International Journal of Contemporary Pediatrics
Nirmala BS et al. Int J Contemp Pediatr. 2023 Mar;10(3):398-400
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291
DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20230444

Case Report

A case of diazoxide unresponsive congenital hyperinsulinemic hypoglycemia with missense mutation in ABCC8 gene

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Received: 26 December 2022
Accepted: 31 January 2023

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ABSTRACT

Hypersecretion of insulin by pancreatic ß-cells causes hypoglycemia called congenital hyperinsulinism (CHI). It can inhibit brain development in infants. It is associated with mutations in the ABCC8 or KCNJ11 genes encoding for the SUR1 and KIR 6 (subunits of the ATP-sensitive potassium (KATP channel) a rare genetic disorder. It has an incidence rate of 1 in 50,000 in general populations and 1 in 2000 in areas with a higher rate of consanguinity. Here, we report a case of hyperinsulinemic hypoglycemia with ABCC8 gene mutation in a late preterm female infant who developed late-onset hypoglycemia. The infant developed hypoglycemic seizures on day 3 of life and her metabolic workup revealed hyperinsulinemia. A high glucose infusion rate and enteral feeding could not maintain the infant's serum glucose level. PET scan showed no abnormal somatostatin receptor avid lesion in pancreatic parenchyma. Hence genetic workup was done which showed a missense mutation in the ABCC8 gene which was c.4154C>G/p.Ser1385Cys. Over 9 months of follow-up, the infant is treated with octreotide and diazoxide, hasn't had any hypoglycemic events and has normal growth and psychomotor development for her age.

Keywords: Congenital hyperinsulinemia, ABCC8 gene mutation, Diazoxide, Hypoglycemia

INTRODUCTION

Congenital hyperinsulinism (CHI) also known as persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a rare group of genetic diseases. It is the most common cause of persistent hypoglycemia in neonates and infants. It is caused by the dysregulated secretion of insulin from pancreatic β-cells.[1]

Early diagnosis and treatment are important to prevent permanent brain damage due to hypoglycemia. ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF4A, HNF1A, HK1, KCNQ1, CACNA1D, FOXA2, EIF2S3, PGM1, and PMM2 are 16 genes known to be associated with the regulation of insulin secretion from pancreatic β-cells.[2] ABCC8 mutation is the most common mutation causing CHI. The most common mutation affects the adenosine triphosphate-sensitive potassium channel (KATP).[2]

The molecular diagnosis could only be found in about 45% of the cases; still, many other genes are yet to be discovered.[3] Symptoms differ on the type and location of the mutated gene and have a significant impact on the response to different drugs.[4]

There are two treatment options, i.e. medical and surgical. Medical treatment includes use of diazoxide, and octreotide. First-line therapy is oral diazoxide at 5 to 20 mg/kg/day in divided doses; it acts by opening the KATP channel in pancreatic βcells, and thus inhibits insulin secretion. Octreotide (second-line therapy) is a somatostatin that binds to the somatostatin receptor-5 and by its antagonistic effects inhibits insulin secretion. Surgical treatment consists of pancreatectomy.[5]

CASE REPORT

A late preterm female baby of 35 weeks of gestation was born to a non-consanguineous couple via normal vaginal delivery. At birth required 1 cycle of the bag and mask ventilation. Post-resuscitation care was uneventful. On day 3 of life, the baby was admitted to NICU for asymptomatic hypoglycemia with blood glucose levels of 36 mg/dl. The septic screen was negative. Antenatally there was no history of diabetes mellitus in the mother. Serum growth hormone, cortisol, ammonia, and lactate levels were normal. Urinary ketone bodies were negative and the ABG was normal. On day 5 the baby developed multiple episodes of convulsions and apnea with hypoglycemia requiring mechanical ventilator support and Hypoglycemia correction requiring a glucose infusion rate of 12 mg/kg/min. When feeds reached a maximum of 180 ml/kg and IV fluids were being tapered the child again had hypoglycemic episodes. A critical sample taken during the hypoglycemic episode showed hyperinsulinemia with insulin levels of 7 mIU/l. Hence steroids were started but the baby continued to have hypoglycemia. Thus, she was started on diazoxide by day 7 of life, however, blood glucose levels were still fluctuating, subcutaneous injections of octreotide were started on day 9 of life. The Octreotide dose was increased to the maximum dose eventually. Magnetic resonance imaging (MRI) brain was normal and ultrasonography (USG) abdomen showed no abnormalities in the pancreas. She was discharged on diazoxide and octreotide with glucose levels within normal range. The child had a hypoglycemic episode at 4 months of age due to skipping of medications. A PET scan was done to rule out insulinoma was also normal. Currently, the child is stable and has attained milestones appropriate for her age.

Molecular diagnosis

Whole exome sequencing, showed a missense mutation in the ABCC8 gene with heterozygous inheritance suggestive of familial hyperinsulinemic hypoglycemia.

DISCUSSION

Hyperinsulinism can be primary, due to a defect in the β cells of the pancreas, or secondary due to mutation of the genes regulating insulin secretion.[6] Secondary hyperinsulinism is more common and mostly seen in large for gestational age, macrosomia, and in cases of perinatal asphyxia. The prevalence is 1 in 50,000 live births worldwide.[1]

CHI is classified based on responsiveness to treatment and histopathological diagnosis into focal, diffuse, or atypical forms.[9] It can cause serious brain damage and even death in severe cases due to hypoglycemia.[7] The identification of recessively inherited mutations provides informative genetic diagnosis which allows prenatal diagnosis and better management.

