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GRAND ROUND

Congenital Hyperinsulinemia of Infancy: Role of Molecular Testing in Management and Genetic Counseling

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Abstract
Congenital hyperinsulinemia (CHI) is a genetically and clinically heterogenous disorder. In addition to the standard care of management of the proband, genetic counseling regarding the risk of recurrence in the future siblings is an important part in the management of the disorder. The counseling needs identification of accurate etiology and is challenging due to the complexity of the molecular mechanisms of CHI. This case highlights the importance of molecular testing which not only helped in planning the management of the proband with CHI but also helped in providing genetic counseling for which the family had consulted the medical genetics department.

Keywords Congenital hyperinsulinemia · Refractory hypoglycaemia · Preconceptional counselling · Loss of heterozygosity

Introduction

Congenital hyperinsulinemia (CHI) is a complex and heterogeneous disorder that occurs due to dysregulated insulin secretion from pancreatic beta cells. Its incidence can vary between 1 in 50,000 live births to as high as 1 in 2500 live births in countries with high degree of consanguinity [1]. The clinical features can range from asymptomatic to severe hypoglycemic episodes not responding to medical management. Till recently, a total of 14 genes are implicated in monogenic forms of CHI [2]. The most common and most severe monogenic form is caused by inactivating mutations of two subunits (SUR1 or Kir6.2) of the β-cell plasma membrane K^+ATP channel encoded by *ABCC8* and *KCNJ11* genes, respectively. For clinical management and prognostication, these patients can be divided into diazoxide-responsive and -nonresponsive cases. Diazoxide-responsive patients usually do not require confirmation of diagnosis by genetic testing for clinical management. However, molecular testing is of paramount importance for genetic counseling in both these groups and for the treatment in diazoxide-nonresponsive patients. In this study, a patient is described where molecular testing helped in decision making for further treatment options and for genetic counseling. The unique mode of inheritance of the disorder and complex issues in providing an accurate risk of recurrence in future siblings of the proband are also highlighted.

Report of Case

A 36-wk-old late-preterm female, an outcome of a nonconsanguineous marriage with uneventful antenatal history was born via emergency cesarean section in view of cephalopelvic disproportion with birth weight of 3800 g (> 97th centile by Fenton growth chart). At 2 h of life, she developed lethargy and poor feeding and was found to have low blood sugar levels. After initiation of intravenous dextrose, the requirement increased up to glucose infusion rate (GIR) of 12 mg/kg/min following which she was referred to the authors' institute for further workup. Earlier pregnancy had resulted in a macrosomic female baby (birth weight 4000 g) who had severe birth asphyxia and expired at 6 h of life. There was no documentation of hypoglycemia. There was no family history of early onset diabetes or similar illness. On examination, the proband was macrosomic (weight > 90th centile and length between 50 and 90th centile) with hypertrichosis on the ears. Critical samples revealed insulin level

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113 µU/mL (normal: < 2 µU/mL during period of hypoglycemia), cortisol 15 µg/dL (normal: > 15–20 µg/dL) and growth hormone of 15.5 ng/mL (normal: > 7 ng/mL). Blood gas analysis report was normal. Blood ketones were absent. Due to refractory CHI, she was started on diazoxide therapy (dose increased up to 20 mg/kg/d) but had poor response. Subsequently, she received injection octreotide (up to 45 µg/kg/d) and was later started on tablet sirolimus (1.5 mg/m^2/d) with oral corn starch in view of poor response to high-dose octreotide. Clinical management and monitoring for complications was performed as per published standards [3, 4]. Despite these efforts, there was partial response to medical management.

