The Genetics Corner: A Genetics consultation for a Family History of Permanent Neonatal-Onset Diabetes Mellitus

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Case History:

A genetics consultation was requested for a 2 day old term AGA male infant of a poorly controlled diabetic mother, whose gestation was complicated by two admissions for uncontrolled diabetes mellitus (DM) with ketoacidosis treated with insulin. Mother's HbA1c was elevated x3 (8.8 at 14 weeks, 8 at 22 weeks 5 days and 7.2 at 27 weeks 4 days). She told her OB providers that she had "monogenic diabetes", but she did not provide any other information about her diagnosis. Birth weight was 3260 grams (43rd%ile.) The infant's glucose was closely monitored after delivery with a maximum level of 135 mg/dL on day 2 of life. His physical examination was normal. Echocardiogram revealed moderate right ventricular hypertrophy.

The family history was pertinent for early onset diabetes mellitus in the patient's mother, who was diagnosed at 4 months, and in all three siblings: a 9-year old maternal half-sister diagnosed at 7 days, an 8-year old maternal half-sister diagnosed at 30 days and a 4-year old maternal half-brother diagnosed at birth. The maternal grandfather and paternal grandmother had DM type II.

Consultant's report:

Permanent neonatal diabetes mellitus (PNDM, MIM 606176) is a monogenic form of diabetes mellitus characterized by persistent hyperglycemia in infants younger than 6 months. It is distinct from the typical childhood-onset autoimmune diabetes mellitus type I. Both autosomal recessive and autosomal dominant types of PNDM exist and five responsible genes have been identified: ABCC8, GCK, INS, KCNJ11, PDX1. Pathogenic variants in KCNJ11 are the most common cause of PNDM, accounting for 30% of affected patients. Syndromic PNDM also occurs: pancreatic agenesis can accompany cardiac defects (MIM 600001) or cerebellar agenesis (MIM 607194).

We suspected autosomal dominant PNDM in this child based on the early onset and vertical transmission of diabetes mellitus in his family. When we reviewed the medical records of the oldest affected child, we found that the molecular diagnosis had been established in 2009 when a heterozygous pathogenic variant had been identified in KCNJ11: c.602G>A.

KCNJ11 encodes the Kir6.2 subunit of the octameric ATP-sensitive potassium channel (KATP), which normally closes in response to glucose. This closure precipitates a cascade of events that leads to insulin secretion by pancreatic beta cells. Gloyn, et al. (2004) demonstrated that heterozygous activating mutations in KCNJ11 cause PNDM. Intrauterine growth retardation, polyuria, and dehydration, although not present in this case, are common. This channelopathy can also affect the central nervous system. When there are developmental delay and epilepsy, the condition is called DEND syndrome: developmental delay, epilepsy, and neonatal diabetes.

"This case illustrates the challenges of effective medical communication and documentation and offers many missed opportunities for genetic education and counseling. Although the diagnosis of PNDM had been made ten years prior, it did not "stick" and important information pertinent to the pregnant mother's diagnosis and management was not available to her providers. "

PNDM caused by KCNJ11 variants can be effectively treated with (often high dose) oral sulfonylurea (glibenclamide), which binds to the receptor, SUR1, and closes the KATP channel. Oral agents can be started as soon as the genetic disorder is confirmed.

Over the next several days, this infant's glucose levels rose, he was diagnosed with PNDM and treated with glyburide. Targeted variant testing for this familial change was ordered for the new baby, rather than the larger and more expensive gene panel. The mother's physicians were also made aware of the diagnosis. They ordered targeted variant analysis for the familial variant in her and transitioned her therapy from insulin to oral sulfonylurea.

This case illustrates the challenges of effective medical communication and documentation and offers many missed opportunities for genetic education and counseling. Although the diagnosis of PNDM had been made ten years prior, it did not "stick" and important information pertinent to the pregnant mother's diagnosis and management was not available to her providers. The mother was informed about her daughter's and her own diagnosis of PNDM, shortly after the birth of her first child, when she was a 17-year old primigravida. Her first affected daughter was in the NICU for five weeks. After discharge, she was referred for genetic outpatient follow up, but she was never seen (insurance authorization was requested but never received).

Although two more affected children were subsequently born, genetic testing had only been performed on her first affected daughter. No other family members had gene testing, including the mother. Ten years later, the mother remembered that she and

her children had "monogenic diabetes," but she did not recall the details, and nothing about this diagnosis was documented in her own medical record. The mother's obstetric providers presumed that she had DM type 1 and treated her as such, with insulin, with poor results.

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Practical applications:

1. All patients diagnosed with diabetes before the age of 6 months should undergo genetic testing for PNDM.

2. PNDM caused by KCNJ11 can be effectively treated with high dose oral sulfonylurea.

3. Genetic consultation is warranted in pregnant women and infants with "monogenic diabetes" because establishing the genetic diagnosis can change treatment

4. Be curious. When a genetic disorder is segregating in the family, search for test results in near relatives. With permission from the parent, health care providers can access medical records on older affected siblings.

References:

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The author has no relevant disclosures.

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