Unusual Simultaneous Presentation of Maturity Onset Diabetes of the Young in Siblings

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Background

While Type 1 Diabetes Mellitus is the most common form of diabetes diagnosed in childhood, there are other etiologies that must be explored as possible causes (1). One such example is Maturity Onset Diabetes of the Young (MODY), a rare monogenic form of diabetes mellitus that accounts for ~1-5% of diabetes diagnoses (2,3). MODY is often misdiagnosed at time of presentation as Type 1 Diabetes Mellitus (T1DM) or Type 2 (T2DM) (4).

MODY1, a pathogenic variant representing a mutation of the HNF4A gene on chromosome 20, is inherited in an autosomal dominant fashion and accounts for <10% of identified MODY diagnoses (5). The exact mechanism of hyperglycemia in the HNF4A mutation is poorly understood but is thought to be a defect in gene expression that causes a critical effect on insulin secretion (6). Patients typically present with polyuria, polyphagia, and elevated HbA1c, but with an in-range C-peptide and negative pancreatic beta cell antibodies, as would be seen in T1DM. MODY1 treatment differs from that of T1DM and often involves use of sulfonylureas to increase insulin secretion (7).

Figures

Table1: 11-year-old female labs

	At Presentation
HgA1c	12.5 %
Random Blood Glucose	396 mg/dL
Insulin	10.5 IU/mL

Table 2: 18-year-old male labs

	At Presentation
HgA1c	8.3 %
Random Blood Glucose	299 mg/dL
Insulin	14.7 IU/mL

Figure 1. Pedigree

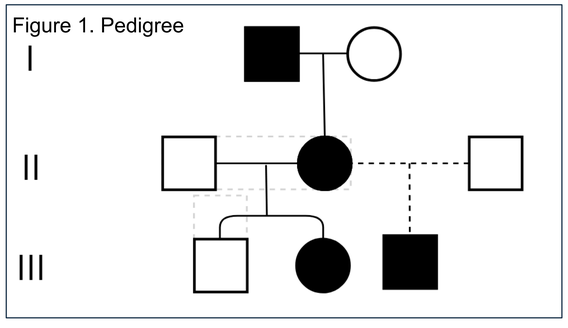


Table 3: **Genetic Results**

HNF4A Autosomal Dominant variant c.340 C>T p.(R114W)

Case Series

A previously healthy non-obese 11-year-old female presented to urgent care after a random home glucose measurement of 419 mg/dl on her mother's glucometer. Urgent care confirmed hyperglycemia at 396 mg/dl with glucosuria. She was sent to ER where she was found to have persistent hyperglycemia, glucosuria, elevated A1c (12.2%), elevated insulin level (10.5 IU/mL), and no ketonuria.

Interestingly, the patient's non-obese 18-year-old maternal half brother, who had accompanied the patient to the urgent care simultaneously noted headache, nausea and abdominal pain for the previous two weeks. He was evaluated and was found to be hyperglycemic. He was also sent to the ER where he had blood glucose of 299 mg/dL, glucosuria, elevated A1c (8.3%), elevated insulin level (14.7 IU/mL), and no ketonuria.

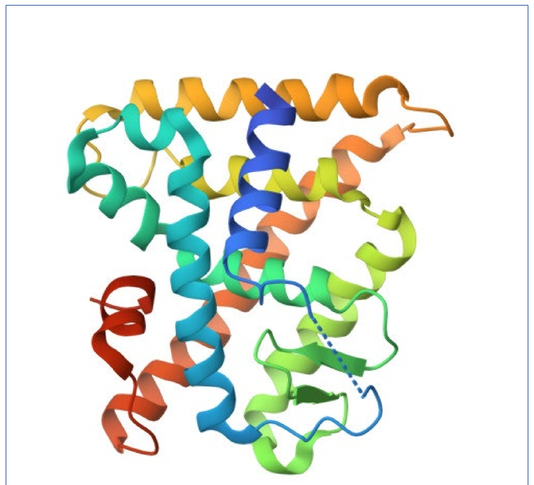
Endocrinology was consulted. Despite the most likely diagnosis of T1DM in children this age, an alternative differential of MODY was suspect due to the simultaneous presentation of the siblings and their relatively stable clinical picture. Based on this suspicion, both received a low dose of long-acting insulin (Glargine) and were sent home to follow up with endocrinology the following day.

At follow up, diabetes autoimmune panels were ordered for both siblings. Further questioning revealed a significant family history of apparent type 2 diabetes in the mother since early 20s, and in the maternal grandfather. The patients were kept on the same dose of Glargine with no fast-acting insulin coverage.

They returned three weeks later. The 18-year-old reported that he could not continue insulin due to low blood sugars, and the 11-year-old continued without issue. Diabetes autoimmune panels were negative for both siblings, so the patients were referred for genetic counseling and testing. Both siblings were positive for HNF4A autosomal dominant variant c.340 C>T p.(R114W), consistent with a MODY1 diagnosis (8). Both patients transitioned from insulin to glyburide (ideal therapy).

Conclusion

Although T1DM is the most likely diagnosis in children presenting with hyperglycemia, one must maintain a high index of suspicion of other less common etiologies. The early recognition and diagnosis of MODY is necessary to ensure appropriate management and aid patients with long term management.



HNFA4 Molecular Structure (8)

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