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Case Report

Variable Expressivity and Incomplete Penetrance in Monogenic Diabetes

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Abstract

We present a case of monogenic diabetes which demonstrates marked incomplete penetrance and variable expressivity. A 3-month-old child presented with transient neonatal diabetes mellitus and was found to carry a heterozygous variant in the *ABCC8* gene (variant identified - c.4136G>T,p.Arg1379Leu). Her mother was also found to have the same *ABCC8* heterozygous variant but has always been euglycemic with no hypoglycaemia or hyperglycaemia. Hence two individuals with the same genotype expressed a highly variable phenotype ranging from transient neonatal diabetes mellitus to normoglycemia.

Keywords: Monogenic diabetes; Incomplete penetrance; *ABCC8* gene mutation; Variable expressivity

Introduction

Monogenic Diabetes (MD) accounts for about 1-5% of all diabetes cases with different subtypes such as neonatal diabetes (NDM), maturity onset diabetes of young (MODY) and syndromic forms such as Wolfram syndrome and Wolcott-Rallison syndrome [1]. Mendelian diseases, though individually rare, collectively represent a significant portion of the global population, affecting more than 5%. It encompasses more than 6000 rare phenotypes including MD. The phenomenon unique to Mendelian diseases is incomplete penetrance with variable expressivity [1]).

Penetrance refers to the proportion of individuals who carry a specific genotype and exhibit the expected clinical phenotype associated with that genotype. In other words, it is the likelihood or probability that a person with a particular genetic variant will express the associated trait or disease. If everyone with a particular genotype presents with clinical symptoms by a particular age, then it is said to be fully penetrant, whereas if it falls below this, it is said to be reduced or incomplete penetrance. The severity of the phenotype caused by a particular genotype can vary among affected individuals (wide variation in terms of severity and age of onset).

This phenomenon is defined as variable expressivity displayed by that particular genotype. A said genotype can vary both in the severity of presentation and in level of penetrance across the population. This variable expressivity and penetrance are different from pleiotropy. Pleiotropy implies that different variants of a particular gene cause multiple phenotypes [2].

Case presentation

3-month-old female infant, second child of non-consanguineous parentage, full term birth by normal vaginal delivery (birth weight 3kg) presented in severe diabetic ketoacidosis (DKA). She presented to the emergency room with a Glasgow coma scale of 3,

blood glucose was 31mmol/L, beta hydroxy butyrate 5.2mmol/L, venous pH 6.9, bicarbonate 4.2mmol/L and glycated hemoglobin (HbA1c)12.5%. She was critically ill and required intubation and mechanical ventilation. The working diagnosis was neonatal diabetes considering the age of onset, presenting in severe DKA. The DKA was managed as per the ISPAD (International Society for pediatric and Adolescent Diabetes) protocol. DKA resolved within 8 hours and she was extubated in around 24 hours. The child was initially initiated on insulin Detemir 1 unit once a day and bolus insulin Lispro 0.5 units pre feeds if blood glucose was >14mmol/L. She was discharged on detemir 2units twice a day and bolus insulin pre feeds as correction bolus with target blood sugar 14mmol/L.

Diagnostic Assessment

Using whole genome sequencing (WGS) the patient and the mother (aged 28years) were found to carry a heterozygous variant in *ABCC8* gene (variant c.4136G>T, Arg1379Leu) on exon 11. In silico analysis based on PolyPhen-2, CADD, GERP and pLI, predicted that this mutation was likely to be pathogenic (Table 1 summarises the variant details detected by WGS). The father and healthy sibling were negative for this finding. Meng Li et al demonstrated the same variant in a proband after the proband was diagnosed early onset type 2 diabetes mellitus (T2DM) at the age of 16 years. Functional studies revealed that the variant was located on the nucleotide binding domain 2 of the *ABCC8* gene. The hyperglycaemia was the possible result of the variant impacting the ATPase activity [3]).The variant Arg1379Leu has been reported before with the phenotype of transient neonatal diabetes in an infant who was 42 days of age at the time of presentation with DKA . The mother was negative for the variant and the father was unavailable for testing [4].

