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Atypical Adolescent Presentation of Novel INSR Mutation with Hyperglycemia

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Abstract

The human Insulin receptor (INSR) mutation can result in inherited insulin resistance syndrome. Severe insulin resistance (IR) results secondary INSR mutations have been reported in adult, adolescent and children manifesting with hyperinsulinemic hypoglycaemia (HH). Rabson-Mendenhall Syndrome and Donohue's Syndrome, Type A insulin resistance syndrome are resultant of the INSR mutation. We report a case of an adolescent boy who was presented with very high blood sugars requiring high doses of insulin, with a novel heterozygous INSR mutation.

Keywords: INSR mutation; Hyperglycemia; Novel mutation; Adolescent

Introduction

The human Insulin receptor (INSR) gene is located on the autosome 19p13.2-13.3 encoding for a protein for tyrosine specific protein kinases and mutation in them can result in inherited insulin resistance syndrome. Severe insulin resistance (IR) results secondary INSR mutations have been reported in adult, adolescent and children manifesting with hyperinsulinemic hypoglycaemia (HH), these mutations reduce the number of insulin receptors that reach the cell membrane or disrupt the function of these receptors. Rabson-Mendenhall Syndrome and Donohue's Syndrome, Type A insulin resistance syndrome are resultant of the INSR mutation. Both homozygous or compound heterozygous mutations in the INSR gene are associated with severe forms of these diseases and are known to result in neonatal hypoglycaemia and insulin resistance in adults [1]. Heterozygous mutations in the tyrosine-kinase domain of the INSR gene result in extreme hyperinsulinemia with increased or normal blood glucose concentrations2-3. We report a case of an adolescent boy who was presented with very high blood sugars requiring high doses of insulin, with a novel heterozygous INSR mutation.

A 15-year-old boy presenting with polyuria, polydipsia, was worked up for urinary tract infection and diagnosed incidentally with hyperglycemia, with HBA1C-11.1%, without metabolic acidosis. His BMI was 28.9. Further work up revealed negative Anti GAD antibodies and C-peptide was 5.59ng/ml, TSH, Cortisol and anti-TTg were all in normal range. On examination he had acanthosis nigricans and was Tanner stage V with bone age of 17yrs. He was born Term, AGA, 3kg with uneventful neonatal period, with no history of neonatal hypoglycemia. There was no history suggestive of any episodes of hypoglycemia during childhood. There was a family history of T2DM in mother and grandmother diagnosed at <35yrs of age, managed on oral hypoglycemics [2].

He was started on basal bolus regime with a total daily insulin requirement of 1.3units/kg. His blood sugars normalized within 6-7 days of starting insulin, within 2 months of treatment his insulin requirement reduced to <0.3units/kg/day and was eventually tapered off insulin and shifted to Metformin, which was eventually stopped as he had normal blood sugars. He never had any incidence of hypoglycemia post meal while on Metformin. Due to the drastic fall in sugars, C-Peptide value and euglycemia without treatment, an underlying genetic cause was suspected, and genetic testing was done.

Analysis of insulin gene sequencing showed a novel heterozygous missense variation in Exon 5 of INSR gene (chromosome 19) that results in amino substitution of threonine for leucine at codon 388, OMIM phenotype that codes for Familial hyperinsulinemic hypoglycemia. He is currently in follow up without any medications and remains euglycemic [3].

Heterozygous mutations of INSR have been linked to hypoglycemia ranging from post prandial hypoglycemia to hypoglycemia only induced secondary to oral glucose challenge, very few cases of symptomatic hypoglycemia have been reported. There are several INSR mutations reported in adolescents and adults presenting with severe insulin resistance and hyperglycemia or post-prandial hypoglycemia [1].

The precise mechanism of postprandial hypoglycemia is unclear. Heterozygous mutations cause IR in coexistence with hypoglycaemia, which may be due to selective impairment of INSR function in skeletal muscle causing defective peripheral glycogen formation and IR, whilst the preserved INSR function in the liver leads to suppressed hepatic glucose production causing hypoglycaemia [4,5].

Our case had an atypical presentation, presenting very high blood sugars requiring high insulin doses, within 2 months was off medication with normal blood sugars despite severe insulin resistance, and no episodes of hypoglycemia. This presentation is very uncommon in INSR mutations.

INSR mutations resulting in IR get diagnosed earlier in females due to presentation with acanthosis nigricans, hirsutism, and menstrual cycle disturbances, whereas remains underdiagnosed in males in absence of signs of hyperandrogenism. It is important to diagnose this mutation as they are prone to post prandial hypoglycemia and hence should be warned against long periods of fasting [6,7].

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