the age of 53 days when he was admitted at Princess Rahma Children's Hospital in Irbid in the North of Jordan with fever, irritability and convulsions. Laboratory investigations showed persistent hyperglycemia. After two days, the patient was referred to Prince Rashed Military Hospital in Irbid as a case of diabetic ketoacidosis, where he was found to have hypoactivity, ejection systolic murmur, hepatomegaly, and spastic lower limbs.

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Table I: Causes of neonatal diabetes.

Pancreatic pathophysiology	Protein, chromosome or gene affected	Inheritance	Features in addition to neonatal diabetes and low birth weight
	KATP channel	Autosomal dominant or recessive	Developmental delay and epilepsy
	Chromosome 6q24	Variable	Macroglossia and umbilical hernia
Reduced β-cell function	GCK (recessive mutation)	Autosomal recessive	Both parents have heterozygous GCK associated hyperglycemia
	SLC2A2	Autosomal dominant	Hypergalactosemia, hepatic failure
	GLIS3	Autosomal recessive	Congenital hypothyroidism, glaucoma, liver fibrosis and cystic kidney disease
	PTF1A	Autosomal recessive	Pancreatic and cerebellar agenesis
Reduced pancreas mass	PDX1	Autosomal recessive	Pancreatic agenesis
	HNF1B	Autosomal dominant	Exocrine pancreas insufficiency and renal cysts
	EIF2AK3	Autosomal recessive	Spondyloepiphyseal dysplasia, renal failure, recurrent hepatitis and mental retardation
Increased β-cell destruction	FOXP3	X-linked	Immune dysregulation, intractable diarrhea, eczematous skin rash and elevated IgE
	INS	Autosomal dominant	None

Abbreviations: EIF2AK3, eukaryotic translation initiation factor 2-α kinase 3 gene; FOXP3, forkhead box P3 gene; GCK, glucokinase gene; GLIS3, GLIS family zinc finger 3 gene; HNF1B, HNF1 homeobox B gene; INS, insulin gene; KATP channel, ATP-sensitive potassium channel; PDX1, pancreatic and duodenal homeobox 1gene (previously termed IPF1); PNDM, permanent neonatal diabetes mellitus; PTF1A, pancreas specific transcription factor, 1a gene; SLC2A2, solute carrier
Family 2, member 2 gene (previously termed GLUT2); TNDM, transient neonatal diabetes mellitus.

Laboratory investigations showed severe diabetic ketoacidosis, random blood sugar 516 mg/dl, positive serum acetone, blood gases pH of 6.9, HCO3 4.5 meq/L. He had slightly elevated liver enzymes, and total bilirubin of 2.8mg/dl, CSF analysis and culture were negative, urine and blood cultures were negative.

Radiological investigations including echo-cardiography revealed Atrial Septal Defect (ASD) secundum 0.5 cm, brain CT scan showed intracerebral hemorrhage, and frontal atrophy.

The patient was referred to the pediatric endocrine clinic at Queen Rania Al Abdullah Hospital for Children at age of four months; he was on Crystalline +NPH insulin 30/70 morning dose, dinner time, and evening meal 2+1+1 units respectively by subcutaneous injection. However, he had poorly controlled blood sugar.

Clinical examination showed that the patient was developmentally delayed; he had gross head lag, and umbilical hernia. The patient was shifted to twice daily Crystalline+NPH insulin 30/70 morning and evening dose 3+2 units respectively, and thyroid function test was performed which showed primary hypothyroidism with TSH >75μ IU and low T4, so the patient was started on L-thyroxin 50microgram tablets single daily dose. Follow up thyroid function test was normalized, and the dose of Crystalline+NPH insulin30/70 was increased to 5+3 units morning and evening doses.

At age of six months the patient started to have convulsions with normal blood sugar, he was started on Phenobarbitone 15 mg tablets twice daily, and he was controlled on Phenobarbitone 15 mg tablets three times daily. Brain MRI was reported abnormal with smoothening of brain surface and decreased gyral pattern while EEG recorded as abnormal.

Genetic testing for the patient and his parents were sent to Genetic Molecular laboratory, Exeter, UK and the results revealed that the patient had WRS (Fig. 1), while his parents are carriers. The patient was screened for epiphyseal dysplasia which is part of the syndrome by skeletal survey and was normal at that time.

Follow-up regarding his HbA1c was 7.9 % and thyroid function test was normal. Follow-up skeletal survey at age of one and half year revealed epiphyseal dysplasia involving proximal and distal femoral epiphysis and proximal tibial epiphysis as shown in Figures 2 and 3, while the upper limbs, the skull, chest and vertebrae were normal.

