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Neonatal Diabetes Mellitus: An Update on Diagnosis and Management

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Synopsis

Neonatal diabetes mellitus (also termed congenital diabetes, or diabetes of infancy) is highly likely to be due to an underlying monogenic defect when it occurs under 6 months of age. Early recognition and urgent genetic testing are important for predicting the clinical course and raising awareness of possible additional features, and in many cases these are essential for guiding appropriate and cost-effective treatment. Additionally, early treatment of sulfonylurea-responsive types of neonatal diabetes may improve neurological outcomes. It is important to distinguish neonatal diabetes mellitus from other causes of hyperglycemia in the newborn. Other causes include infection, stress, inadequate pancreatic insulin production in the preterm infant, among others. Insulin-dependent hyperglycemia that persists longer than a week should raise suspicion for neonatal diabetes mellitus and prompt genetic testing.

This review explores the diagnostic approach, mutation types, management and clinical course of neonatal diabetes.

Keywords

neonatal diabetes; monogenic diabetes; genetic; insulin; Glyburide

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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 mutation(s) in a single gene. Neonatal (or congenital) diabetes mellitus (NDM) is now known to occur in approximately 1 in 90,000-160,000 live births. [1] There are over 20 known genetic causes for neonatal diabetes mellitus.

NDM may be categorized by phenotypic characteristics into transient, permanent and syndromic forms. In a large international cohort study of 1,020 patients clinically diagnosed with diabetes prior to 6 months of age, 80 percent had a known genetic diagnosis. [2] Mutations in *KCNJ11* and *ABCC8* (affecting the pancreatic beta-cell K-ATP channel) may be treated with oral sulfonylureas and account for about 40 percent of these patients. Preliminary studies indicate that early sulfonylurea treatment, in contrast to insulin, may improve neurodevelopmental outcomes in sulfonylurea-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 the patient. [4]

Hyperglycemia in the Neonatal Period

While 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 is especially true in the preterm or low birth weight infant.[5] The prevalence of high glucose levels in preterm infants is 25-75 percent. [6,7] Neonatal hyperglycemia is more common in the first three to five days after birth, but can be found in infants up to 10 days of life; it usually resolves within two to three 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 non-hyperglycemic critically ill preterm neonates.[6,9] However, there is no clear consensus related to treatment of neonatal hyperglycemia and 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, due to the low risk of short term hyperglycemia in neonates and the high risk of insulin-induced hypoglycemia, Rozance et al.[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, we recommend intervention with insulin when glucose levels are persistently over 250 mg/dL. Irrespective of 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 below).

Term infants and premature infants born at > 32 weeks gestational age (GA) are more likely to have a monogenic cause for their diabetes than are very premature infants born at < 32 weeks GA. [5] However, according to the same study, 31 percent of all preterm infants with diabetes born at < 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 to 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 to 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 etiology. Neonatologists should become suspicious of diabetes when hyperglycemia persists for longer than seven to ten days. Some literature alternatively suggests pursuing genetic testing when hyperglycemia persists beyond the first two to three weeks of life. [9] However, genetic testing should be sent immediately in patients who present with acute extreme hyperglycemia (serum glucose greater than 1000 mg/dL) without an identified cause, regardless of time course. Of note, some forms of NDM such as 6q24 may be transient, presenting only for a few days to weeks before resolving. We recommend sending genetic testing immediately, even if hyperglycemia resolves.

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 presence or absence of a pancreas will guide diagnosis and therapy considerations. Timing of appearance of diabetes-related autoantibodies in neonates has not been well studied. Literature analyzing antibodies in the offspring of parents with type 1 diabetes conclude that maternal antibodies may be present in the neonate for up to six months. In addition, specific detection of insulin antibodies after six months of age was associated with developing disease. [12] We would therefore suggest that testing for autoantibodies within the first six months of life will not change the decision about mandatory genetic testing and thus may not be essential.

Neonatal diabetes may not always present in the immediate neonatal period. More recent studies show that monogenic forms of NDM may still occur up to 12 months of age, albeit at a reduced frequency. [1,13] The likelihood of monogenic diabetes causing hyperglycemia in children older than 12 months of age is much lower. Patients may present insidiously (with polyuria, polydipsia, or failure to thrive), acutely (with ketoacidosis or altered mental status), or incidentally without symptoms. [14]

Odds of presenting with diabetic ketoacidosis (DKA) increases with age; this is likely the result of difficulty recognizing early signs of diabetes in infancy.[1] Currently there is very little published regarding presenting signs and symptoms of diabetes in infancy. A recent

study at the University of Chicago, reported that 66.2% of subjects with monogenic diabetes, of all types, presented with DKA. [1] When patients present between six and 12 months of life, monogenic diabetes is less likely, but genetic testing should still be pursued. Antibodies for type 1 diabetes should be drawn, including glutamate decarboxylase (GAD 65), zinc transporter-8 (ZnT8), insulin and islet antigen-2 (IA-2) autoantibodies. Laboratory assessment should also include urine and serum ketones, serum glucose, serum insulin and c-peptide levels. Incidence studies in Europe show that the number of predicted new cases of type 1 diabetes in the zero to five-year age group will double by the year 2020. [15] Making the distinction of neonatal diabetes from type 1 diabetes as early as possible is paramount for management and treatment decisions.

