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Wolcott Rallison Syndrome caused by a Novel Mutation in EIF2AK3 Gene

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Abstract

Wolcott-Rallison syndrome (WRS) is an autosomal recessive disorder characterized by early-onset diabetes, skeletal dysplasia, and growth retardation1. Some patients of WRS may develop central hypothyroidism, hepatic dysfunction, renal insufficiency or central nervous system abnormalities2,3. This is a very rare disorder and, less than 100 cases have been described till 20094. Mutations in the eukaryotic translation initiation factor 2α kinase (EIF2AK3) gene are responsible for this disorder5. We hereby report a case of Wolcott-Rallison syndrome caused by a novel mutation in EIF2AK3 gene

Keywords: Wolcott rallison, Neonatal diabetes, Beta cell disorders

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Introduction

A 5-month-old female child was brought to our hospital with complaints of multiple episodes of multi-focal tonic clonic seizures for the last 1 day. She was the first in order of birth, born from a non-consanguineous marriage, delivered at term with weight appropriate for gestational age, without significant perinatal problems. There was no significant family history.

On routine investigations patient was found to have persistent hyperglycemia. Other investigations including CSF examination, liver and kidney function tests, skull ultrasound and serum electrolytes were within normal limit. All cultures including blood, CSF, and urine culture were sterile. We investigated her further for hyperglycemia and found that her C-peptide levels were inappropriately low (<0.30 ng/mL) for her blood sugar levels. Considering the possibility of infantile diabetes, her blood samples were sent to Royal Devon and Exeter NHS foundation trust, Exeter, UK, for genetic testing. Analysis of exons 1, 6, 7, 9, 11, 14, 16 and 17 of the EIF2AK3 gene (AF110146.1) was done by Sanger sequencing as previously described (Rubio-Cabezas JCEM 2009). Primer sequences are available on request. She was found to be homozygous for a novel EIF2AK3 missense mutation, p.R1064Q (c.3191G>A), in exon 17. This mutation has never been reported before, but it affects a highly conserved nucleotide and in silico evidence suggest that it is likely to be pathogenic. This result is consistent with a diagnosis of Wolcott Rallison syndrome. Both the parents were found to be heterozygous for this novel mutation.

The infant was managed initially with intravenous regular insulin infusion, and later shifted to subcutaneous NPH insulin at discharge. She remains under follow up, with reasonable glycemic control (on NPH insulin @ 0.5 IU/kg/day), and no episode of ketoacidosis or hypoglycemia. Currently she is 13 months old, and till date there is no evidence of skeletal dysplasia or hepatic and renal dysfunction. Mild motor delay was present in development. Seizures are controlled on oral phenytoin.

Discussion:

Mutations in the gene encoding the EIF2AK3 protein are responsible for Wolcott Rallison syndrome. Our patient was found to be homozygous for a novel missense mutation (p.R1064Q) in exon 17 of the EIF2AK3 gene. Her mother and father were confirmed to be heterozygous carriers.

The age at onset ot diabetes in Wolcott–Rallison syndrome is variable, ranging from 2 weeks to 30 months in some cases6,7. Our patient presented at the age of 5 months. Early onset, insulin dependent diabetes is present in all the patients of this syndrome8.

Clinically, our patient presented with history of seizures, and had developmental delay (motor), however there was no evidence of any liver, kidney or skeletal involvement till date, but these manifestations may be delayed by several years8. Developmental delay is a common finding in WRS, and its severity is variable. Severe cases have been reported with neuro-motor deficit and epilepsy9.

Making a genetic diagnosis in patients with WRS is important not only for genetic counseling, but also because the disease has a multisystem involvement and variable presentation, and thus patients can be monitored for various system complications.

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