Targeted sequencing of *ABCC8* and *KCNJ11* genes by sanger sequencing revealed a heterozygous missense c.4256G>A (p. Arg1419His) variant in *ABCC8* gene (NM_0012871741.1), likely pathogenic according to American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) criteria. This variant was published as pathogenic in literature in patients with CHI [5]. Second variant in this gene was not identified. The identified variant was found to be inherited from the father who was also heterozygous for this variant. The mother did not harbor any sequence variation in these two genes. As this variant (paternally inherited heterozygous variant) was usually compatible with focal disease, ^{18}F-DOPA PET-CT was performed to look for focal form of CHI. This investigation revealed fluorodopa concentrating tumor in the uncinate process of pancreas. In view of refractory hypoglycemia, failure of medical management and a focal lesion, surgical resection of focal lesion with possible partial/near total pancreatectomy (due to difficulty in accessing location of the lesion) was planned following detailed discussion with the family. But the procedure had to be abandoned due to failed central venous access and feeding jejunostomy was done after consent. The patient had survived one episode of life-threatening gastroenteritis with sepsis at one-and-half year of age but at 2 y of age, she succumbed to a similar illness.

Later, the couple was referred to the authors' department for preconceptional counseling and recurrence risk of CHI in subsequent pregnancies.

Discussion

This report describes an infant presenting with severe CHI nonresponsive to medical management. The child had paternally inherited likely pathogenic variant in heterozygous form in *ABCC8* gene. The other disease-causing sequence variant was not reported and hence the possibility of severe phenotype due to autosomal recessive inheritance was ruled out. Focal nature of lesion on nuclear scan confirmed the possibility of second hit due to somatic mutation causing biallelic loss of function and localized insulinoma. This means that both the copies of the gene *ABCC8* were mutated in the cells of insulinoma; one copy of the gene with inherited sequence variation and the other copy of the gene that got mutated during somatic cell divisions.

For precise genetic counseling, it is necessary to understand the complex genetics involved in this form of CHI. Mutations in *ABCC8* and *KCNJ11* genes account for 50% of genetic causes and 89% of diazoxide unresponsive CHI [6] and is characterized by defective pancreatic β-cell K^+ATP channel subunits SUR1 and Kir6.2, respectively. Both autosomal dominant and recessive forms exist. Autosomal recessive form is the most severe type which presents in immediate newborn period and not amenable to medical management. Autosomal dominant form occurs at a later age with varied presentation and usually responds to diazoxide treatment. In the present case, autosomal recessive form of the disease was initially suspected due to clinical presentation, but molecular testing on DNA from peripheral blood revealed a heterozygous variant which was also identified in asymptomatic father, and a second variant was not identified. This ruled out the possibility of autosomal recessive form of CHI where both the copies need to harbor pathogenic sequence variations.

Monoallelic recessive paternally inherited form of *ABCC8* or *KCNJ11* gene variants is a known phenomenon that causes severe CHI refractory to medical management. Focal pancreatic lesion results from germline paternal mutation of *ABCC8* or *KCNJ11* gene located at 11p15.1 region along with postzygotic loss of the corresponding maternal region on chromosome 11p (second hit phenomenon) and this phenomenon is known as loss of heterozygosity (LOH) [7]. The molecular pathology is clearly depicted in Fig. 1. This focal lesion, in turn, leads to abnormal secretion of insulin, thus explaining the clinical severity and diazoxide nonresponsiveness in the present case. Since the mutation in the second copy of the gene is limited to insulinoma cells only, it cannot be detected by molecular test on the peripheral blood. As surgery was not performed in the present patient, genetic testing to confirm the somatic mutation in focal pancreatic tissue could not be done.

Following identification of paternally inherited variant, it is imperative to perform a functional nuclear scan in the affected individual to look for focal forms of CHI. Detection of monoallelic recessive inheritance (paternal) of K^+ATP mutation has a high sensitivity (97%) and specificity (90%) in predicting focal forms of pancreatic lesions [6] and this accounts for 30% – 40% of cases with CHI [2]. Identification of a focal lesion has major impact on the management of these infants. While a near total pancreatectomy is required for diffuse forms causing refractory hypoglycemia, partial/focal pancreatectomy is sufficient for focal forms. Choosing