Types of Diabetes

Prognosis and treatment options for monogenic forms of NDM depend heavily on which gene is affected. Advances in genetic testing have allowed for more efficient and comprehensive testing to be readily available. [16] Despite the fact that genetic testing is expensive, in the case of neonatal diabetes, it is clearly cost-effective largely because of the high proportion of patients whose treatment will improve on the basis of such testing. [17] Therefore, genetic testing is indicated for all cases of diabetes diagnosed under 12 months of age. Here we provide details on some of the most common forms of infancy-onset diabetes (Tables 1).

KCNJ11, ABCC8

Activating heterozygous mutations in the genes encoding either subunit of the ATP-sensitive potassium channel (K_{ATP} channel; *KCNJ11* or *ABCC8*) of the pancreatic beta-cell are the most common cause of permanent neonatal diabetes, and the second most common cause of transient NDM. [2] Combined, these mutations account for more than 50% of all cases of NDM. [18]

Mechanism of action—In the normal pancreatic beta-cell, increased glucose across the GLUT 2 transporter is metabolized by the enzyme glucokinase, resulting in increased production of ATP. This causes closure of the K_{ATP} channel, which in turn depolarizes the cell membrane, activating the influx of calcium through voltage-gated calcium channels that subsequently allows for exocytosis of insulin granules. *KCNJ11* encodes for the inner subunit (Kir6.2) of the K_{ATP} channel, while *ABCC8* encodes for the outer subunit (SUR1). Mutations in either gene cause the K_{ATP} channels to remain inappropriately “stuck open” even in the presence of hyperglycemia. Without channel closure, the cell membrane is not able to depolarize effectively, and thus, insulin cannot be released from the beta-cell.

Presentation—Although *KCNJ11*/*ABCC8* mutations typically lead to onset of diabetes before 6 months of age, diagnosis after 6 months is also possible. In a recent study of subjects diagnosed under one year of age, median age at diagnosis for *KCNJ11*/*ABCC8* subjects was 9.6 weeks (IQR 6.1-18.3 weeks).[1] Estimates of DKA frequency at diagnosis vary between 30-75%.[1,19,20] Intrauterine growth restriction, and thus small-for-gestational age birthweight, is common in patients with these conditions.

Treatment—While many patients may be managed with insulin during the initial hospitalization and diagnosis, the majority of patients with mutations in these genes can be treated with high dose sulfonylurea medications, often in high doses (typically 0.5-1 mg/kg/day of glyburide or even greater, depending mostly on the specific mutation). Sulfonylureas act on the K_{ATP} channel to promote closure, allowing for insulin to be released from the beta-cell. Use of sulfonylureas in pediatric patients is considered an off-label use and will be discussed below in more detail.

Associated features—Due to the presence of K_{ATP} channels in the brain, patients with mutations in *KCNJ11*, particularly those with permanent forms, may exhibit increased frequency of attention deficit hyperactivity disorder, sleep disruptions, developmental delays and seizures. [21,22] This may vary from mild delays without seizures to more severe delays with seizures (DEND syndrome). Patients with certain mutations may have such mild delays that they remain unnoticed by their caregivers and healthcare providers until they emerge later in life as specific deficits become apparent when compared to their unaffected siblings. [21] Sulfonylurea therapy may improve neurological function in addition to improving glycemic control, [23–25] and earlier initiation of sulfonylureas may offer more benefit. [3] These associations have not been as well characterized in patients with permanent *ABCC8* mutations or in transient forms of either gene.

6q24-related NDM

Overexpression of genes at chromosome 6q24 is the most common cause of transient neonatal diabetes. [26]

Mechanism of action—This NDM disorder can occur through any of three distinct mechanisms (Figure 1), most often epigenetic: uniparental disomy of chromosome 6 (UPD6; in which there are only two copies of 6q24 but both come from the father), duplication of the paternal 6q24 allele (in which there are three copies of 6q24, but two are from the father), or loss of maternal methylation (in which there is a defect in the silencing of the maternal allele, which can be recessively inherited). Paternal duplications are autosomal dominant, and thus carry a 50% transmission risk when inherited from the father. [27]

Presentation—Patients with 6q24-related NDM typically present within the first few days or weeks of life [28], usually without DKA. [1] Although the patient's hyperglycemia may go away within the first year or so of life, hypoglycemia is possible during the remission period. [29] Although the exact risk is uncertain, it appears to be highly likely that the hyperglycemia will return during the teenage years; this persists into adulthood in most cases. [28]

Treatment—Insulin is typically used during the early neonatal phase, although there is a possibility of response to sulfonylurea in some cases. [30] The best treatment option during the later relapse phase remains unclear, but these patients have been shown to have the ability to produce insulin and thus should not be treated as though they have type 1 diabetes. Although insulin has often been used in these older patients, recent studies have shown that non-insulin therapies used for type 2 diabetes may be highly effective. [31,32]

Associated features—Patients with 6q24-related neonatal diabetes may also present with macroglossia or umbilical hernia.

