CASE REPORT

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An Infant With Neonatal Diabetes and Double Outlet Right Ventricle – Wolcott- Rallison syndrome

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ABSTRACT

Introduction: Wolcott–Rallison syndrome (WRS) is a rare, autosomal recessive disorder with infancy-onset diabetes mellitus, multiple epiphyseal dysplasia, osteopenia, mental retardation or developmental delay, and hepatic and renal dysfunction as main clinical findings. Cardiovascular system is very rarely affected and there are a limited number of publications where WRS is associated with congenital heart disease. The aim of this interesting case is to report an infant with Wolcott – Rallison syndrome, type I diabetes mellitus, and complex congenital heart disease, diagnosed in a pre term neonate. Case report: A case of preterm neonate who presented immediately after delivery with hyperglycemia and heart murmur. Clinical and laboratory investigation showed diabetes mellitus type I and double outlet right ventricle. Genetic examination showed classic mutations in the EIF2AK3 gene - eukaryotic translation initiation factor 2α kinase 3. Conclusion: Diabetes in neonatal age raises doubts about the possibility of association with the syndrome and other diseases.

Keywords: congenital heart defect, type 1 Diabetes, Wolcott–Rallison syndrome, hyperglycemia, echocardiography.

1. INTRODUCTION

Wolcott-Rallison syndrome is a rare autosomal recessive disease, named by Drs Wolcott and Rallison, who first described this syndrome in three affected siblings, characterized by neonatal/early-onset non-autoimmune insulin-requiring diabetes, associated with skeletal dysplasia and growth retardation. WRS is now recognized as the most frequent cause of neonatal/early-onset diabetes in patients with consanguineous parents (1).WRS is caused by mutations in the gene encoding eukaryotic translation initiation factor 2α kinase 3 (EIF2AK3), also known as PKR-like endoplasmic reticulum kinase (PERK) (2).

Double outlet right ventricle (DORV) is a rare cardiac malformation in which aorta and pulmonary trunk are connected to the right ventricle (3). There are 4 types of DORV and the type of DORV that occurs depends on where the VSD is located in relation to the great arteries. Associated genetic disorders and extracardiac anomalies can significantly exacerbate the clinical management and outcome of these infants. So far there have been referring cases associated with neonatal diabetes (4, 5).

2. AIM

In this report, we describe an infant with Wolcott–Rallison syndrome, more common variant of double outlet right ventricle and type I or insulin-dependent Diabetes mellitus (6).

3. CASE REPORT

A 2 days old premature female neonate, born at 34th gestational weeks, from healthy parents, and controlled pregnancy, weighing 1600 grams, after the routine neonatal examination and heart murmur detection, was referred for cardiac investigation. Family history for congenital heart disease, consanguinity, and diabetes were negative. Initially vigorous, at the second day of life she was noted to be dehydrated, anxious and cyanotic. An arterial blood gas was obtained, and showed a pH of 7.35, with a partial pressure of oxygen of 29 mmHg, and partial pressure of carbon dioxide of 74 mmHg. Routine lab analysis revealed normal values, as well as glucose concentration which in some measure were regularly above 15 mmol. After the initial signs of respiratory distress, the infant was given supplemental oxygen and surfactant, with saturations

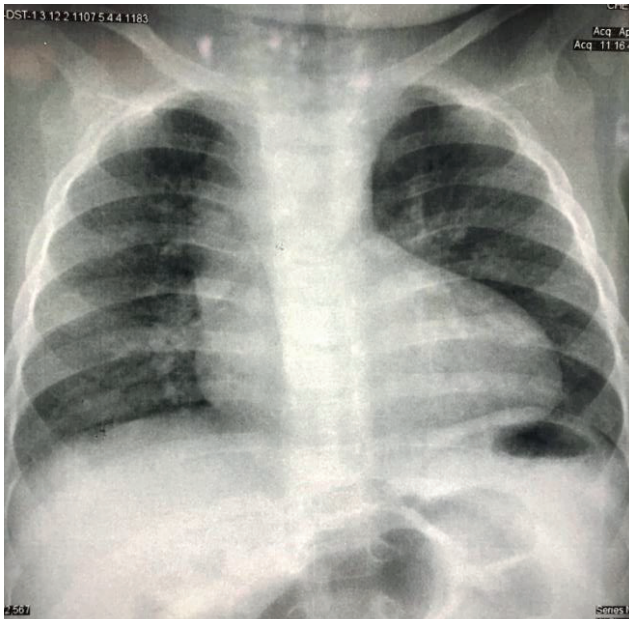

Figure 1. X-ray chest showed boot shaped heart "coeur en sabot" (apex lifted up with concavity in the region of pulmonary artery and oligemic lung)

