

A patient with a rare Monogenic Diabetes Syndrome

Authors:

Vimal Mavila Veetil, Divya Pachat, Sudha Krishnanunni, Naseerali M C, Abdul Majeed P
Department of Endocrinology,
Medical Genetics and Pediatrics, Aster MIMS, Calicut

Case Report

This female child, first born of a consanguineous couple from Oman (Arab Ethnicity) presented with antibody negative diabetes mellitus at 9 months of age. She was apparently normal till 9 months of age when she developed diabetic ketoacidosis and acute liver failure during a minor febrile illness. Child was treated as a case of type 1 diabetes and was discharged on insulin.

She was evaluated in detail when two weeks later she had a similar attack again with DKA, elevated liver enzymes, mild hepatomegaly, concomitant with bronchiolitis. Apart from a positive islet cell antibody test rest of the parameters like Anti GAD Antibodies, antibody profile against liver/kidney/smooth muscle, mitochondrial, reticulin and paretal cells, anti nuclear antibodies, GGT, hepatitis B screening, ammonia and TFT were normal. Once improved symptomatically, she was discharged with a diagnosis of Type -1 DM and biochemical hepatitis.

She was brought to our center at 11 months of age for further work up and was approached by a multidisciplinary team involving endocrinology, paediatrics and medical genetics.

On examination, she had a normal anthropometry and few dysmorphic features- depressed nasal bridge, tented upperlip, tapering fingers and clinodactyly. Glycemic indices were slightly high, liver enzymes remained elevated and repeated anti GAD antibody were negative ruling out auto immune diabetes. Hence further evaluations were done to look for the causes of permanent neonatal diabetes mellitus (PNDM).

In view of the ethnicity, consanguinity, infantile diabetes which presented as DKA and hepatic involvement, a possibility of Wolcott- Rallison Syndrome (WRS) was considered. Her dysmorphic features had also been described in some previous reports of the syndrome. But her skeletal survey did not reveal any evidence of epiphyseal dysplasia associated with the disorder.

However considering the possibility of onset of skeletal manifestations at a later age, eukaryotic translation initiation factor 2alpha kinase (EIF2AK3) gene mutational analysis was carried out. This revealed a previously reported homozygous frameshift mutation in exon 9 (c. 1635_1638delGAAA) of the gene confirming the diagnosis.



Discussion and Conclusion

WRS is a rare autosomal recessive disease, characterized by neonatal/early-onset non-autoimmune insulin-requiring diabetes associated with skeletal dysplasia and liver dysfunction. Other manifestations vary between patients in their nature and severity and include frequent episodes of severe liver dysfunction, renal impairment, exocrine pancreas insufficiency, intellectual deficit, hypothyroidism, neutropenia and recurrent infections. Bone fractures may be frequent. It is caused by mutations in the gene encoding eukaryotic translation initiation factor 2 α kinase 3 (EIF2AK3).

Though only around 60 cases are reported so far, WRS is now recognised as the most frequent cause of PNDM in areas of high consanguinity.(1) Because of the high clinical variability, syndrome often goes unrecognized leading to delay in diagnosis and perhaps early death. Given the high morbidity and mortality associated with WRS, an early identification of the disease is crucial in clinical management and prenatal diagnosis. We recommend the exclusion of this condition in all cases of neonatal/early-onset diabetes with consanguineous parents, irrespective of the phenotype

References

1.Rubio-Cabezas O, Patch AM, Minton JA, Flanagan SE, Edghill EL, Hussain K, et al. Wolcott-Rallison syndrome is the most common genetic cause of permamanent neonatal diabetes in consanguineous families. J Clin Endocrinol Metab. 2009;94(11):4162-70.