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CASE REPORT

Double whammy: Coexistence of Mature onset diabetes of the young and autoimmune diabetes: A case report

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ABSTRACT

Maturity-Onset Diabetes of the Young (MODY) encompasses genetic disorders caused by mutations in single genes associated with beta cell dysfunction, constituting 1-6% of all diabetes cases. Mutations in ATP binding cassette transporter subfamily C member 8 (ABCC8) causes MODY 12 which accounts for 1% among MODY cases. It can present in childhood, adolescence or adulthood. Despite growing awareness, accurate MODY diagnosis remains challenging, often leading to misclassification as type 1 or type 2 diabetes. Correct identification is crucial for tailored treatment and implications for family members.

The coexistence of MODY and autoimmune related diabetes is a very rare phenomenon with only a handful of cases reported. We describe a unique case where the index patient was initially diagnosed with type 1 diabetes at age 8 due to antibody positivity, leading to insulin treatment. After 15 years, he presented with evidence of all microvascular complications. Interestingly, his brother also developed diabetes at age of 14 years but with out antibody positivity. Due to a strong family history, both siblings underwent genetic testing, revealing a heterozygous mutation in the ABCC8 gene (C.4799630 G>A; P-Arg 1600His).

Introduction:

Maturity onset diabetes of the young (MODY) is a collection of inherited disorders of non autoimmune diabetes caused by mutations in single genes leading to dysfunction of pancreatic beta cells. They account for 1-6 % of diabetes[1] .These are characterised by autosomal dominant inheritance, early onset of diabetes at < 25 years of age, preservation of endogenous insulin secretion with no signs of autoimmune process or insulin resistance. 14 types of MODY have been defined so far. MODY 1-5 have been studied more in detail. There is sparse data about other rare forms of MODY. On the other hand, type 1 diabetes is the most common type of diabetes in younger population which occurs due to autoimmune destruction of beta cells. It constitutes a bout 40-50 % of diabetes in young[2].The concurrent occurrence of two different varieties of diabetes, namely MODY and type 1 diabetes, in the same patient has been very rarely reported. We describe one such patient who presented with evidence of all microvascular complications of diabetes. He was initially treated as having type 1 diabetes due to antibody positivity at the time of diagnosis. However, genetic analysis performed many years later revealed a mutation in the ATP binding cassette transporter subfamily C member 8 gene (ABCC8), which is associated with MODY 12.

Case report:

A 23-year-old male presented to us in April 2022 for diabetes management. He was diagnosed with diabetes at the age of 8 years and treated with insulin for a presumed diagnosis of type 1 DM. He was tested positive for islet cell and glutamic acid decarboxylase (GAD) antibodies (GAD 65 antibody: 1.9 IU/ml (<1), islet cell antibody: 65IU/ml (< 40). His C peptide levels were <0.05ng/ml. He never experienced any episodes of diabetic ketoacidosis (DKA) during the 15-year period. On presentation he already had evidence of microvascular complications which included non proliferative diabetic retinopathy, peripheral neuropathy, and diabetic nephropathy. A renal biopsy confirmed diabetic kidney disease, which is currently managed conservatively (GFR: 15). He measured 167 cm in height, weighed 65 kg, with a BMI of 19.37. His HbA1c ranged between 9-10. His insulin regimen included 15 units of Glargine and Aspart 10-10-8. Additionally, he was hypothyroid and receiving 75mcg Levothyroxine replacement therapy.

Upon further inquiry, he mentioned that his older sibling, aged 27, was diagnosed with diabetes at 14 and treated with insulin therapy. However, the sibling tested negative for islet cell and GAD antibodies, showing no evidence of microvascular complications during evaluation. There was no history of diabetes in either of the parents.

Given the strong family history of both brothers developing diabetes at a young age and lacking features of insulin resistance, genetic testing was conducted to explore potential genetic causes. whole exome sequencing revealed a heterozygous variant in the ABCC8 gene (C.4799630 G>A; P-Arg 1600His), associated with the MODY12 subtype. Due to the patient's renal dysfunction, a sulphonylurea therapy trial was not feasible. Consequently, the patient continued on insulin therapy with dose titrations.

Discussion:

The term "Maturity onset type diabetes of childhood" or "of the young" was first described by Dr. Fujans in 1964 after observing mild asymptomatic diabetes in non-obese children, adolescents, and young adults[3].Dr. Tattersall and Dr. Fajans confirmed the autosomal dominant mode of inheritance in this diabetes form in 1974, proposing the 'MODY' abbreviation for the first time[4]. Genetic molecular studies started in 1992, reporting 14 MODY subtypes. Two new possible genes, Regulatory Factor X6 (RFX6) from the UK and NK6 Homeobox 1 (NKX6-1) from India, have been detected. There's significant geographic variability in MODY subtype prevalence. In the UK and Europe, over 90% of MODY cases are GCK-MODY, HNF1A-MODY, and HNF4A-MODY, while in Japan, these varieties account for only 50%[5]. Mohan et al. observed MODY 3 (7.2%) as the most frequent in South Indians, followed by MODY 12 (3.3%)[6], indicating racial disparities. Clinical criteria for MODY diagnosis include early-onset diabetes (<25 years), diabetes in two or ideally three family members (autosomal dominant mode of inheritance), non-insulin dependence, absence of obesity, and absence of diabetic ketoacidosis (DKA). MODY is often misdiagnosed as type 1 or type 2 diabetes.([7])

