DIAGNOSE IT

Case Reports in Pediatric Endocrinology

BEST CHILDREN'S HOSPITALS U.S. News & World Report DIABETES & ENDOCRINOLOGY 2019-20

Spring 2020

DIAGNOSE IT is an ongoing series of case reports presented by Nursen Gurtunca, MD, and Pushpa A. Viswanathan, MD. This publication is designed to educate physicians and allied health care professionals through a discussion of some of the most interesting and complex cases seen within the Division of Endocrinology, Diabetes, and Metabolism at UPMC Children's Hospital of Pittsburgh.

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Case Overview

A 7-month-old full-term male infant, who was appropriate for gestational age (birth weight of 6lb 4oz/2840g), presented to the emergency department with concerns of decreased oral intake, weight loss, and fussiness. An abdominal ultrasound showed that he had gallstones. He was suspected of having cholecystitis and subsequently was scheduled for surgery. A preoperative laboratory evaluation showed significant hyperglycemia [320 mg/dL (18 mmol/L)], elevated beta-hydroxybutyrate [(3.16 mmol/L; reference range < 0.27)], normal venous pH (7.35) and bicarbonate (20 mmol/L), and elevated HbA1c (16.6%). His hyperglycemia persisted after treatment with fluids and antibiotics. A detailed family history revealed that his father had been diagnosed with type 1 diabetes mellitus (T1DM) at age 15 and treated with insulin for the past 10 years. Twin paternal half-brothers born prematurely had transient neonatal hyperglycemia that resolved spontaneously.

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1: What Is Your Working Diagnosis?

Reader's note:

Answer "a," "b," or "c" for each question.

The correct answers to all questions are on page 4.

❑ **a) Hyperglycemia due to the stress of acute illness**

❑ **b) T1DM**

❑ **c) Neonatal diabetes mellitus (NDM)**

Hyperglycemia due to acute illness, as in cholecystitis that was suspected in our patient, can occur.[1] However, the significantly elevated HbA1c level is suggestive of long-standing hyperglycemia. High blood sugar (> 300 mg/dL) that persists beyond a few days and family history are suspicious for diabetes mellitus. Although the presentation of diabetes mellitus after 6 months of age and paternal history of T1DM diagnosed at 15 years of age would suggest autoimmune diabetes mellitus in this patient, NDM may still occur up to 12 months of age. A key point in the history in this case is that the paternal twin half-brothers, who were slightly premature, had hyperglycemia in the newborn period. Although hyperglycemia in premature neonates is common, occurrence in this family is another clue for autosomal dominant inheritance.

It is now widely accepted that diabetes presenting before 6 months of age is unlikely to be autoimmune type 1 diabetes and indicates NDM, a subtype of monogenic diabetes.[2] Monogenic diabetes resulting from a single gene defect is inherited commonly as a dominant mutation. Recessive, non-Mendelian, and rarely, de novo inheritance have been reported.[3] Monogenic diabetes accounts for 1% to 6% of pediatric diabetes cases.[3] It is important also to consider NDM in infants presenting with hyperglycemia at 6 to 12 months of age. Important clues that should raise the suspicion of NDM in this age group are negative islet cell autoantibodies, the presence of congenital defects, IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, and elevated IgE), and unusual family history, such as in this patient.

2: How Would You Initially Manage This Patient?

❑ **a) Subcutaneous insulin administration (multiple daily insulin injections or continuous subcutaneous insulin infusion-CSII)**

❑ **b) Intravenous insulin infusion**

❑ **c) Oral sulfonylurea (SU)**

This patient did not need intravenous insulin infusion, as he was not acidotic. He was successfully managed and stabilized on small doses of subcutaneous insulin injections. However, his glucose levels were extremely variable with subcutaneous insulin, although his HbA1c level decreased from 16.6% to 7.6% after two months of subcutaneous insulin injections.

During the neonatal period and infancy, subcutaneous insulin dosing can be difficult due to small insulin doses, frequency of feeding, and variability of intake. Because of these factors, CSII can be considered for use in this patient population. Oral sulfonylurea should not be used for the initial stabilization of hyperglycemic infants with ketosis/acidosis.

3: What Is the **Practical** Next Step in the Clinical Approach to This Patient?