Diagnostic biochemical features for congenital hyperinsulinemia include GIR >8 mg/kg/min and lab values of blood glucose of <3 mmol/L with inappropriately high insulin levels, low serum ketone bodies, and low serum FFA.[8]

Our patient had high serum insulin of 7 mIU/l at the time of hypoglycemia requiring high GIR 12 mg/kg/min while ketone bodies remained negative. Recurrent and persistent hypoglycemia in the neonatal period can be caused by congenital hyperinsulinism, glycogen storage disorders, hypoketotic hypoglycemia, growth hormone deficiency, cortisol deficiency.[7]

Treatment of CHI requires a multidisciplinary approach with an aim to prevent brain damage. The nutritional approach consists of hypertonic glucose infusion and enteral feeding whereas medical treatment includes the administration of diazoxide and octreotide. Surgery should be considered when CHI patients fail to respond to both nutritional approach and medical treatment.[10]

In our infant, serum glucose levels fluctuated despite of GIR of 12 mg/kg/hour and enteral feeding. Hence diazoxide and octreotide were required to maintain glucose levels of more than 70. The child was tried on stopping octreotide and was continued on diazoxide but the child developed recurrent hypoglycemic readings. Hence was continued on both diazoxide and octreotide.

It is important to perform genetic analysis early to identify diazoxide resistance in hypoglycemia so that brain damage can be prevented in suspected CHI patients.

Congenital hyperinsulinism is most often sporadic while familial disease though uncommon connotes different genetic changes. The Homozygous mutation is commonly associated with severe forms of the CHI, diazoxide resistance, and K+ ATP channel mutation. On the other hand, the autosomal dominant disease is a milder form, is diazoxide-responsive, and involves a non-K ATP mutation.[1]

Mutations in the 16 different genes have been described that lead to dysregulated insulin secretion. CHI caused by a mutation in either ABCC8 or KCNJ11 is the most common form. These genes regulate the ATP-sensitive K+ channels which are involved in insulin secretion.[8] In this infant for the proband the whole exome sequencing showed heterozygous missense mutation, c.4154C>G/p.Ser1385Cys which is associated with hyperinsulinemic hypoglycemia familial (HHF1). The mutation is C>G at nucleotide 4154 (c.4154C>G) resulting in the substitution of cystine for glutamine at codon 1385 (p.Ser1385Cys). This mutation resides in exon 34 of the ABCC8 gene on chromosome 11. This entails long-term comorbidities such as diabetes, pancreatic exocrine dysfunction, and neurobehavioral deficits.[1]

Eighty percent of diazoxide resistance cases are due to the focal form, which is cured by surgical treatment. Thus, diazoxide resistance warrants further workup to determine if surgery is indicated or not.[1]

CONCLUSION

Persistent hyperinsulinemic hypoglycemia in infancy is rare and should be kept as a differential diagnosis in neonates with refractory hypoglycemia. Molecular genetic diagnosis should be considered in diazoxide unresponsive hypoglycemia for early diagnosis and prevention of hypoglycemia induced brain damage in infants.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Hussain S, Flanagan S, Ellard S. A Case Report on Congenital Hyperinsulinism Associated with ABCC8 Nonsense Mutation: Good Response to Octreotide. J ASEAN Federation Endocrine Soc. 2016;31(2):178.
2. Stanley CA. Perspective on the genetics and diagnosis of congenital hyperinsulinism disorders. J Clin Endocrinol Metab. 2016;101(3):815-26.
3. Hussain K. Insights in congenital hyperinsulinism. Endocr Dev. 2007;11:106-21.
4. Meissner T, Mayatepek E. Clinical and genetic heterogeneity in congenital hyperinsulinism. Eur J Pediatr. 2002;161(1):6-20.
5. Hussain K, Aynsley-Green A, Stanley CA. Medications used in the treatment of hypoglycemia due to congenital hyperinsulinism of infancy (HI). Pediatr Endocrinol Rev. 2004;2(1):163-7.
6. Grimberg A, Ferry RJ, Kelly A, Koo-McCoy S, Polonsky K, Glaser B, et al. Dysregulation of insulin secretion in children with congenital hyperinsulinism due to sulfonylurea receptor mutations. Diabetes. 2001;50(2):322-8.
7. Park K, Lim KI, Sohn YB, Lee HS, Hwang JS. Case report describing a patient with diazoxide resistant congenital hyperinsulinism resulting from compound heterozygous mutations in the ABCC8 gene. Ann Pediatr Endocrinol Metab. 2022;10.
8. Thakur S, Flanagan SE, Ellard S, Verma IC. Congenital hyperinsulinism caused by mutations in ABCC8 (SUR1) gene. Indian Pediatr. 2011;48(9):733-4.
9. Kliegman R Stanton B St Geme JW Schor NF Behrman RE Nelson WE. Nelson Textbook of Pediatrics. Edition 21 ed. Philadelphia PA: Elsevier. 2020.
10. Eichenwald EC Hansen AR Martin C Stark AR. Cloherty and Stark's Manual of Neonatal Care. Eighth edition. Philadelphia: Wolters Kluwer. 2017.

Cite this article as: Nirmala BS, Handu K, Lavanya S, Kariyappa P. A case of diazoxide unresponsive congenital hyperinsulinemic hypoglycemia with missense mutation in ABCC8 gene. Int J Contemp Pediatr 2023;10:398-400.