INS

Alterations in the insulin gene (*INS*) are the second most common cause of permanent neonatal diabetes. [33]

Mechanism of action—Mutations in the insulin gene appear in most cases to lead to mis-folding of the insulin protein. These proteins accumulate in various subcellular compartments and appear to increase endoplasmic reticulum (ER) stress and subsequent beta-cell death. [34,35,36]

Presentation—Patients with *INS* mutations may appear clinically similar to patients with early-onset type 1 diabetes. Although most cases will be diagnosed before 6 months of age, cases diagnosed near 12 months and even into the toddler years have been reported. Letourneau et al found a median age at diagnosis of 10 weeks (IQR 6.1-17.4) with 30% presenting in DKA.[1]

Treatment—Patients will require insulin therapy. Anecdotal evidence suggests that early, aggressive treatment with insulin may help to preserve some beta-cell function.

Associated features—No other specific features are known to be associated with *INS*-related neonatal diabetes.

Less common forms

Mutations in over 20 genes are now known to cause diabetes onset within the first year of life, but the majority of these are exceedingly rare recessive conditions. Among these more rare causes, a few are relatively more common and are worth mentioning, since early recognition of associated features can be important for long-term outcome:

GATA6, PDX1—*GATA6* and *PDX1* are transcription factors critical to pancreatic development. Mutations in either gene can result in a varying degree of pancreatic hypoplasia, including possible complete agenesis. [37] Insulin therapy, as well as pancreatic enzyme replacement therapy, is necessary for appropriate growth and glycemic control.

EIF2AK3—Homozygous mutations in *EIF2AK3* induce endoplasmic reticulum stress, and thus beta-cell death, and are the most common cause of NDM among consanguineous families. [2] Several other features may include episodic hepatic dysfunction and skeletal dysplasia; however, because these are usually not apparent in the neonatal phase, early genetic testing will help guide monitoring and management. [38] Insulin treatment is required.

FOXP3—Mutations in *FOXP3* cause a monogenic form of autoimmune diabetes, most often as part of IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). [39] Since associated features of IPEX are severe enough to often cause

death within the first year of life, stem cell transplantation is often considered. Early genetic diagnosis would be essential in guiding clinical decision-making.

Early-onset autoimmune type 1 diabetes

Most cases diagnosed with diabetes after 6 months of age will have autoimmune type 1 diabetes. Among subjects diagnosed less than 1 year of age, those with likely T1D had a median diagnosis age of 42.6 weeks (IQR 37.4-50.4) and 87.5% presented in DKA at diagnosis. [1] They may be less likely to have a low birth weight. The majority of these patients will test positive for at least one diabetes autoantibody. For those who have negative autoantibody and/or genetic testing, a type 1 diabetes genetic risk score assessment (most often done on a research basis) may be helpful to discern the true etiology. [37] There is some evidence to suggest that early-onset T1D cases may experience more aggressive beta-cell decline than those diagnosed at older ages.

Management Considerations

The initial approach to hyperglycemia includes assessing the quantity of glucose being administered, and reducing the GIR when it does not affect patient nutrition and growth. In the neonate, ideal glucose infusion rates should be 6-12 mg/kg/minute to maintain appropriate minimums for growth without inefficient conversion of energy to fat. [9] Patients with hyperglycemia are initially managed on an intravenous insulin infusion. Guidelines for dosing and titrating insulin infusions in neonates are lacking in the literature. In studies assessing early insulin therapy in very low birth weight infants, an initial dose of 0.05 units/kg/hour was commonly used. [6] However, other studies show effective glucose control with insulin rates ranging as low as 0.02 units/kg/hour, much lower than the standard dose of 0.1 units/kg/hour used in older children in DKA.[41] In infancy, insulin infusion rates should be titrated by small increments of 0.01 units/kg/hour in response to glucose levels less than 200 (decrease infusion rate) or greater than 250 mg/dL (increase infusion rate). However, dosing should ultimately be guided by clinical judgement. The capillary blood glucose (BG) level should be monitored at least every hour while on intravenous insulin infusion. When hyperglycemia is persistent and insulin dependence is established, the provider should consider transition to subcutaneous insulin injections, in part to avoid complications related to central venous catheters. This should be guided by recommendations from a Pediatric Endocrinologist.

