ScieniQ Publishers

Journal of Diabetes & Metabolic Disorders

Case Report

Wolcott Rallison Syndrome- A Rare Case of Neonatal Hyperglycaemia

Deepak Bhosle[1]* and Kishor Kharche[2]

[1]*Consultant Diabetologist, Deogiri Diabetes Care Centre, Aurangabad (Maharashtra), India*
[2]*Consultant Endocrinologist, United Cigma Hospital, Aurangabad, (Maharashtra), India*

***Corresponding author**
Deepak Bhosle, Consultant Diabetologist, Deogiri Diabetes Care Centre, Aurangabad (Maharashtra), India, Tel: 7770087870

Received: 30 Mar 2021
Accepted: 08 Apr 2021
Published: 19 Apr 2021

Abstract
Wolcott-Rallison Syndrome is a rare autosomal recessive disorder which is a form of neonatal diabetes associated with skeletal dysplasia and growth retardation. Very few cases have been reported in the world literature and especially in the Indian context, where a common finding is history of consanguineous parents. Here we present a case of Wolcott-Rallison Syndrome in a two month old female child born to consanguineous parents who was diagnosed to have neonatal diabetes, which upon evaluation of the cause, genetic testing was sent to Molecular Genetics Laboratory - University of Exeter-UK. The result of the genetic testing reported, a homozygous EIF2AK3 gene mutation in the patient. The patient was screened for other features of Wolcott-Rallison Syndrome, including skeletal survey for skeletal dysplasia which is not present in early life and recognized later. The genetic testing for patients with neonatal diabetes is of great importance for definite diagnosis and management, detecting associated findings, complications and prevention of complications.

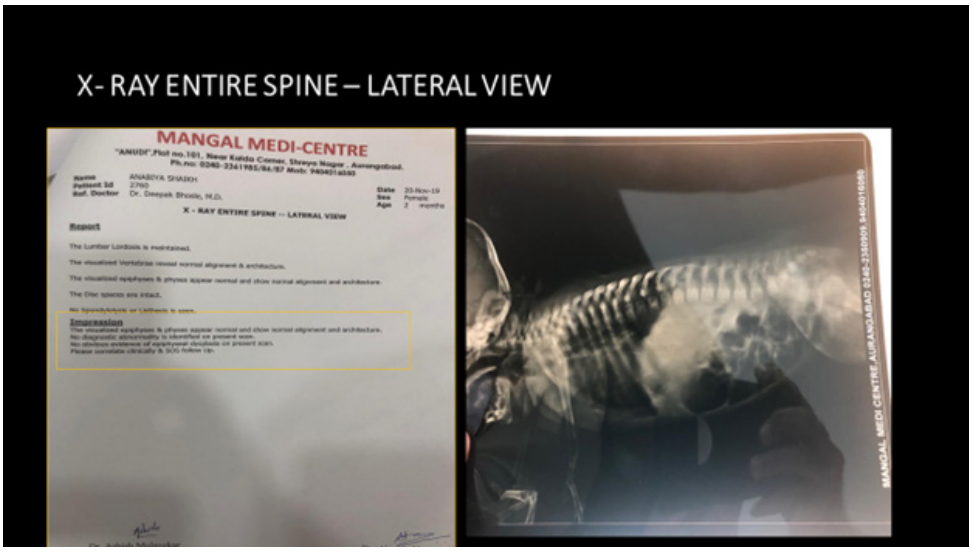
Keywords: Diabetes, Neonatal, Wolcott-Rallison Syndrome