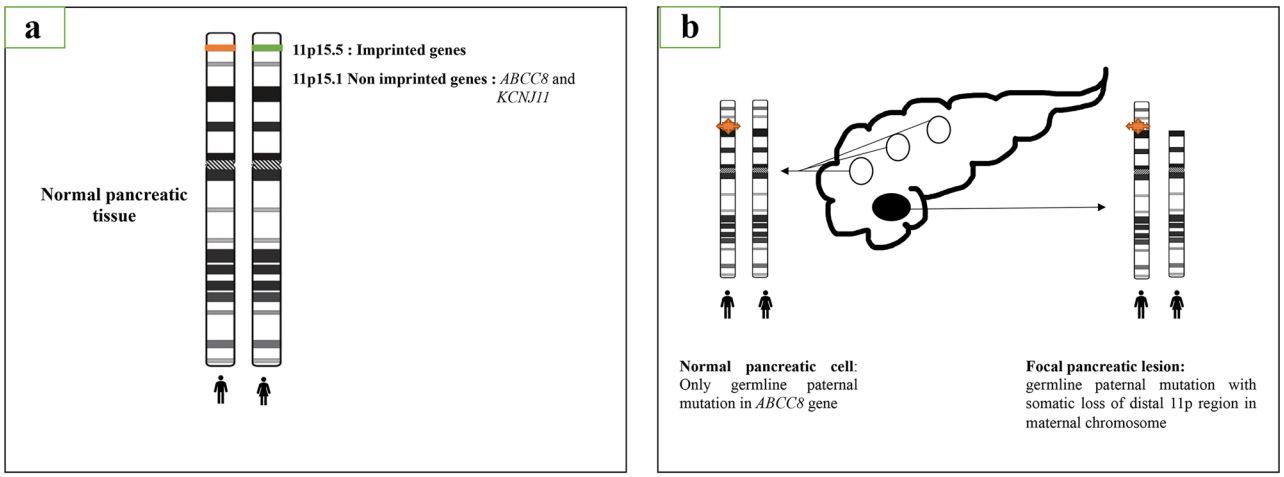

Fig. 1 **a** Location of genes in normal pancreatic tissue: paternally expressed growth promoting gene (*IGF2*—orange color) and maternally expressed growth suppressing genes (*P57KIP2* and *H19*—green color) are located at 11p15.5 region; non imprinted *ABCC8* and *KCNJ11* genes are located at 11p15.1 region. **b** Molecular pathology in the present patient: pancreatic cells without tumor contain only germline paternal *ABCC8* mutation (white circles) and the other copy of *ABCC8* gene is normal. Focal lesion in uncinate process (dark circle): germline paternal *ABCC8* mutation along with somatic loss of distal 11p region on maternal chromosome (second hit) resulting in biallelic defect at cellular level. This results in disproportionate expression of several imprinted genes involved in cell proliferation within the 11p15 region causing focal hyperplasia of pancreatic islet cells

appropriate treatment can thereby prevent late complications like diabetes and exocrine pancreatic deficiency arising out of total pancreatectomy. Thus, children with CHI who are not medically responsive to diazoxide should undergo early genetic testing followed by 18F-DOPA PET/CT scan, especially if a paternally inherited variant is detected.

The availability of etiological diagnosis helped in providing appropriate counseling for this family. While the prior risk of inheriting the paternal variant in the offspring is 1:2, the risk of second hit by chance in pancreas causing maternal LOH has been previously reported as 1:600 [8]. Hence, the overall risk of CHI presenting with such a severity in the future progeny is 1:1200 and can be considered minimal. The couple was counseled that prenatal testing can detect whether fetus has inherited the paternal variant or not (1:2 chance) but the phenotype can be asymptomatic like the father or a clinically manifesting CHI, responsive to medical management due to incomplete penetrance of disease. On the other hand, the risk of severe presentation of CHI due to second hit is negligible (1:1200) but cannot be predicted by prenatal testing as it occurs in somatic tissue. After discussion with the family, they were in favor of prenatal testing and were considering the option of termination if the variant is detected in the fetus probably due to their previous experience of witnessing two children succumbing to the illness.