Subcutaneous Insulin

Initial subcutaneous doses of insulin should be given conservatively, when blood glucose levels are at least above 200-250 mg/dL. We would recommend starting with pre-prandial short acting doses in the amount of 0.1-0.15 units per kilogram per dose, or doses guided by the response to intravenous insulin. The dose should be given prior to feeds when blood sugars are greater than 200-250 mg/dL. Due to frequency of oral intake in newborns, insulin should only be given pre-prandially. All pre-prandial blood sugars should be checked at least initially, but insulin doses may only be needed with every other feed (3-4 times per day). The smallest, feasible subcutaneous dose of any insulin, including long acting (glargine) and short acting (lispro or aspart), without dilution is 0.5 units.

Smaller doses of U-100 that would otherwise be immeasurable are possible by dilution, preferably with an insulin-specific compatible diluent (typically available through the manufacturers). Diluting one part of aspart or lispro to nine parts diluent will yield a concentration of one-tenth of the original concentration (U-10). Therefore, doses of 0.1-0.9 units of insulin (U-100) may be used as subcutaneous injections. Such a preparation of lispro may be used for up to 28 days when stored at 41 degrees F (and up to 14 days when stored at 86 degrees F) [42], while the preparation of aspart may be used up to 28 days when stored at 86 degrees F or less. [43] Of note, U-10 insulin aspart may be stable for up to 7 days at 98.6 degrees F or less when used in a continuous subcutaneous insulin infusion (CSII) pump (insulin pump). [44] However, diluted insulin is typically not necessary for use with insulin pumps because they are capable of administering very small doses of U-100 preparations (see below). Clinical personnel, patients and families should use caution with diluted preparations in the hospital and at home, due to potential for dosing errors.

Whether using diluted or undiluted insulin subcutaneously, we would recommend against use of intermediate-acting insulins such as regular and NPH, which have been associated with increased risk of hypoglycemia compared with short and long-acting analogs. [45] Although infants are feeding frequently and clinicians may be tempted to cover basal and bolus requirements with an intermediate insulin, when the feeding schedule ultimately becomes more spaced out, these infants will be at higher risk of hypoglycemia. Just as with older patients, infants should also be placed on a regimen of multiple daily injections of insulin (MDI) with daily or twice daily long-acting insulin and multiple daily doses of rapid-acting insulin to cover hyperglycemia and carbohydrate intake (ultimately using carbohydrate counting when feasible).

Carbohydrate estimation for breastfed infants can be challenging. If a patient is fed pumped breastmilk, carbohydrate content can be estimated at ~2.1 g per ounce of breastmilk. Resources are available to help caregivers estimate quantity of breastmilk, and subsequently, carbohydrates consumed. [46]

Continuous subcutaneous insulin infusion (CSII) therapy

During the neonatal period, dosing can be difficult due to frequent intake and variability in quantity. In addition, infants with neonatal diabetes are susceptible to hypoglycemia due to relatively low insulin requirements. [47] Subcutaneous insulin infusions allow for very small accurate doses to be given in a physiologic way, with a continuous basal dose (as low as 0.025 units/hr) that may be adjusted hourly. In addition, pump technology allows for frequent hyperglycemia or carbohydrate bolus coverage (with doses typically as low as 0.05 units) while minimizing the potential for dangerous ‘stacking’ of boluses.

All pediatric patients with diabetes (including neonatal diabetes), are candidates for CSII regardless of age. [48] Most observational studies have noted a decreased rate of hypoglycemic events, as well as reduced HbA1c, in those receiving CSII rather than MDI. [44]

When deciding on the type of insulin pump to use, the following should be considered:

1. Small basal rate increments to allow for lower hourly infusion rate. Different varieties of insulin pumps may have lowest setting of 0.025 units per hour versus

0.05 units per hour. It may also be important to consider using a pump which can be programmed to deliver no insulin (0.00 units/hr).

2. Communication with a home glucose meter, where data collected from the glucometer is electronically communicated to the pump directly.

3. Types of infusion sets and tubing. For babies with less subcutaneous fat, infusion sets utilizing a steel needle, or sets with a 30 degree insertion with a shorter cannula, may be more effective. Similar to older patients who have more lean mass and less fat, such catheters may be more effectively threaded into the subcutaneous tissue manually rather than using an inserter device. However, if using sites that have more fat—including the buttocks—a 90 degree insertion set may be used. One should consider that the buttocks may be a problematic site due to friction with clothing and diapers and exposure to stool. Of note, shorter tubing is generally preferred for small dose administration.

