Multidisciplinary Approach in Diagnosis and Risk Assessment of Variable Inheritance of Familial Hyperinsulinism: A Case Series

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Abstract

Background: Familial hyperinsulinism (FHI) is a complex disorder of dysregulated insulin secretion and decreased glucose, presenting with variable onset and severity even among families. This case series involves two known cases with diffuse forms of FHI in pathogenic *ABCC8* variants and associated pregnancy risks in the current fetus.

Clinical data and Family history: Case 1 involves A couple who is a known carrier of c.2420T>C with previous two neonatal deaths sought counseling. They wanted to understand the possible implications of prenatal sanger-reported heterozygous variants in the fetus and variable inheritances. Case 2 Involves A 4.6-year-old female with clinically suspected hyperinsulinemic hypoglycemia and asymptomatic hypoglycemia. Her scan revealed a diffuse uptake in the pancreas, and she was detected to have a heterozygous c.4353G>A variant, which was also present in father with diabetes onset at 25 years.

Discussion and Genetic Counselling: FHI has two major histological subtypes: diffuse and focal forms. The diffuse form is more severe and typical autosomal recessive inheritance (AR). An autosomal dominant (AD) inheritance follows a comparatively milder focal form. An AD inheritance having a diffuse form is a rare scenario, present in only 10-20% of cases. Case 1 follows the expected pattern of diffuse form of FHI with AR inheritance. The couple, however, were apprehensive about the heterozygous variant in fetus and possible of AD inheritance. Due to family history, the counseling focussed on AR inheritance and low risk of the fetus, like parents. Case 2 presents complications in diagnosis, and in conjunction with a endocrinologist, the case findings were reviewed, supporting the rare presentation of FHI with AD and variable penetrance. The couple was counseled regarding the 50% recurrence risk in pregnancy and prenatal testing.

Conclusion: The multidisciplinary approach proved beneficial in understanding FHI, providing an accurate diagnosis and recurrence risk in pregnancy, further improving prenatal decision-making.

Introduction

Familial Hyperinsulinism (# 256450) all or some insulin-producing cells in the pancreas is a complex disorder of dysregulated insulin secretion and decreased glucose with intrafamilial variability in phenotype and severity. Presenting symptoms in newborns include apnea, seizures, and unresponsiveness, while in childhood milder cases may emerge. Further upon histological subtyping, diffuse and focal are the two major forms present. This case series focused on *ABCC8*, a vital gene that is considered a major causative. *ABCC8* is located in cytoband 11p15.1 region, resulting from a defect in the kATP channel. The gene has variable inheritance patterns, including an AR or AD inheritance. Understanding the condition, histology, and inheritance could provide possible options for potential treatment. This study broadly elaborated on two cases with diffuse forms of FHI in pathogenic *ABCC8* variants, multi-disciplinary approaches, and associated pregnancy risks in the current fetus. [1, 2]

Clinical data and Family history

Case I

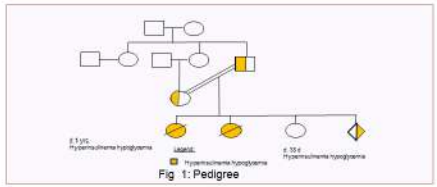

Fig 1: Pedigree

Case II

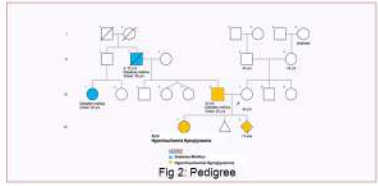

Fig 2: Pedigree

Case	History	Report
G1	Death – 1.7 years History of hypoglycaemic seizure from day 2 of birth, Nesidioblastosis and global developmental delay and hypotonia	Genetic test report revealed Homozygous missense variant in *ABCC8* gene which is associated with hyperinsulinemia hypoglycaemia familial-1 by both AD/AR inheritance
G2	Death – 38 days after birth hypoglycaemia, underwent pancreatic surgery on 35th day (NICU 3 days), PET/CT scan – nesidioblastosis and neonatal seizures	Genetic test report revealed Homozygous missense variant in *ABCC8* gene which is associated with hyperinsulinemia hypoglycaemia familial-1 by both AD/AR inheritance
G3	Normal	Sanger report (prenatal CVS) – Normal – No variant detected in the sample
G4	20 weeks GA First trimester screening report –NT- 1.1 mm, Nasal bone present, Tricuspid Doppler – Normal	Prenatal CVS sanger report showed the same variant of *ABCC8* gene present in heterozygous state.
Parents		Parental sanger study confirmed both parents are heterozygous to the same variant in *ABCC8* gene

