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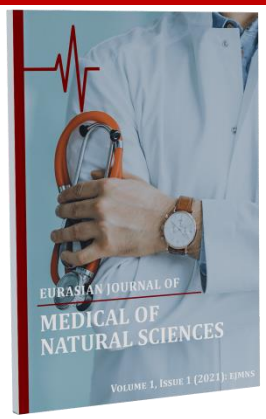

DIABETES MELLITUS IN NEWBORNS

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ABSTRACT

This article provides a comprehensive exploration of diabetes mellitus in newborns, delving into its causes, diagnostic methods, and treatment options. By highlighting the genetic and autoimmune factors contributing to neonatal diabetes, it offers valuable insights for medical professionals. The discussion on clinical symptoms and genetic testing aims to enhance early detection, enabling prompt intervention. Emphasizing the significance of insulin therapy and long-term management, the article addresses the complex nature of diabetes in newborns. Additionally, it underscores the potential impact on developmental aspects, advocating for proactive measures and holistic care. Overall, the article serves as an informative guide for healthcare professionals and families navigating the intricacies of diabetes mellitus in the neonatal context.

Introduction. Rarely, neonates can be affected by diabetes mellitus, a condition usually associated with adults. This presents special challenges and calls for specialized care. This article clarifies this uncommon but serious health issue by examining the causes, symptoms, diagnosis, and treatment of diabetes mellitus in newborns. When it manifests before the age of six months, neonatal diabetes mellitus—also known as congenital diabetes or diabetes of infancy—is most likely caused by an underlying monogenic defect. In many cases, early detection and prompt genetic testing are crucial for guiding appropriate and economical treatment, as well as for projecting the clinical course and bringing to light potential additional features. In addition, enhanced the neurological outcomes may result from early treatment of neonatal diabetes treated with sulfate 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 examines the types of mutations, management strategies, and clinical trajectory of neonatal diabetes.

Although it can be identified in the first few days of life, there are other reasons why newborns experience hyperglycemia, which can complicate the diagnosis of diabetes. This is particularly valid for infants who are low birth weight or preterm. Between 25 and 75 percent of preterm infants have elevated glucose levels. Although it can occur in infants as late as 10 days of life, neonatal hyperglycemia is more common in the first 3–5 days after birth and usually goes away in 2–3 days.

In this group, increased parenteral glucose administration, sepsis, elevated stress-related counter-regulatory hormones, and medication are common causes of hyperglycemia. 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. 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. 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 .

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. 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. 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.

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. 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.

Neonatal Diabetes (ND) mellitus is a rare genetic disease (1 in 90,000 live births). It is defined by the presence of severe hyperglycaemia associated with insufficient or no circulating insulin, occurring mainly before 6 months of age and rarely between 6 months and 1 year. Such hyperglycaemia requires either transient treatment with insulin in about half of cases, or permanent insulin treatment. The disease is explained by two major groups of mechanism: malformation of the pancreas with altered insulin-secreting cells development/survival or abnormal function of the existing pancreatic βcell. The most frequent genetic causes of neonatal diabetes mellitus with abnormal βcell function are abnormalities of the 6q24 locus and mutations of the ABCC8 or KCNJ11 genes coding for the potassium channel in the pancreatic βcell. Other genes are associated with pancreas malformation or insufficient βcells development or destruction of βcells.

Clinically, compared to patients with an ABCC8 or KCNJ11 mutation, patients with a 6q24 abnormality have lower birth weight and height, are younger at diagnosis and remission, and have a higher malformation frequency. Patients with an ABCC8 or KCNJ11 mutation have neurological and neuropsychological disorders in all those tested carefully. Up to 86% of patients who go into remission have recurrent diabetes when they reach puberty, with no difference due to the genetic origin. All these results reinforce the importance of prolonged follow-up by a multidisciplinary pediatric team, and later doctors specializing in adult medicine. 90% of the patients with an ABCC8 or KCNJ11 mutation as well as those with 6q24 anomalies are amenable to a successful switch from insulin injection to oral sulfonylureas.

CLINICAL DESCRIPTION. Depending on how long a baby has been insulin-dependent, there are two clinical types of neonatal diabetes. Treatment in the transient form can be discontinued at any point between the initial weeks of life and age five. Treatment for the permanent forms must last forever.

The clinical difference between transient and permanent neonatal diabetes is not always underpinned by distinct molecular mechanisms. Abnormalities of the 6q24 locus are exclusively linked to transient neonatal diabetes. However, mutations of the ABCC8,KCNJ11, and INS genes are linked to both permanent and transient forms (17,18,25). Other genetic causes are associated with permanent neonatal diabetes. Neonatal diabetes is usually diagnosed before 6 months of age. However, the age of diagnosis varies depending on genetic causes:

diabetes due to a 6q24 locus abnormality appears before the age of 1 month in 93% of cases and before the age of 3 months in 100% of cases. In ABCC8 and KCNJ11 gene mutations, it appears before the age of 1 month in 30% of cases and between 1 and 6 months in 66% of cases.

At birth, patients have a birth-weight below the 10th percentile in 62% of cases , highlighting the crucial role of insulin secretion in fetal growth. This intrauterine growth retardation is found in all genetic groups with a greater proportion in patients

with a 6q24 abnormality than those carrying a ABCC8 or KCNJ11 mutation (92 vs. 48%, $p<0.001$).