4. Alarm features

5. Waterproof casing in active children

In general, assessment of capillary blood sugars in early infancy can be difficult due to limited surface area and trauma related concerns. Continuous glucose monitoring can be a very helpful tool for glucose control and parental reassurance, regardless of treatment modality. Studies with continuous glucose monitoring systems (CGMS) in very low birth weight infants reveal higher prevalence of abnormal glucose levels as compared to standard sampling methods. A study by Iglesias et al. showed no adverse events associated with CGMs and, with less associated fibrosis as compared to adults, sensors may be placed for longer periods of time in preterm infants. [49] The thigh or upper buttock area in patients with little subcutaneous fat, provide ideal insertion sites for insulin pumps and CGMs. [50]

Sulfonylureas

Sulfonylurea-responsive mutations are the most common cause of neonatal diabetes. Up to 90-95% of patients with NDM caused by *KCNJ11* may be successfully transitioned completely off of insulin therapy with significant decrease in glycated hemoglobin levels. [19] In addition to the importance of the specific mutation, two large studies have also shown an association of improved and expedited response with initiation of therapy at an earlier age; this may result from impaired perinatal expansion or reduced replication of beta-cells with age. [51,52]

A significant proportion of patients exhibit a spectrum of neurodevelopmental disability related to the expression of mutated K-ATP channels in the brain, where sulfonylurea (SU) therapy may also lead to beneficial effects on neurocognitive development. [53] Patients with *KCNJ11* mutations have reduced general intellectual ability including reasoning, vocabulary, reading and auditory working memory, as compared to sibling controls. [21] There is some evidence for improved neurocognitive outcomes with SU therapy, but the degree of benefit may depend on earlier age of treatment. [23,47]

A trial of glyburide may be considered in newly diagnosed neonatal diabetes because of the relatively high chance of having a mutation responsive to treatment (Figure 2). In patients referred to the Monogenic Diabetes Registry, we found that there was a mean delay of 10 weeks from the time of diabetes diagnosis to genetic diagnosis of NDM (range 1.6 to 58.2 weeks). [30] Due to potential neurocognitive effects of delaying therapy, we thus suggest that a trial of sulfonylurea therapy can be considered even before a genetic diagnosis is made, although genetic testing must be done in all cases. In patients with NDM who are responsive to SU therapy, glycemic outcomes are favorable and side effects are minimal. [19] There is some risk of hypoglycemia, although the risk appears to be much lower compared to insulin therapy. [30]

Approach to transitioning from insulin to oral glyburide[19]

If the patient is on CSII (pump), the basal rate should be reduced by 50 percent prior to glyburide administration. The basal rate may be adjusted or suspended as needed to prevent hypoglycemia during transition. Glyburide tablets can be crushed and readily prepared in aqueous suspension; although the stability has not been well studied, we have not experienced any problems with use of such a suspension for 14 days. An initial dose of 0.1 mg per kilogram per dose twice daily before meals is most often used. Point of care blood glucose should be assessed at least pre-meal and at bedtime. On each subsequent day, if blood glucose is greater than 200 mg/dL at the time glyburide is due, the dose can be increased by 0.1 mg per kilogram per dose. The dose may thus be increased each day, progressing up to a dose of at least 1 mg/kg/day (usually achieved within 5-7 days) if pre-meal capillary blood sugars continue to be greater than 200 mg/dL. [30] If the patient's POC glucose is less than 200 mg/dL, the usual prandial insulin dose should be reduced by at least 50 percent. In addition, doses of insulin should only be administered at least 2-3 hours after glyburide is dosed to avoid hypoglycemia. Table 2 summarizes our general approach to transition from insulin to oral glyburide therapy.

The original protocol [19] used a blood glucose of 126 mg/dL as a threshold for dose titration. In our experience it is often better to allow a reasonable level of hyperglycemia so as to avoid hypoglycemia while insulin is also being given, especially in neonates. While it is very important to avoid extreme hyperglycemia, we have found 200 mg/dL to be a reasonable threshold for dose titration, but this may be altered based on specific clinical scenarios and the clinical judgment of the treating team.

Response to oral medications should be achieved in those with channel mutations including *KCNJ11* and *ABCC8*. However, some non-channel mutations such as 6q24 have been responsive to sulfonylurea therapy as well. [31] If desired effect is difficult to assess, glucose and c-peptide levels may be drawn before a meal and again 90-120 minutes after meal is eaten (and glyburide is given). Patients with appropriate response to glyburide should have an appreciable increase in c-peptide level following glyburide dosing and a meal. If no clinical response or appreciable C-peptide difference is seen, then SU treatment should be discontinued and the patient managed on insulin therapy until genetic testing results are available.

Glyburide transition may also be done as an outpatient, depending on the family's comfort level with diabetes and insulin management. Once insulin has been completely discontinued, or a steady dose of glyburide has been achieved, patients should continue to monitor blood glucose levels before meals and at bedtime. Patients should also see their provider monthly for the first 6 months, followed by every 3 months thereafter.