In addition, few studies have shown that adult carriers of dominant variants in *ABCC8* or *KCNJ11* gene can develop dominantly inherited diabetes later in life probably due to the apoptosis of the pancreatic β-cell [9]. Controversies still exist regarding development of diabetes as only few cases have been reported where the proband or family member harboring CHI causing variant has developed diabetes mellitus during their adolescence to mid-adulthood period [10, 11]. However, active screening of family member harboring a pathogenic variant is feasible to recognize diabetes in early stages. The father of the index patient is 32-y-old (BMI - 31.0 kg/m^2; no history of diabetes in family) was worked up for diabetes and was found to have HbA1C of 5.9% (prediabetes range) and impaired fasting glucose (fasting blood glucose - 107 mg/dL; postprandial - 90 mg/dL). He has been asked to follow few lifestyle modifications. His oral glucose tolerance test (OGTT) along with HbA1c will be monitored 6 monthly. If he develops overt diabetes mellitus in spite of lifestyle modifications, sulfonylureas (glibenclamide, gliclazide, etc.) will be preferred agents.

The authors through this case wanted to raise awareness amongst clinicians regarding the change the molecular testing has brought in the management of this infant and highlighted the complexities of genetic counseling due to the unique genetic mechanism involved in this form of CHI.

Conclusion

A case of focal form of CHI caused by paternally inherited *ABCC8* variant with monoallelic recessive mode of inheritance has been reported. Early molecular testing is, therefore, essential in medically nonresponsive cases of CHI to plan optimal treatment regimen and to provide appropriate genetic counseling.

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Authors' Contributions HS and SRP conceived the idea of the project; PD and LS were involved in the clinical case management; HS and SRP were involved in the counseling of the family; SRP and PD finally critically reviewed the manuscript. SRP will act as guarantor for the paper.

Declarations

Conflict of Interest None.

References

1. Arnoux JB, Verkarre V, Saint-Martin C, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. Orphanet J Rare Dis. 2011;6:63.
2. Galcheva S, Demirbilek H, Al-Khawaga S, Hussain K. The genetic and molecular mechanisms of congenital hyperinsulinism. Front Endocrinol (Lausanne). 2019;10:111.
3. Demirbilek H, Hussain K. Congenital hyperinsulinism: diagnosis and treatment update. J Clin Res Pediatr Endocrinol. 2017;9:69–87.
4. Shah P, Rahman SA, Demirbilek H, Güemes M, Hussain K. Hyperinsulinaemic hypoglycaemia in children and adults. Lancet Diabetes Endocrinol. 2017;5:729–42.
5. Tornovsky S, Crane A, Cosgrove KE, et al. Hyperinsulinism of infancy: novel ABCC8 and KCNJ11 mutations and evidence for additional locus heterogeneity. J Clin Endocrinol Metab. 2004;89:6224–34.
6. Snider KE, Becker S, Boyajian L, et al. Genotype and phenotypse correlations in 417 children with congenital hyperinsulinism. J Clin Endocrinol Metab. 2013;98:E355–63.
7. Joyce CM, Houghton JA, O'Halloran DJ, O'Shea PM, O'Connell SM. Inheritance of a paternal *ABCC8* variant and maternal loss of heterozygosity at 11p15 retrospectively unmasks the etiology in a case of congenital hyperinsulinism. 2020;8:1217–22.
8. Ismail D, Smith VV, deLonlay P, et al. Familial focal congenital hyperinsulinism. J Clin Endocrinol Metab. 2011;96:24–8.
9. Thornton PS, MacMullen C, Ganguly A, et al. Clinical and molecular characterization of a dominant form of congenital hyperinsulinism caused by a mutation in the high-affinity sulfonylurea receptor. Diabetes. 2003;52:2403–10.
10. Abdulhadi-Atwan M, Bushman J, Tornovsky-Babaey S, et al. Novel de novo mutation in sulfonylurea receptor 1 presenting as hyperinsulinism in infancy followed by overt diabetes in early adolescence. Diabetes. 2008;57:1935–40. Erratum in: Diabetes. 2008;57:2552.
11. Huopio H, Reimann F, Ashfield R, et al. Dominantly inherited hyperinsulinism caused by a mutation in the sulfonylurea receptor type 1. J Clin Invest. 2000;106:897–906.