Neonatal Hyperinsulinaemic Hypoglycaemia and Early Onset Diabetes Secondary to Biallelic ABCC8 (MODY 12) Mutation

Larsen N, Khine C, Khan SMS

Sherwood Forest Hospitals
NHS Foundation Trust

Case Presentation

A 21-year-old lady diagnosed with T2DM in early adulthood was referred to our young adult diabetes clinic for investigation and management.

Her history and previous investigations included:

- A several year history of persistent fasting and post-prandial hyperglycaemia
- Raised HbA1c of 51mmol/mol
- Neonatal hyperinsulinaemic hypoglycaemia with normal pancreatic imaging and macrosomia
    - medically managed with diazoxide, chlorthiazide and somatostatin. These medications were weaned off in teen age without any consequences.
- No family history of diabetes

Given the history a suspicion of misdiagnosed MODY was raised (figure 1) and C-peptide and pancreatic islet autoantibodies were requested. These showed that she had a good insulin reserve and negative autoantibodies for T1DM.

Genetic testing was requested which showed biallelic ABCC8 mutations; c.1672-20a>G (likely pathogenic) and c.3992-9G>a (pathogenic).

Management:
After a trial of lifestyle modification, she responded well to SGLT2 inhibitors and GLP1 agonists to improve glycemic control and help in weight loss. Insulin therapy was not required.

Gene	% of MODY Cases
GCK (MODY2)	30-50%
HNF1A (MODY3)	30-65%
HNF1B (MODY5)	<5%
HNF4A (MODY1)	5-10%
ABCC8 (MODY12)	<1%

Table 1: Frequency of gene loci causing MODY. *The gene encoding ABCC8 makes up <1% of cases and can lead to a range of phenotypically presentations.*

- Early-onset diabetes (typically age <35 years)
- Normal/non-obese BMI
- History of neonatal diabetes and/or hypoglycaemia
- Mild, stable and non-progressive fasting hyperglycaemia
- Family history of diabetes demonstrating autosomal dominant inheritance pattern
- Features not in keeping with T1DM
    - Absence of pancreatic islet autoantibodies
    - Measurable C-peptide 3-5 years after diagnosis (insulin production persisting beyond honeymoon period)
    - Daily insulin requirements <0.5 Units/kg
    - Lack of ketoacidosis when not on insulin
- Good response to sulfonylureas
- Extra-pancreatic features (e.g., renal, hepatic, gastrointestinal)

Figure 1: Clinical Findings Suggestive of MODY *A list of common symptoms associated with MODY. Identification of these should lead to consideration and investigation of MODY as a diagnosis. Highlighted in red are those features present in this case.*

Discussion

The *ABCC8* gene encodes the sulphonylurea receptor 1 subunit (SUR1) of the ATP-sensitive potassium channel in the pancreatic beta cell. Mutations can lead to phenotypically diverse presentations ranging from largely inconsequential GCK type MODY to significant neonatal hypoglycaemia and early onset diabetes [2] – as observed in this case. Regarding management, insulin is reported to cause significant hypoglycaemia and weight gain whilst treatment with SGLT2 inhibitors and gliclazide have shown better results.

Early molecular testing and proper management of MODY with oral hypoglycaemic agent are beneficial for patients and families preventing unnecessary insulin therapy and the risks associated (hypoglycaemia, infection etc.). A low diagnostic threshold should be considered for patients with features noted in figure 1.

References

(1) Zsolt Gaál, Zsuzsanna Szűcs, Irén Kántor, Andrea Luczay, Péter Tóth-Heyn, Orsolya Benn, Enikő Felszeghy, Zsuzsanna Karádi, László Madar, and István Balogh. "A Comprehensive Analysis of Hungarian MODY Patients-Part I: Gene Panel Sequencing Reveals Pathogenic Mutations in HNF1A, HNF1B, HNF4A, ABCC8 and INS Genes." Life (Basel, Switzerland) 11.8 (2021): 755. Web.

(2) Bowman, P., S E Flanagan, E L Edghill, A. Damhuis, M H Shepherd, R. Paisey, A T Hattersley, and S. Ellard. "Heterozygous ABCC8 Mutations Are a Cause of MODY." Diabetologia 55.1 (2012): 123-27. Web.