Conclusions

Neonatal diabetes mellitus is caused by a single gene mutation. These patients will most often present within the first six months of life, but less commonly may present up to 12 months of life. Early clarification of the molecular etiology by genetic testing is paramount. Patients with channel mutations, such as *KCNJ11* and *ABCC8*, can be transitioned to sulfonylurea agents, allowing for simplified administration, decreased treatment costs, and potential neurodevelopmental improvements. Genetic testing may also guide longitudinal monitoring for other associated problems in forms with syndromic features, as well as for screening of family members. Patients with 6q24 have a transient hyperglycemia in infancy with onset of diabetes in adolescence. It is important to distinguish monogenic neonatal diabetes mellitus from other causes of hyperglycemia in the newborn. Insulin-dependent hyperglycemia that persists longer than a week to ten days, should raise suspicion for an underlying monogenic cause of diabetes and prompt genetic testing.

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Best Practices Box

- There are over 20 known monogenic causes of neonatal diabetes mellitus, which may be transient or permanent (see Table 1).
- Genetic testing should be pursued in any infant with neonatal diabetes, even if hyperglycemia resolves. An underlying monogenic cause can lead to major differences in clinical management and is highly likely when diabetes is diagnosed under 6 months, and less likely but still possible in infants with diabetes between 6-12 months of age.
- Hyperglycemia due to stress or illness may occur in neonates, especially in those who are premature or had very low birth weight (Figure 2). Diagnosis of diabetes (and genetic testing) should be considered:
  - When hyperglycemia (glucose >250 mg/dL) persists beyond a few days without alternative explanation.
  - When true serum glucose levels exceed 300 mg/dL, regardless of time course.
  - In any infant requiring insulin before 6-12 months of age.
- In neonates or infants, we would recommend using CSII (continuous subcutaneous insulin injection), to titrate insulin more precisely and better control blood sugar levels.
- Sulfonylurea responsive mutations are the most common causes of neonatal diabetes and early treatment with sulfonylureas may improve neurocognitive deficits associated with these mutations. A trial of sulfonylurea (glyburide) may be considered even before genetic testing results are available (Figure 2).
- Depending on the age of the patient and comfort level of the family, transition insulin therapy to oral glyburide may be done inpatient or from home. See Table 2 for guidance on medication transition.

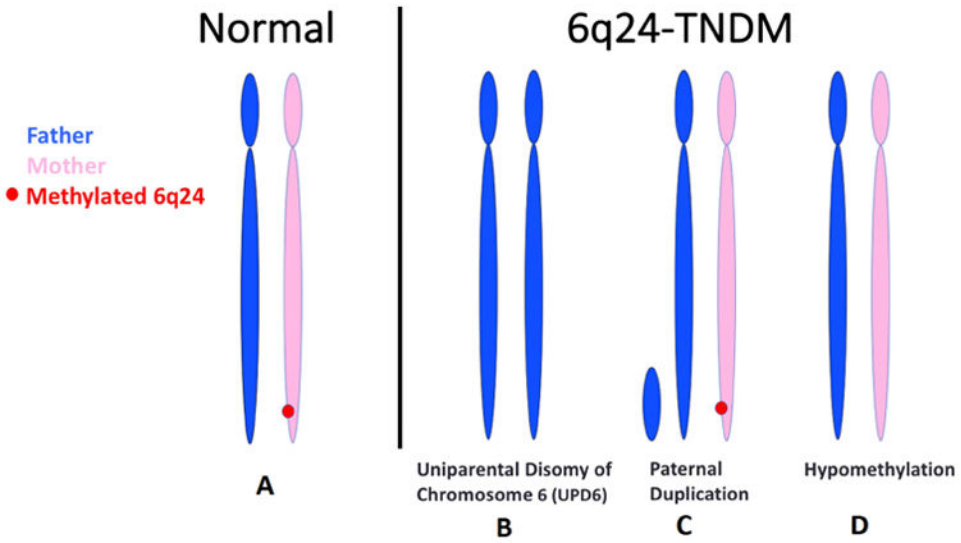

Figure 1.

Mechanisms of overexpression of imprinted genes causing 6q24-related neonatal diabetes. Diabetes in all cases results from overexpression of genes that are normally either silenced by maternal methylation or expressed when paternally inherited. Overexpression thus occurs when A) both copies are paternally inherited in uniparental paternal disomy (UPD6, which can be either complete disomy or heterodisomy), B) an additional copy is paternally inherited due to a duplication that includes 6q24, or C) there is a defect in maternal methylation (which can be due to recessive mutations in ZFP57). Although parent of origin determination or detection of duplication can be possible through a variety of methods, the most comprehensive direct way of testing of overexpression of genes at 6q24 from any cause is methylation-specific multiplex ligation-dependent probe amplification (MS- MLPA) or methylation-specific PCR/sequencing-based and is rarely offered in most commercial laboratories.