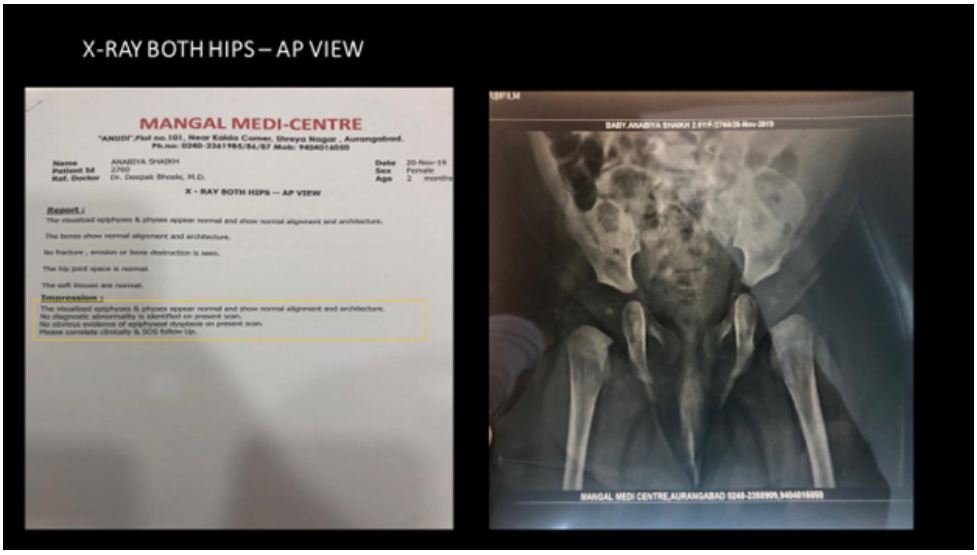
Introduction
Diabetes mellitus is the third most common chronic disease of childhood is diagnosed in the first six months of life [1-5]. Monogenic diabetes presenting in infancy may be divided into transient and permanent neonatal diabetes. Both present with hyperglycaemia in infancy however in the former the patient may resolve spontaneously at 3 months with no more insulin requirement until later in life when the disease may relapse. In the latter, insulin supplementation is required for life in the majority of cases [4,6]. Genetic studies of monogenic forms of diabetes-related disorders can significantly increase our knowledge of β cell function and may point to potential candidate genes for the common forms of diabetes. 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. Wollcott-Rallison syndrome is a rare autosomal recessive disorder characterised by permanent insulin requiring diabetes developing in the newborn period or early infancy, an early tendency to skeletal fractures, and spondyloepiphyseal dysplasia [1-8]. The syndrome results from mutations in the gene encoding the eukaryotic translation initiation factor 2-a kinase 3 (EIF2AK3, also called PERK or PEK) [9]. This enzyme phosphorylates EIF2A at Ser51 to regulate the synthesis of unfolded proteins in the endoplasmic reticulum [10]. Targeted disruption of the Eif2ak3 gene in mice also causes diabetes because of the accumulation of unfolded proteins triggering b cell apoptosis [11-13].

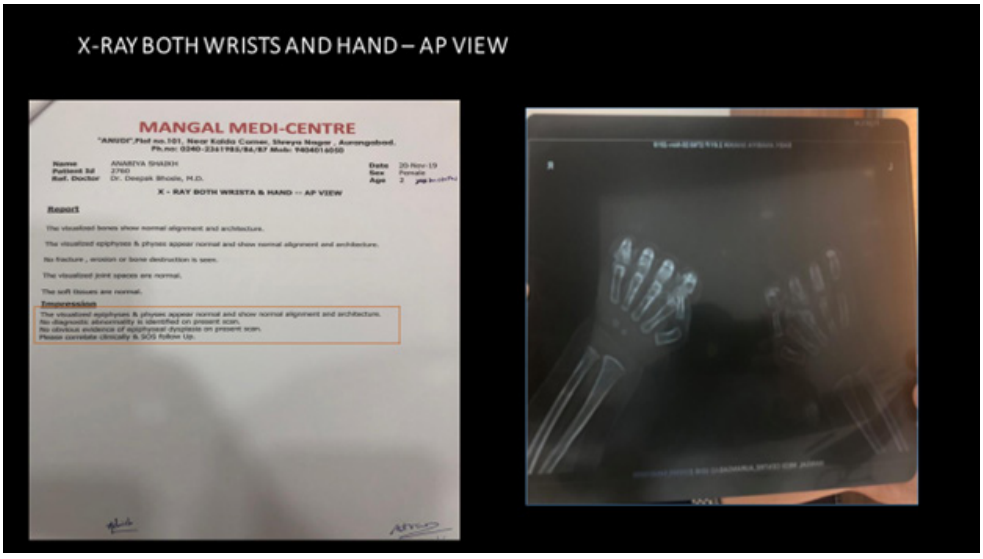
Case Report
A two-month-old female child was born to consanguineous parents at term by normal vaginal delivery with a birth weight of 3.2 kg. She was healthy till the age of 24 days, after which she was admitted to a pediatric hospital in Aurangabad, Maharashtra, India, with history of accidental hyperglycemia. Laboratory investigations showed persistent hyperglycemia. Laboratory investigations showed severe random blood sugar 482 mg/dl, blood gases pH of 6.9, HCO3 4.5 meq/L. albumin –ve, Sr.SGPT --- 21 U/L Sr.SGOT --- 49 U/L, Sugar: ++++, Protein : absent Bile salt: absent, Urine ketones : - ve, she had slightly elevated liver enzymes, normal total bilirubin. Haematological indices were normal.