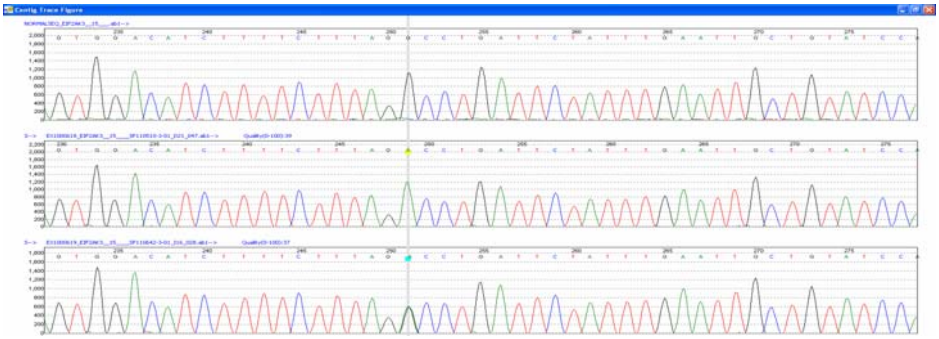

Fig. 1: Electropherogram (6150RK) EIF2AK3 exon15 p.G1010D c.3029G>A

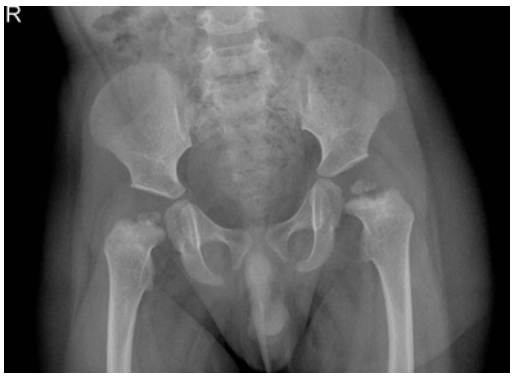

Fig. 2: Pelvis X-ray showing proximal femoral epiphyseal dysplasia

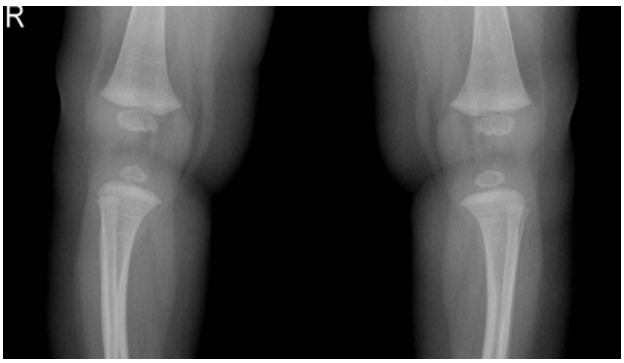

Fig. 3: Both knees X -ray showing bilateral distal femoral and proximal tibial epiphyseal dysplasia

Discussion

WRS is a rare autosomal recessive multisystemic disorder due to biallelic mutation in EIF2AK3, the gene encoding the eukaryotic translation initiation factor-2@kinase3 which code for a transmembrane enzyme localized exclusively in the endoplasmic reticulum, this enzyme is activated by the accumulation of unfolded proteins in the endoplasmic reticulum lumen during stress, resulting in phosphorylation of the @ subunit of the eukaryotic initiation factor 2 at residue Ser 51 and down regulation of protein synthesis, lack of this enzyme activity will lead to cell death by apoptosis.[6,8,10,12,15]

The high level expression of EIF2AK3 in both β cells and bone tissue explains the development of neonatal diabetes and skeletal abnormalities in all patients with WRS while other variable system involvement is due to lower expression of this gene in these tissues.[8] In the vast majority of cases the onset of diabetes is observed during the first months of life, in all but two of the cases reported to date diabetes onset was before the age of six months. Diabetes is an obligate feature of WRS, it is permanent, not autoimmune and insulin dependent.[1,2,6,8-16] In this case, the patient was diagnosed with diabetes at age of 53 days, and was started on insulin therapy from the start.

WRS is characterized by multiple epiphyseo-metaphyseal dysplasia affecting the long bones, pelvis and vertebrae while the skull is usually spared. Bone mineralization is affected and multiple and frequent fractures can be observed.[1,2,6,8-16] The patient in this case had epiphyseal dysplasia involving mainly the proximal and distal femur, although these changes were not apparent in early life due age dependent epiphyseal maturation. Therefore, follow up skeletal survey is mandatory to detect the skeletal abnormalities.

Intellectual deficit or developmental delay is common and was reported in 18 out of 29 patients, some cases were severe with neuro-motor deficit microcephaly with simplified gyral pattern and epilepsy,[1,2,6,8,13] while our patient has global developmental delay, microcephaly, epilepsy with abnormal EEG, and decreased gyral pattern on brain MRI. Hepatic dysfunction is one of the features of WRS, manifested by recurrent acute episodes of hepatitis with or without

cholestasis, although episodes of liver failure and chronic hepatic dysfunction is possible. These episodes are typically recurrent with spontaneous remission.[1,2,6,9,12-14,16] Our patient was found to have high liver enzymes on presentation at age of 53 days, although he was hypoactive and was managed as a case of sepsis, the elevated liver enzymes could be partly attributed to sepsis and not related to WRS. Clinical and laboratory follow-up for liver function test over the last one and half year was normal.

Other clinical features of WRS are variable central hypothyroidism which has been reported in six out of 26 patients in the series of Ozbec *et al*.[1,11,13] Interestingly, this case was found to have primary hypothyroidism rather than central and was started on treatment since the age of four months. Though one previous case of primary hypothyroidism was reported not to be a feature of WRS,[8] this conclusion that may need to be revised.

Additional clinical features including cardiac malformation and pulmonary hypoplasia were described,[1,6,11,13] echocardiography revealed ASD secundum which closed later as proved by echocardiographic follow-up.

Other clinical features that have be reported including episodes of self limiting impaired renal function,[1,11,13,14,16] neutropenia, discoloration of teeth and skin abnormalities, dysmorphism, and glopal pancreatic dysfunction,[1,14] were not found in this case.

Conclusion

WRS is a rare disease, but we should consider it in our differential diagnosis for patients with neonatal diabetes especially in the presence of consanguineous marriage which is common in our community, moreover primary hypothyroidism could be one of the features of WRS.

Acknowledgments

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