- ❑ **a) Autoantibodies for T1DM (glutamate decarboxylase, zinc transporter-8, insulin, and islet antigen-2 autoantibodies)**
- ❑ **b) Genetic testing for NDM**
- ❑ **c) Empiric trial of oral SU**

The best practice from a management standpoint is to perform genetic testing for NDM in this age group even though NDM due to monogenic gene defects is less likely in the 6- to 12-month age group. Testing for autoantibodies for T1DM can be considered. However, urgent genetic testing can resultin genetic diagnosis of NDM in one to two weeks and ensure more appropriate treatment. This approach will eliminate the lengthy hospital stay or repeat hospitalization for a trial of empiric SU treatment. An empiric trial of oral SU treatment may be considered in nonsyndromic NDM infants, especially when central nervous system disturbances are present. Such a trial, however, should only be pursued after initial stabilization.[2]

The most common causes of NDM are due to activating mutations in the *ABCC8* and *KCNJ11* genes encoding, respectively, the sulfonylurea receptor 1 (SUR1) and potassium inward rectifier (Kir6.2) subunits of the voltage-dependent potassium channel. Correct function of the potassium channel is necessary for the secretion of insulin in response to hyperglycemia. *ABCC8* and *KCNJ11* gene mutations account for approximately 40% of all cases of NDM.[6]

These mutations in *KCNJ11* and *ABCC8* can cause transient neonatal diabetes, permanent neonatal diabetes, or **D**evelopmental delay, **E**pilepsy and **N**eonatal **D**iabetes (DEND) syndrome.[6] While the mutations in *KCNJ11* identified so far all had been de novo or dominant mutations, *ABCC8* mutations causing NDM can be de novo or have either dominant or recessive inheritance.[4] Mutations in *KCNJ11* mostly (90%) cause permanent NDM, whereas mutations in *ABCC8* more often cause transient NDM (66%).[3]

Reaching a molecular diagnosis will have immediate clinical consequences for about half of the patients with NDM, as identification of a mutation in either of the two genes encoding the ATP-sensitive potassium channel allows switching from insulin injections to oral sulfonylureas. Ninety percent of patients with mutations in these two genes are sensitive to oral sulfonylurea treatment, and their glycemic control can be greatly improved by switching from insulin to sulfonylurea therapy.[5] This has led to international guidelines suggesting immediate referral for genetic testing after a clinical diagnosis of neonatal diabetes. This information also facilitates genetic counseling within the affected families and predicts clinical prognosis.

Our patient gene sequencing analysis revealed a heterozygous pathogenic mutation in *ABCC8* (c.3544C>T; p.R1182W) known to cause transient neonatal diabetes.

4: How Would You Adjust Your Treatment Plan?

❑ **a) SU transition as an outpatient**

❑ **b) SU transition as an inpatient**

❑ **c) CSII**

SU transition is best done as an inpatient in infants as they are at risk for severe hypoglycemia and ketosis; close monitoring is mandatory. Additionally, confirmatory testing such as pre- and postprandial c-peptide levels may be needed. It may be done in select cases as an outpatient, depending on the family's comfort level with diabetes and insulin management. CSII should be considered if the patient is not responsive to SU.

Our patient was readmitted at 9 months of age for the initiation of oral sulfonylurea treatment (0.3 mg/kg/day), which rapidly normalized blood sugars. Baseline c-peptide was 0.3 ng/mL and increased to 1.9 ng/mL after two doses. He achieved good glucose control, with his HbA1c level decreasing to 5.3% on SU. On follow-up, he experienced hypoglycemia, and the dose of SU was gradually decreased. He was eventually weaned off SU after 12 weeks. His HbA1c level, off any treatment, has remained at 5.3%. He has been growing appropriately for age and meeting developmental milestones on time.

Given the genetic diagnosis in the index case, the father was transitioned to oral SU and weaned off insulin before confirmatory genetic testing that was denied by his insurance. He rapidly achieved euglycemia on SU only, and his HbA1c level improved.

Clinical Pearls

1. Although *ABCC8* mutations lead to neonatal diabetes typically in the first 6 months of age, diagnosis of this monogenic cause after 6 months should be considered.
2. Urgent genetic testing should be pursued very early on in any infant with NDM. This will ensure appropriate treatment initiation and genetic counseling of the family.
3. Transient neonatal diabetes mellitus may relapse as permanent diabetes later in life.
4. Oral SU treatment may be effective even after many years of insulin treatment in patients with activating mutations of the potassium channel.[7]

Answers to Questions

1. (c) 2. (a) 3. (b) 4. (b)

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For a referral or consultation, please contact the Division of Endocrinology, Diabetes, and Metabolism at 412-692-5170.

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About the Division

The Division of Pediatric Endocrinology, Diabetes, and Metabolism at UPMC Children's Hospital of Pittsburgh provides diagnostic and therapeutic services for children with diabetes mellitus, hypoglycemia, and disorders of physical growth, sexual maturation, thyroid function, pituitary function, and calcium and phosphorous metabolism, as well as other gender disorders. Patients are evaluated in collaboration with multidisciplinary teams to come to a unifying diagnosis and provide the best outcomes for patients and families. For a referral or consultation, please contact us at 412-692-5170.
Visit us online at CHP.edu/Endocrinology.

About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 15th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2018) and ranking on *U.S. News & World Report's* Honor Roll of America's Best Children's Hospitals (2019–20).

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