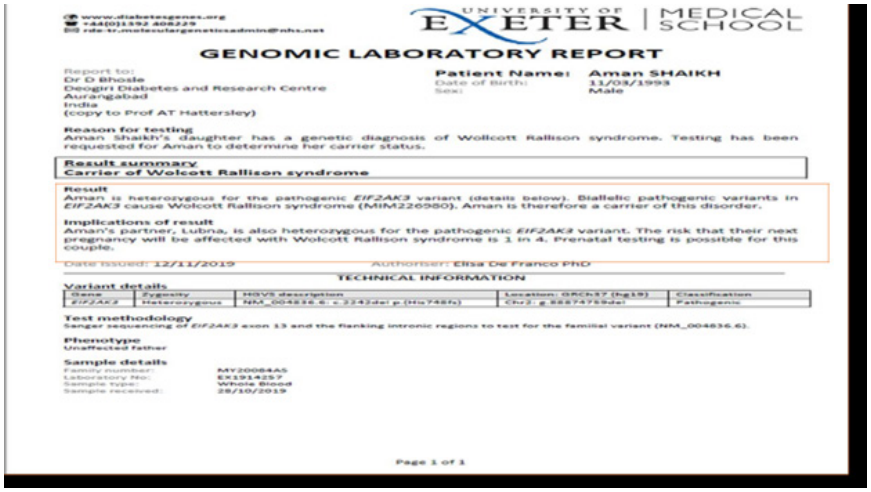
The management of hyperglycemia was done with Inj. Glargine insulin along with Inj. Novorapid and monitored every 4 hrly. At discharge, fairly good glycaemic control was achieved with a combination of short acting and long acting insulin.

Genetic testing for the patient was sent to Genetic Molecular laboratory, Exeter, UK and the results revealed that the patient had WRS. The patient was screened for epiphyseal dysplasia which is part of the syndrome by skeletal survey and was normal at that time. Usg findings were normal except clear visualization of pancreas due to stomach gas bubble.


X- RAY ENTIRE SPINE – LATERAL VIEW
MANGAL MEDI-CENTRE
X - RAY ENTIRE SPINE -- LATERAL VIEW
Report
Impression


X-RAY BOTH HIPS – AP VIEW
MANGAL MEDI-CENTRE
X - RAY BOTH HIPS -- AP VIEW
Report :
Impression :


X-RAY BOTH WRISTS AND HAND – AP VIEW
MANGAL MEDI-CENTRE
X - RAY BOTH WRISTS & HAND -- AP VIEW
Report
Impression



GENOMIC LABORATORY REPORT

Patient Name: Aman SHAIKH
Date of Birth: 11/03/1993
Sex: Male

Report to:
Dr D Bhosle
Deogiri Diabetes and Research Centre
Aurangabad
India
(copy to Prof AT Hattersley)

Reason for testing
Aman Shaikh's daughter has a genetic diagnosis of Wolcott Rallison syndrome. Testing has been requested for Aman to determine her carrier status.

Result summary
Carrier of Wolcott Rallison syndrome

Result
Aman is heterozygous for the pathogenic *EIF2AK3* variant (details below). Biallelic pathogenic variants in *EIF2AK3* cause Wolcott Rallison syndrome (MIM#226980). Aman is therefore a carrier of this disorder.

Implications of result
Aman's partner, Lubna, is also heterozygous for the pathogenic *EIF2AK3* variant. The risk that their next pregnancy will be affected with Wolcott Rallison syndrome is 1 in 4. Prenatal testing is possible for this couple.

Date issued: 12/11/2019 Authorised: Elisa De Franco PhD

TECHNICAL INFORMATION

Variant details

Gene	Zygosity	HGVS description	Location: GRCh37 (hg19)	Classification
EIF2AK3	Heterozygous	NM_004836.6: c.2342del p.(His782fs)	Chr3: g.88874759del	Pathogenic

Test methodology
Sanger sequencing of *EIF2AK3* exon 13 and the flanking intronic regions to test for the familial variant (NM_004836.6).