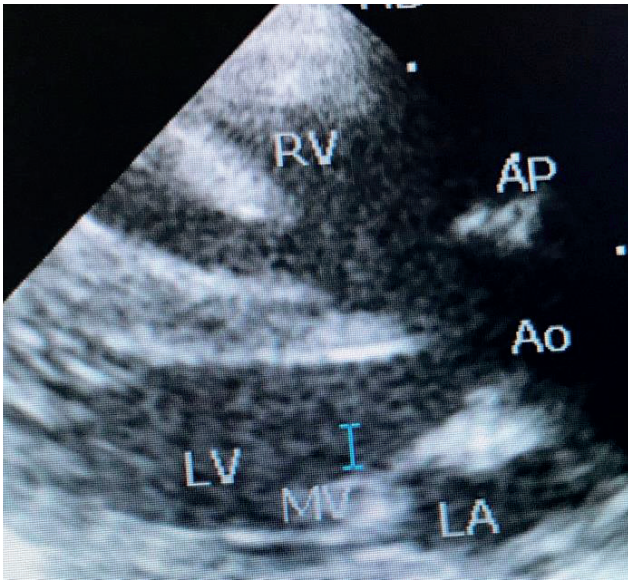

Figure 2. Long-axis view presented nonrestrictive ventricular septal defect, overriding of the aorta and both great vessels mostly outgoing from the right ventricle (RV – right ventricle, LV – left ventricle, MV – mitral valve, Ao – aorta, LA – left atrium, AP – pulmonary artery)

increasing to mild 87 %. The infant was transferred to a tertiary medical facility level for evaluation.

ECG examination revealed a right ventricular lift and incomplete right block. Clinical examination showed equal and full pulses in all extremities, and no hepatomegaly. There was a normal first heart sound, systolic murmur, single second heart sound, and no diastolic murmur. A chest radiograph revealed an augmented cardiac silhouette with a narrow mediastinum (Figure 1). The pulmonary vasculature was increased in appearance. Echocardiography demonstrated concordant atrioventricular and discordant ventriculo-arterial connections. There was a normal pulmonary and systemic venous return. There was a large hole and voluminous velocity left-to right shunting at the atrial level. Both AV valves had normal morphology within normal functionality, normal anterograd flow and good systolic coaptation. There was a large perimembranous and juxtapulmonary ventricular septal defect with muscular posterior rim, and within the aorta to the right of the pulmonary artery (Tausig–Bing type of the double outlet right ventricle). Inspection revealed the normal arising of both coronary arteries. There was a large patent arterial duct, with left-to-right shunting (Figure 2). The infant continued on 100 % inspired oxygen via a hood. At 4th days of age, the value of glucose concentration continued to be above15 mmol/l, and a lab sign of metabolic acidosis were presented. After consulting the endocrinologist, insulin-therapy was introduced. After that, the value of serum glucose was normalized.

A routine abdomen ultrasound examination demonstrated enlargement of both kidneys (9 x 4.2cm). Liver ultrasound examination was normal.

Routine lab analysis showed normal range excluding HbAlc which was extremely high–114 mmol/mol or 12.6 %, (normal value 29 – 42 mmol/mol or 4.5 – 5.7 %).

Genetic examination showed classic mutations in the EIF2AK3 gene–eukaryotic translation initiation factor 2α kinase 3.

4. DISCUSSION

WRS is a rare disease, with fewer than 60 cases described in the literature. In the large majority of cases, affected individuals are from populations in which consanguineous marriages are frequent, (7).The disease is characterized by insulin-requiring diabetes that generally appears during the neonatal period or in the first six months of life, with a frequent acute presentation of severe diabetic ketoacidosis at disease onset (8).