Case	History and report
G1	clinically suspected hyper insulinemic hypoglycaemia and asymptomatic hypoglycaemia. Previous Medication - diazoxide and hydrochlorothiazide **(Unresponsive)** Current medication- **octreotide** Clinical exome sequencing report – Heterozygous variant in *ABCC8* Gene PETCT scan - diffuse uptake in pancreas
Father	ABCC8 variant present in heterozygous state ?Type II diabetes, Onset – 25 years
Mother	Variant Absent
Fetus (G3)	18 weeks GA; Prenatal (Amniotic Fluid) Sanger study showed fetus harbouring the same variant in *ABCC8* gene in heterozygous state

Result

Case I: Autosomal recessive - Diffuse form; **Case II**: Autosomal dominant - diffuse form

Fig 3: Sanger testing was performed on the extracted amniotic fluid sample in case 2

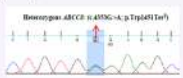

Fig.3.a.Father – Heterozygous Variant present

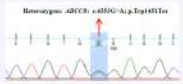

Fig.3.b. Fetus – Heterozygous Variant present

Discussion / Conclusion

FHI has two major histological subtypes: diffuse and focal forms. The diffuse form is more severe and typical autosomal recessive inheritance (AR). An autosomal dominant (AD) inheritance follows a comparatively milder focal form. An AD inheritance having a diffuse form is a rare scenario, present in only 10-20% of cases. [3] A pre-operative assessment using 18F-DOPA-PET/CT acts as a gold standard for detecting focal lesions, helping the diagnosis. Studies have also reported instances of diffuse forms unresponsive to diazoxide, linked to single paternally inherited mutations, acting via different mechanisms, suggesting a complex genetic landscape underpinning the disease. Literature reported heterozygous paternally inherited *ABCC8* mutations leading to diffuse form as observed from the histology of the resected pancreatic tissue, highlighting the global presence and genetic diversity of the condition. [4, 5]

In case 1, the couple, were apprehensive about the heterozygous variant (c.2420T>C) *ABCC8* gene which is seen in the fetus and the possibility of AD inheritance associated with FHI, which was present in first two neonates who died. Both neonates had nesidioblastosis which is characterized by diffuse islet cell hyperplasia, and they had homozygous variants, meaning these case findings and genetic testing pointed towards an expected pattern AR inheritance. The couple was explained about autosomal recessive disorders which arise when both copies of altered gene are inherited from unaffected parents carrying only one copy each. The fetus also had a heterozygous variant like the parents, and reassured about the low risk to the fetus.

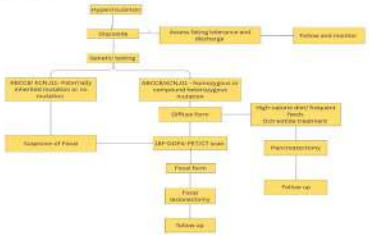

Fig 4: Suggested Management Pathway [6]

Case 2 presents complications in diagnosis focused a rarer scenario of diffuse form FHI with AD such as the child's condition clinically matching with FHI and PET-CT scan revealing a diffuse uptake. Genetic findings of the child and father having heterozygous variant in (c.4353 G>A) in *ABCC8* gene and variability associated with the condition were also discussed. These findings hinted that the case presented a rare scenario diffuse form. Management of CHI demands a multidisciplinary approach, involving a team of specialized healthcare professionals for optimal patient outcomes. Early and accurate diagnosis, alongside careful surgical intervention by experienced surgeons, endocrinologist is critical in the effective treatment of CHI. The couple was counseled regarding the 50% recurrence risk in pregnancy, prenatal testing and variability. Further the testing revealed that the fetus also had the heterozygous variant like the father and sister. Understanding the postnatal presentation is also based on the intrafamilial variability in phenotype and severity.

Fig 5. Multidisciplinary approach [7]

Conclusion: In cases involving different inheritance patterns, counseling plays a vital role by helping patients gain a better understanding of their condition, inheritance, clinical variability and the appropriate management strategies. Additionally, the multidisciplinary approaches are beneficial in understanding FHI, providing an accurate diagnosis and recurrence risk in pregnancy, further improving prenatal decision-making.

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