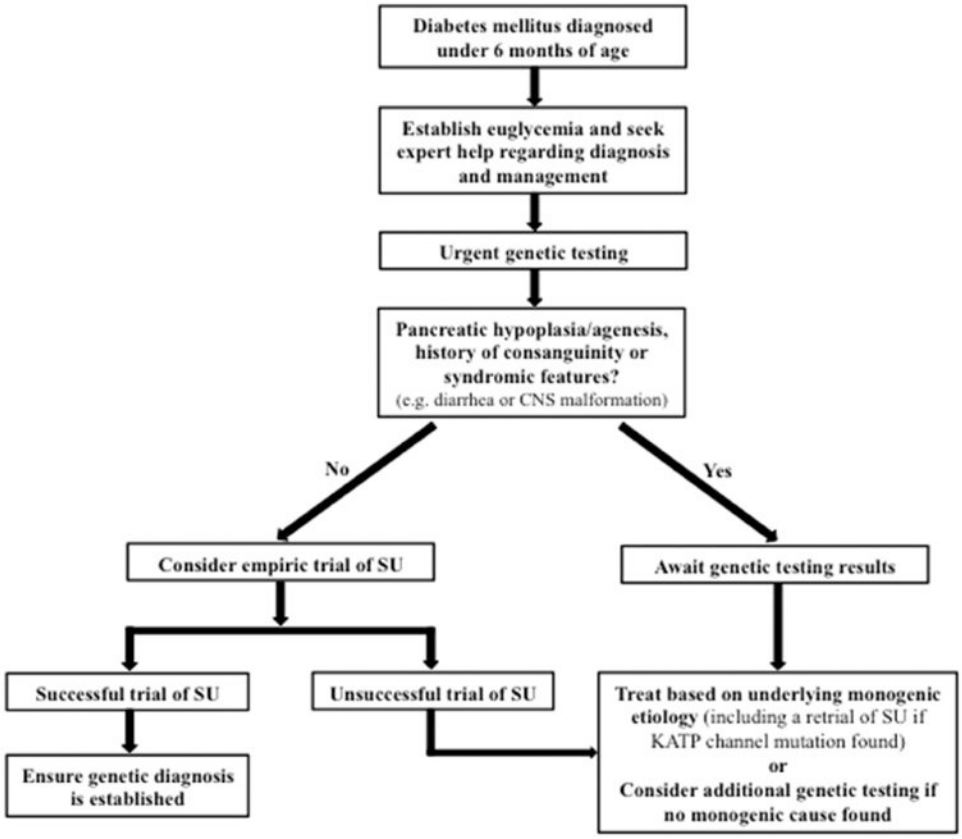

Figure 2.
Algorithm for considering sulfonylurea trial.

Table 1

All known monogenic causes of neonatal diabetes with associated features, from more common to less common (top to bottom).

Gene	Transient vs. Permanent	Inheritance	Features	Treatment
KCNJ11	Either	Spontaneous (80%), AD (20%)	Low birthweight, developmental delay, seizures (DEND syndrome), may have other neurologic features	Insulin Sulfonylurea
ABCC8	Either	Spontaneous, AD	Low birthweight	Insulin Sulfonylurea
6q24	Transient	Spontaneous, AD for paternal duplications	Low birth weight, possible IUGR; Diagnosed earlier than channel mutations (closer to birth); relapsed cases may respond to SU	Insulin
INS	Either	Spontaneous (80%), AD (20%) AR (Rare--T or P)	Low birthweight	Insulin
GATA6	Permanent	Spontaneous, AD	Pancreatic hypoplasia or agenesis; exocrine insufficiency; cardiac defect	Insulin
EIF2AK3*	Permanent	Spontaneous, AR	Wolcott-Rallison syndrome; skeletal dysplasia (1-2 years old) episodic acute liver failure; exocrine pancreatic insufficiency	Insulin
GCK*	Permanent	Spontaneous, AR (neonatal diabetes), AD (GCK-MODY)	Low birthweight	Insulin
PTF1A	Permanent	Spontaneous, AR	Neurologic abnormalities, exocrine insufficiency, kidney involvement	Insulin
FOXP3	Permanent	X-linked	Autoimmune thyroid disease; exfoliative dermatitis; enteropathy (IPEX syndrome)	Insulin
ZFP57	Transient	Spontaneous, maternal Hypomethylation Imprinting	Variable phenotype Low birth weight, macroglossia, developmental delay	Insulin
GLIS3*	Permanent	Spontaneous, AR	Hypothyroidism, kidney cysts, glaucoma, hepatic fibrosis	Insulin
PDX1	Permanent	Spontaneous, AR (neonatal diabetes), AD (PDX1-MODY)	Pancreatic hypoplasia or agenesis; exocrine insufficiency	Insulin
SLC2A2	Either	Spontaneous, AR	Fanconi-Bickel syndrome (hepatomegaly, RTA)	Insulin
SLC19A2	Permanent	Spontaneous, AR	Neurologic deficit (stroke, seizure) Visual disturbance; cardiac abnormality	Insulin Thiamine (rarely)
GATA4	Permanent	Spontaneous, AR	Pancreatic hypoplasia or agenesis; exocrine insufficiency; cardiac defect	Insulin
NEUROD1	Permanent	Spontaneous, AR	Neurological abnormalities (later), learning difficulties, sensorineural deafness	Insulin
NEUROG3	Permanent	Spontaneous, AR	Diarrhea (due to lack of enteroendocrine cells)	Insulin
NKX2-2	Permanent		Neurological abnormalities (later), very low birth weight	Insulin
RFX6*	Permanent	Spontaneous, AR	Low birthweight; intestinal atresia, gall bladder hypoplasia; diarrhea	Insulin
IER3IP1*	Permanent	Spontaneous, AR	Microcephaly; infantile epileptic encephalopathy	Insulin
MNX1*	Permanent	Spontaneous, AR	Neurological abnormalities (later)	Insulin
HNF1B	Transient	Spontaneous, AD	Pancreatic atrophy, abnormal kidney and genitalia development	Insulin