Chromosome position	Gene	Inheritance	Variant identified	Effect	Poly-Phen-2 prediction score	CADD score	GERP score	pLI score
11:17417461	ABBC8	Dominant/ heterozygous	c.4136G>T,p. Arg1379Leu	Missense	1	51	5.06	1.89E-14
CADD: Combined Annotation Dependent Deletion; GERP: Genomic Evolutionary Rate Profiling; pLI: probability of being loss of function intolerant.								

Table 1: Variant identified by WGS with clinical relevance to the patient phenotype.

Treatment and follow-up

The HbA1c after 1.5 months of the initial presentation was 6.2% and the child was off insulin therapy due to frequent hypoglycemic episodes. Dexcom G6 continuous glucose sensor showed time in range (TIR%) as 91%. She was developmentally appropriate for age. Following the whole genome sequencing of the family members, the mother was evaluated with fasting blood glucose and HbA1c and was found to be normoglycemic. Currently our patient is 17 months old, with normal developmental milestones for age and is off insulin from 5 months of age with an HbA1c of 5.5%.

Discussion

The incomplete penetrance and variable expressivity are observed in some cases of MD. This is due to a wide spectrum of factors which can be broadly classified into age, sex, ethnicity, lifestyle, environmental factors (like intrauterine hyperglycemia) and genetic factors (especially genetic modifiers) [1,2]. Figure 1 shows the factors influencing incomplete penetrance and variable expressivity in MD families. Meihang Li et al has shown that less than half of the MD cases have an affected parent which reflects the highly reduced penetrance pattern in MD [1,5]. Incomplete penetrance is a well-documented phenomenon in cases with *ABCC8* mutation. P.Klee et al described a novel variant His863Tyr in *ABCC8* in a three generation family which led to NDM in a child, asymptomatic T2DM in father and impaired fasting glucose in a the grandmother [6]. Gonsorcikova et al described a family with 6 members having a novel V84I mutation in *ABCC8*. The proband was a 12 yr old boy with fasting hyperglycemia. Subsequently the twin brother, sister, mother, maternal aunt and grandfather were detected to have fasting hyperglycaemia [7]. Lenfant et al described a case of a 6-year-old girl with juvenile onset diabetes and congenital cataract who was found to have a heterozygous mutation in *ABCC8* and homozygous mutation in *CRYBB1*. Both the healthy mother and sibling were found to be heterozygous for the same *ABCC8* mutation suggesting incomplete penetrance [8]. Our patient and her healthy mother have been shown to have the same genotype but variable penetrance which led to a highly variable phenotype which was transient neonatal diabetes and normoglycemia respectively.

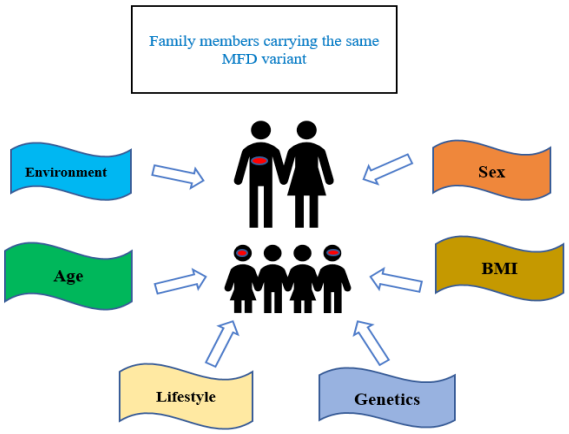

Figure 1: Factors influencing incomplete penetrance and variable expressivity in MD families.

Learning points:

- Heterozygous variants in the *ABCC8* gene can present with marked variable penetrance and expressivity for MD (ranging from transient NDM to normoglycemia).
- Genetic testing for NDM is mandatory in patients presenting with diabetes before 6 months.
- The molecular basis of this marked variable penetrance and expressivity for *ABCC8* gene mutations needs further study.

Contributors

All authors made individual contributions to authorship.SC and KH was involved in the patient management, manuscript preparation and submission. IM was involved in the genetic studies and literature review. DM was involved in literature review. AA, KF was involved in the genetic studies. KH is the senior author who was involved in the overall supervision in patient care and manuscript finalization.

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Disclosures

None

Informed patient consent for publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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