

Case Report

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 presented with very high blood sugars requiring high doses of insulin, with a novel heterozygous INSR mutation.

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 results in extreme hyperinsulinemia with increased or normal blood glucose concentrations [2,3]. We report a case of an adolescent boy who 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 an HBA1C-11.1%, without metabolic acidosis. His BMI was 28.9. Further work up revealed negative Anti GAD antibodies and C-peptide was 5.59 ng/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 17 years. He was born Term, AGA, 3 kg 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 < 35 years of age, managed on oral hypoglycemics.

He was started on basal bolus regime with a total daily insulin requirement of 1.3 units/kg. His blood sugars normalized within 6-7 days of starting insulin, within 2 months of treatment his insulin requirement reduced to < 0.3 units/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 (c.1163T > C p.Ile388Thr).

He is currently in follow up without any medications and remains euglycemic. 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 [4-6].

Our case had an atypical presentation, presenting with 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 [7].

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.

REFERENCES

1. Taylor SI, Cama A, Accili D, Barbetti F, Imano E, Kadowaki H, et al. Genetic basis of endocrine disease. 1. Molecular genetics of insulin resistant diabetes mellitus. *J Clin Endocrinol Metab.* 1991; 73(6): 1158-1163. doi: 10.1210/jcem-73-6-1158. PMID: 1955495.
2. Højlund K, Hansen T, Lajer M, Henriksen JE, Levin K, Lindholm J, et al. A novel syndrome of autosomal-dominant hyperinsulinemic hypoglycemia linked to a mutation in the human insulin receptor gene. *Diabetes.* 2004; 53(6): 1592-1598. doi: 10.2337/diabetes.53.6.1592. PMID: 15161766.
3. Huang Z, Li Y, Tang T, Xu W, Liao Z, Yao B, et al. Hyperinsulinaemic hypoglycaemia associated with a heterozygous missense mutation of R1174W in the insulin receptor (IR) gene. *Clin Endocrinol (Oxf).* 2009; 71(5): 659-665. doi: 10.1111/j.1365-2265.2009.03525.x. Epub 2009 Jan 19. PMID: 19170714.
4. Padidela R, Fiest M, Arya V, Smith VV, Ashworth M, Rampling D, et al. Insulinoma in childhood: clinical, radiological, molecular and histological aspects of nine patients. *Eur J Endocrinol.* 2014; 170(5): 741-747. doi: 10.1530/EJE-13-1008. PMID: 24599222.
5. Jin J, Liang X, Wei J, Xu L. A New Mutation of the INSR Gene in a 13-Year-Old Girl with Severe Insulin Resistance Syndrome in China. *Biomed Res Int.* 2021; 2021: 8878149. doi: 10.1155/2021/8878149. PMID: 33728347; PMCID: PMC7935593.
6. Semple RK, Savage DB, Cochran EK, Gorden P, O'Rahilly S. Genetic syndromes of severe insulin resistance. *Endocr Rev.* 2011; 32(4): 498-514. doi: 10.1210/er.2010-0020. Epub 2011 May 2. PMID: 21536711.
7. Sethi A, Foulds N, Ehtisham S, Ahmed SH, Houghton J, Colclough K, et al. Heterozygous Insulin Receptor (INSR) Mutation Associated with Neonatal Hyperinsulinemic Hypoglycaemia and Familial Diabetes Mellitus: Case Series. *J Clin Res Pediatr Endocrinol.* 2020; 12(4): 420-426. doi: 10.4274/jcrpe.galenos.2019.2019.0106. Epub 2020 Jan 28. Erratum in: *J Clin Res Pediatr Endocrinol.* 2021 Jun 2;13(2):249. PMID: 31989990; PMCID: PMC7711633.