AD, autosomal dominant; AR, autosomal recessive; DM, diabetes mellitus; IUGR, intrauterine growth restriction; NDM, neonatal diabetes mellitus; MODY, maturity onset diabetes of the young; SGA, small for gestational age.

*AR forms may be more likely in populations or families with known consanguinity.

Table 2

Transition from insulin to oral sulfonylurea (SU) therapy (specifically glyburide).

Day	Glucose Monitoring	Insulin Adjustments	Glyburide Dosing
Prep	Monitor capillary blood glucose (BG) before meals, 2 hours post meals, bedtime and 2 a.m. Monitor ketones when BG >300 Have a plan for hypoglycemia	Maintain usual insulin regimen via pump or customary basal-bolus injections. Reduce basal insulin by 50% (Pump: decrease before breakfast on day 1 Long acting: reduce in the evening before transition)	Tablets available (may be halved): 1.25, 2.5, or 5 mg For infants, tabs may be crushed and suspended in formula or water.
1	Monitor capillary BG before meals, bedtime and 2 a.m. If BG before meal is: >200 mg/dL (11.1 mmol/L)➔ <200 mg/dL (11.1 mmol/L)➔	Administer rapid acting bolus insulin as needed based on capillary BG (unless glyburide given within last 2 hours *): ➔Give usual bolus dose ➔Give 50% of usual insulin dose	Start with 0.1 mg/kg before breakfast and dinner (total 0.2 mg/kg/day) Depending on BG at second dose, consider skipping dose if BGs trending low.
2-7	Monitor capillary BG before meals, bedtime and 2 a.m. If BG before SU dose is: >200 mg/dL (11.1 mmol/L)➔ <200 mg/dL (11.1 mmol/L)➔	Continue to wean down basal dose as tolerated. Administer rapid acting bolus insulin as needed based on capillary BG: ➔Give bolus dose from previous day ➔Decrease bolus dose by 50%	Each day dose dose will increase by 0.2 mg/kg/day (0.1 mg/kg/dose) depending on BGs: ➔increase dose by 0.1 mg/kg ➔Continue dose from previous day
Last	On final day and after discharge continue checking BG at least prior to every meal/feed, bedtime and 2 a.m. to monitor response. Relative hypoglycemia may necessitate lowering of glyburide dose in following weeks to months.	In most SU-responsive cases, insulin can be discontinued in 5-7 days, although mild hyperglycemia may occur. Treat with last titrated short acting bolus insulin as needed. In some cases, low-dose basal insulin may be needed as well.	By the end of 5-7 days, the patient will have either clearly responded to a lower dose or will be on at least 1 mg/kg/day. The dose may continue to be increased after discharge, with some patients requiring up to 2-2.5 mg/kg/day (which may be lowered in the following weeks to months.
Notes	If expected response is uncertain, c-peptide levels pre and post (90-120 minutes after) meal and glyburide (no insulin) may be done, particularly when dose maximized at 1 mg/kg/day. If levels pre SU are nearly undetectable but show a significant increment on glyburide, responsiveness is likely. Consider further increase up to 2-2.5 mg/kg/day as needed.	BG ranges and insulin adjustments are only a guideline; the physician should be guided by clinical judgement. If there is any indication that glyburide is helping to control BG levels overall, it is often better to decrease the insulin aggressively so as to avoid hypoglycemia.	Patients with neurodevelopmental disability or those who are older at the time of transition may require higher doses of glyburide. In such cases, the possible benefit of continuing a high dose for the long term should be carefully considered even if the patient still requires insulin.

* If glyburide was given in last 2 hours or with current BG check, recheck with next feed only, do not give insulin.