WRS should be suspected in any infant who presents with permanent neonatal diabetes associated with skeletal dysplasia and/or episodes of acute liver failure. Molecular genetic testing confirms the diagnosis. WRS should be differentiated from other forms of neonatal/early-onset insulin-dependent diabetes based on clinical presentation and genetic testing.

Our patient presented glucose intolerance since the third day of life, and after a careful clinical and lab examination, it was clear that the child was suffering from diabetes. After consultation with endocrinologist, we started immediately with conventional insulin therapy (basis–bolus dose) and the value of glucose was normalized. Despite many consultation and recommendations with the parents on the nature of the disease and the need for continual insulin therapy, it was not given regularly (high level of HbA1C–114mmolmol or 12.6%).

Double outlet right ventricle is a relatively primitive embryologic bulboventricular malformation. Cross-sectional echocardiography has a virtually important role in the comprehensive investigation of the patient with double outlet right ventricle. In our literature review, we were unable to find other reported patients with both double outlet right ventricle and neonatal diabetes. Clinicians

must remain aware of genetic and metabolic disorders, which may alter the clinical management of patients with congenitally malformed hearts (10).

The prognosis is poor, and WRS patients generally die at a young age. In a review of 19 patients with known age at death, only 3 died at 10 years or older. Two patients were reported with a longer survival, until 35 years for one patient and alive at 32 years old for one patient (6). Remarkably, acute liver episodes had not been reported in the patient who survived until age 35 years (6, 9).

5. CONCLUSION

WRS should be suspected in any infant who presents with permanent neonatal diabetes associated with skeletal dysplasia and/or episodes of acute liver failure, occurring neonatally or at a very young age (before 6 months) and originating from a population where there is a high prevalence of consanguinity, or in case of history of neonatal diabetes with rapidly fatal outcome in siblings or in the extended family. An association of WRS with complex heart defects is rare and the need for cardiosurgical correction of the anomaly aggravates the child's condition.

- **Author's contribution:** The authors contributed equally to this review. They read and approved the final version of the manuscript.
- **Declaration of patient consent:** Authors certify that they have obtained patient consent form.
- **Conflict of interest:** none declared.

REFERENCES

1. Senee V, Vattem KM, Delepine M, et al. Wolcott-Rallison Syndrome: Clinical, Genetic, and Functional Study of EIF2AK3 Mutations and Suggestion of Genetic Heterogeneity. Diabetes. 2004; 53: 1876-1883.
2. Ozbek MN, Senée V, Aydemir S, et al. Wolcott-Rallison syndrome due to the same mutation (W522X) in EIF2AK3 in two unrelated families and review of the literature. Pediatric Diabetes. 2010; 11: 279-285
3. Rubio-Cabezas O, Patch AM, Minton JA, et al. Wolcott-Rallison syndrome is the most common genetic cause of permanent neonatal diabetes in consanguineous families. J Clin Endocrinol Metab. 2009; 94: 4162-4170.
4. Stoy J, Edghill EL, Flanagan SE, et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proc Natl Acad Sci USA. 2007; 104: 15040-15044.
5. Iyer S, Korada M, Rainbow L, et al. Wolcott-Rallison syndrome: a clinical and genetic study of three children, novel mutation in EIF2AK3 and a review of the literature. Acta Paediatr. 2004; 93:1195-1201.
6. Bin-Abbas B, Al-Mulhim A, Al-Ashwal A, et al. Wolcott-Rallison syndrome in two siblings with isolated central hypothyroidism. Am J Med Genet. 2002; 111:187-190.
7. Obler D, Juraszek AL, Smoot LB, et al. Double outlet right ventricle: aetiologies and associations". J Med Genet. .2008; 45(8): 481-497.
8. Soszyn N, Fricke TA, Wheaton GR, et al. Outcomes of the arterial switch operation in patients with. Taussig-Bing anomaly. Ann Thorac Surg. 2011; 92(2): 673-679.
9. Imai-Compton C, Elmi M, Manlhiot C, et al. Characteristics and outcomes of double outlet left ventricle. C. Congenit Heart Dis. 2010 Nov-Dec; 5(6): 532-536.
10. Begic E, Begic Z, Jahic Dz,et al. Tetralogy of Fallot – clinical course and treatment as a mirror of contemporary cardiology / cardiac surgery development in correction of congenital heart disease in the adults. Med Arch. 2018; 72(3): 224-226.