Phenotype
Unaffected father

Sample details
Family number: MY200844S
Laboratory No: EX1914257
Sample type: Whole Blood
Sample received: 28/10/2019

Page 1 of 1

Discussion

Few cases of monogenic diabetes mellitus are documented in India. A descriptive cohort study from Chennai (1999–2007: retrospective; 2008–2012: prospective design) included 40 infants with onset of diabetes at age ≤1 year. These constituted 8% of all children with onset of diabetes ≤12 years. Low birth weight was found in 63% of all infants with onset of diabetes ≤6 months of age, and 30% with onset at 6–12 months age.

Delayed diagnosis, recurrent hospitalization, developmental delay, and high childhood mortality (32.5% at 12.5-year follow-up) were noted by the authors.

Data from India reveals a significant prevalence of type 1 diabetes (over 10/100,000 population), with certain urban pockets reporting over 30/100,000 population).

WRS is a rare autosomal recessive multisystemic disorder due to biallelic mutation in EIF2AK3, gene.
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, the patient in this case had no evidence of dysplasia as 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.

The prognosis is poor, and WRS patients generally die at a young age. Mostly Death occurs laterto metabolic symptoms in a situation of multi-organ failure with predominant liver and renal dysfunction, hepatic failure being sometimes associated with encephalopathy.

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 and also to prevent or delay complications arising in this syndrome.

References

1. Cecile J, Marc N (2010) Wolcott-Rallison Syndrome. Orphanet Journal of Rare Diseases 5: 29.
2. Porter JR, Barett TG (2004) Acquired nontype 1 diabetes in childhood: subtypes, diagnosis, and management. Arch Dis Child 89: 1138-1144.
3. Concannon P, Erlich HA, Julier C, et al. (2005) Type 1 diabetes: evidence for susceptibility loci from four genome-wide linkage scans in 1435 multiplex families. Diabetes 54: 2995-3001.
4. Mayer-Davis EJ, Bell RA, Dabelea D, et al. (2009) The many faces of diabetes in American youth: Type 1 and type 2 diabetes in five race and ethnic populations: the SEARCH for diabetes in youth study. Diabetes Care 32(Suppl 2): S99-S101.
5. Rich SS, Concannon P (2002) Challenges and strategies for investigating the genetic complexity of common human diseases. Diabetes 51: 288-294.
6. Aguilar-Bryan L, Bryan J (2008) Neonatal diabetes mellitus. Endocrine Reviews 29: 265-291.
7. Murphy R, Ellard S, Hattersley AT (2008) Clinical implications of a molecular genetic classification of monogenic β-cell diabetes. Nature Clinical Practice Endocinology and Metabolism 4: 200-213.
8. Sperling MA (2006) ATP-sensitive potassium channels--neonatal diabetes mellitus and beyond. N Engl J Med 355: 507.
9. Stoy J, Edghill EL, Flanagan SE, et al. (2007) Insulin gene mutations as a cause of permanent neonatal diabetes. Proceedings of the National Academy of Sciences of the United States of America 104: 15040-15044.
10. von Muhlendahl KE, Herkenhoff H (1995) Long-term course of neonatal diabetes. N Engl J Med 333: 704.
11. Shi Y, Vattem KM, Sood R, et al. (1998) Identification and characterization of pancreatic eukaryotic initiation factor 2 alpha-subunit kinase, PEK, involved in translational control. Mol Cell Biol 18: 7499-7509.
12. Harding HP, Zeng H, Zhang Y, et al. (2001) Diabetes mellitus and exocrine pancreatic dysfunction in perk2/2 mice reveals a role for translational control in secretory cell survival. Mol Cell 7: 1153-1163.
13. Zhang P, McGrath B, Li S, et al. (2002) The PERK eukaryotic initiation factor 2 alpha kinase is required for the development of the skeletal system, postnatal growth, and the function and viability of the pancreas. Mol Cell Biol 22: 3864-3874.

Cite this article: Deepak Bhosle and Kishor Kharche (2021) Wolcott Rallison Syndrome- A Rare Case of Neonatal Hyperglycaemia. Journal of Diabetes & Metabolic Disorders 1: 17-19.