Neonatal Diabetes Mellitus

An Update on Diagnosis and Management

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KEYWORDS

• Neonatal diabetes • Monogenic diabetes • Genetic • Insulin • Glyburide

INTRODUCTION

Diabetes mellitus most commonly occurs after the neonatal period and results from complex interactions between both environmental and incompletely penetrant genetic factors. Advances in molecular genetics over the past decade hastened the realization that diabetes that occurs very early life is most often due to underlying monogenic defects, disorders caused by mutations in a single gene. Neonatal (or congenital) diabetes mellitus (NDM) is now known to occur in approximately 1 in 90,000 to 160,000 live births.[1] There are more than 20 known genetic causes for NDM.

NDM may be categorized by phenotypic characteristics into transient, permanent, and syndromic forms. In a large international cohort study of 1020 patients clinically diagnosed with diabetes before 6 months of age, 80% had a known genetic diagnosis.[2] Mutations in *KCNJ11* and *ABCC8* (affecting the pancreatic beta-cell potassium [K]-ATP channel) may be treated with oral sulfonylureas (SUs) and account for about 40% of these patients. Preliminary studies indicate that early SU treatment, in contrast to insulin, may improve neurodevelopmental outcomes in SU-responsive patients.[3] It is important to diagnose monogenic diabetes as early as possible, as it can predict the clinical course, explain additional clinical features, and guide appropriate management for patients.[4]

HYPERGLYCEMIA IN THE NEONATAL PERIOD

Although neonatal diabetes may be recognized within the first few days of life, there are alternative causes of hyperglycemia in neonates, which can make the diagnosis of diabetes difficult. This difficulty is especially true in the preterm or

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low-birth-weight infant.[5] The prevalence of high glucose levels in preterm infants is 25% to 75%.[6,7] Neonatal hyperglycemia is more common in the first 3 to 5 days after birth but can be found in infants at up to 10 days of life; it usually resolves within 2 to 3 days of onset.[8]

Typical causes for hyperglycemia in this group include increased parenteral glucose administration, sepsis, increased counter-regulatory hormones due to stress, and medications, such as steroids.[8] There is some evidence of insufficient pancreatic insulin secretion and relative insulin resistance in hyperglycemic and nonhyperglycemic critically ill preterm neonates.[6,9] However, there is no clear consensus related to the treatment of neonatal hyperglycemia; many institutions may follow personalized approaches. In the neonatal intensive care unit at the University of Chicago, patients are commonly placed on insulin when point-of-care dextrose persistently reaches 300 mg/dL or greater. Related literature suggests that intervention may be warranted when blood sugar levels are greater than 180 mg/dL. However, because of the low risk of short-term hyperglycemia in neonates and the high risk of insulin-induced hypoglycemia, Rozance and Hay[8] recommend reserving insulin therapy for severe hyperglycemia, defined as glucose levels greater than 500 mg/dL. Another consideration is that significant osmotic changes leading to ventricular hemorrhage may occur at glucose levels greater than 360 mg/dL.[9] Regardless of the cause of hyperglycemia, the authors recommend intervention with insulin when glucose levels are persistently more than 250 mg/dL. Irrespective of the glucose threshold, patients with persistent elevations should be started on an intravenous insulin infusion, although in some circumstances subcutaneous insulin could be considered (discussed in detail later).

Term infants and premature infants born at greater than 32 weeks' gestational age (GA) are more likely to have a monogenic cause for their diabetes than are very premature infants born at less than 32 weeks' GA.[5] However, according to the same study, 31% of all preterm infants with diabetes born at less than 32 weeks' GA were diagnosed with a monogenic cause, strongly suggesting that such infants should have genetic testing.[5] These preterm infants also tend to present earlier with diabetes (around 1 week of age) compared with full-term infants (around 6 weeks of age). Data gathered from the Monogenic Diabetes Registry at the University of Chicago and others show that patients with transient forms of neonatal diabetes present earlier on average (most often within days of birth) as compared with those with permanent forms.[1,10,11]

NDM should be considered in infants with insulin-dependent hyperglycemia, with blood glucoses persistently greater than 250 mg/dL, without an alternative cause. Neonatologists should become suspicious of diabetes when hyperglycemia persists for longer than 7 to 10 days. Some literature alternatively suggests pursuing genetic testing when hyperglycemia persists beyond the first 2 to 3 weeks of life.[9] However, genetic testing should be sent immediately in patients who present with acute extreme hyperglycemia (serum glucose >1000 mg/dL) without an identified cause, regardless of the time course. Of note, some forms of NDM, such as 6q24, may be transient, presenting only for a few days to weeks before resolving. The authors recommend sending genetic testing immediately, even if hyperglycemia resolves.

The initial assessment of children with suspected disease should include laboratory assessment of urine ketones, serum glucose, C peptide, and insulin. A pancreatic ultrasound should be performed, as the presence or absence of a pancreas will guide diagnosis and therapy considerations. The timing of the appearance of diabetes-related autoantibodies in neonates has not been well studied. Literature analyzing antibodies in the offspring of parents with type 1 diabetes (T1D) conclude that maternal antibodies may be present in the neonate for up to 6 months. In addition, specific detection of insulin antibodies after 6 months of age was associated with