The MODY subtypes 1-5 are well studied and described in detail. There is paucity of information on other types of MODY. Here, we highlight MODY 12, more prevalent in the Indian subcontinent than the Western population. MODY 12 results from mutations in the adenosine triphosphate (ATP)-binding cassette transporter subfamily C member 8 (ABCC8) gene, coding for sulfonylurea receptor 1 (SUR1) on chromosome 11. The ATP-sensitive potassium (K-ATPase) channel in β cells, crucial for insulin secretion, comprises two subunits: a pore-forming subunit encoded by the Potassium Inwardly Rectifying Channel Subfamily J Member 11 (KCNJ11) gene and a regulatory subunit encoded by ABCC8([8]. Insulin secretion is influenced by mutations in either gene. ABCC8, with 39 exons encoding 1582 amino acids, exhibits a diverse phenotypic spectrum. Mutations cause transient neonatal diabetes mellitus, permanent neonatal diabetes mellitus, and MODY. In a review of 55 cases of ABCC8-related MODY 12, clinical presentations ranged widely from mild impaired glucose tolerance to severe insulin-dependent diabetes[9].Age at diagnosis ranged from 2 to 53 years. Heterozygous mutations in ABCC 8 genes have been shown to cause hyperinsulinemic hypoglycemia in the neonatal period and infancy, progressing to diabetes later in life.

The coexistence of MODY with autoimmune diabetes is rarely reported. In a study by McDonald et al., GAD 65 antibodies were positive in <1% of the population, and none were positive for islet cell antibody[10]. Other studies also suggest that the antibody positivity rate in MODY is no different from the healthy background population. EM O Donovan reported 3 cases of MODY (HNF1A, HNF4A and ABCC 8) with strong GAD 65 autoantibody positivity. These cases initially achieved glycemic control with sulfonylureas, but when their control deteriorated,

requiring insulin, antibody testing revealed positivity[11].To the best of our knowledge, Ours is the second case where the index patient had an ABCC 8 mutation along with GAD 65 antibody and islet cell antibody positivity.

It is prudent to achieve an accurate diagnosis of MODY promptly, as recent findings challenge the previous belief in its benign nature and reveal associations with complications. A South Indian study demonstrated a higher incidence of microvascular complications, specifically diabetic retinopathy and nephropathy, in HNF1A-MODY, HNF4A-MODY, and ABCC8-MODY compared to type 1 and type 2 diabetes[12]. Consistent with this, F. Reilly et al. reported retinopathy as a common complication in 5 out of 10 patients with activating mutations in ABCC8[13]. Additionally, M. Timmers described a MODY 12 patient with severe Charcot's arthropathy leading to lower limb amputation, along with other microvascular complications[7].

The phenotypic heterogeneity, a well-known MODY feature, is evident in our cases, where two siblings sharing the same mutation within the same family showcase diverse presentations. The index patient displayed evidence of all microvascular complications, including non-proliferative diabetic retinopathy, diabetic nephropathy, and sensory-motor axonal neuropathy, while the elder sibling had none. Notably, the index patient, who also had GAD 65 antibodies and islet cell antibody positivity, manifested complications, while the antibody-negative brother had none. Whether the presence of autoantibodies predisposed the index patient to microvascular complications remains uncertain. It may be worthwhile to assess antibody status in MODY patients who exhibit early complications after diagnosis.

A precise diagnosis holds significant treatment implications. Many individuals are mislabeled as having type 1 diabetes and receive insulin therapy, resulting in glycemic variability and hypoglycemic episodes. Transitioning to sulfonylurea therapy offers stable glycemic control and reduces the risk of hypoglycemia, subsequently lowering the risk of complications. The presence of renal dysfunction in our patient precluded us from attempting sulfonylurea therapy.

Conclusion:

We emphasise the critical role of detailed family history in diagnosing MODY. The presence of positive GAD 65 antibodies and islet cell antibodies should not deter us from considering the possibility of MODY particularly if microvascular complications occur shortly after diabetes diagnosis, and another young family member has a diabetes diagnosis. The absence of diabetes history in the parents should also not dissuade our suspicion of MODY. The coexistence of MODY and autoimmune diabetes is plausible, and a dual diabetes diagnosis may increase the risk of microvascular complications. Future studies are needed to confirm this aspect. We suggest checking the antibody status in MODY patients who develop severe microvascular complications.

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