Half of patients with a detectable pancreas by ultrasound experience remission from the diabetes in our cohort. This occurs at the age of about 4 months. There is a difference

depending on the genetic cause. Patients with a 6q24 locus abnormality are in remission before the age of 1 year in 97% of cases (median age 14 weeks) while remission may go as far as the age of 5 years in patients with an ABCC8 or KCNJ11 mutation (median age 39 weeks) (4,31). Patients with a rare recessive mutation of the INS gene have remission at a median age of 12 weeks (24), whereas the majority of the INS gene mutations are dominant and they never go into remission. The diabetes frequently relapses (in up to 86% of cases) at the onset of puberty, probably due to the insulin resistance of puberty (4,32). There is no difference between the genetic groups. Depending on the genetic cause, patients with neonatal diabetes may have other clinical signs associated with diabetes.

There are neurological disorders and developmental defects associated with neonatal diabetes with normal pancreatic morphology. Neurological disorders ranging from psychomotor disorders to delayed cognitive development associated with severe epilepsy (known as DEND syndrome, or developmental delay, epilepsy, and neonatal diabetes) modify about 25% of patients who have a mutation in the ABCC8 or KCNJ11 genes. Furthermore, we discovered that a 100% of patients with thorough neuro-psychomotor and neuropsychological testing have a language disorder or attention deficit that moves to dyslexia.

Patients with a 6q24 locus abnormality may have developmental defects (macroglossia, umbilical hernia,cardiac malformations, renal and urinary malformations,non-autoimmune anemia, hypothyroidism with gland in situ)and neurological disorders . In neonatal diabetes with abnormal pancreas morphology or with βcell destruction, the associated malformations depend on the genetic causes and are often grouped into defined syndromes (Table 1). Figure 2 illustrates a diagnostic strategy by molecular biology.

Recent long-term follow-up data in TNDM support a decrease in maximal insulin secretion capacity to both glucose and arginine stimuli that reflect low insulin mass . This study also showed that, regardless of the underlying genetic abnormalities or the duration of diabetes, TNDM was associated with learning difficulties at school. The high relapse rate and absence of identified predictors of relapse in TNDM suggest a need for an HbA1c assay at least every 2 years throughout childhood and for an HbA1c assay and oral glucose tolerance test every year throughout adolescence (34). During childhood, close attention should be directed to education and neurodevelopmental milestones, in TNDM patients with and without diabetes.

Drug Treatment. Due to the early onset and associated delayed intrauterine retardation, patients with neonatal diabetes very often receive their initial treatment in a neonatal department. The initial treatment aims to rebalance carbohydrate metabolism. It should be started immediately following diagnosis. The treatment consists of the balance between a calorie and carbohydrate intake necessary to restore normal weight without being excessive to avoid the risk of future insulin resistance (15–18 g/kg/d carbohydrate) and sufficient insulin-based treatment to achieve the correct metabolic equilibrium. Restricting intake below the nutritional recommendations for children with low birth weight is ineffective given the physiopathology of circulating insulin deficiency.

Insulin-based treatment is difficult to manage due to the very low weight. The therapeutic margins between hypoglycemia and hyperglycemia are small, and both are

harmful for neurological development of the newborn. Using an insulin pump with or without dilution of the insulin to 1:10 in 0.9% NaCl (or with a bona-fide diluent if available) can sometimes improve manageability of the insulin during the first weeks of life. Blood glucose meters must be able to give a reliable measurement of capillary blood sugar level with the smallest possible quantity of blood (e.g., 0.3 µl blood). Few "conventional" blood glucose meters meet this criterion. Conventional capillary measurements can be done on the side edge of all the fingers, using auto-lancets offering variable pricking depths. This offers the advantage of sparing newborns' heels. An alternative is to use continuous glucose sensors, either isolated or combined with an insulin pump. In addition to enabling rapid access to interstitial blood glucose (they provide a proxy but do not actually measure the blood glucose value), they can now be coupled to the insulin pump, making it possible to activate the system to stop the insulin pump during hypoglycemia or before it occurs. They also have the advantage of minimizing the number of pricks of the skin. Used under suitable hygiene conditions, there is no increase in skin infections. It is advisable to involve experienced clinicians when treating the child and using these techniques. Patients with ABCC8 or KCNJ11 mutations are treated successfully using hypoglycemic sulfonylureas, which act by binding to the regulator SUR1 subunit of the potassium channel . The mutated channels remain sensitive to sulfonylureas in 90% of cases, having an inhibitory effect on the potassium channel of the pancreatic βcell and restoring insulin secretion in response to a meal.

Sulfonylurea therapy appears to be safe and often successful in neonatal diabetes patients before genetic testing results are available. An empiric inpatient trial of sulfonylurea can be therefore considered . However, obtaining a genetic diagnosis remains imperative to inform long-term management and prognosis.

It has now been demonstrated that treatment with Sulfonylureas provide a better metabolic equilibrium than insulin by normalizing the HbA1c while strongly reducing the incidence of hypoglycemia in cases of neonatal diabetes with ABCC8 or KCNJ11 mutations. It was also shown recently that hypoglycemic sulphonylureas were able to improve neurological, neuropsychological and visuomotor impairment if they are introduced early in the child's life . Finally, a recent study has shown that it could sometimes be used successfully to replace insulin in neonatal diabetes associated with chromosome 6 methylation abnormalities. This emphasizes the importance of making a genetic diagnosis rapidly after diagnosing neonatal diabetes, and especially the early introduction of sulphonylureas. The clinician's aim will be to treat the child with the maximum dose that normalizes blood glucose levels (pre-prandial target: 70–120 mg/dL—post-prandial target: 100–145 mg/dL) without causing hypoglycemia, in order to optimize the drug's effect on the central nervous system. Sulphonylureas are currently only available as a 5 mg tablet and are not licensed for indications in neonatal diabetes. However, glibenclamide has recently obtained the orphan-drug indication from the European Medicine Agency (EMA) in neonatal diabetes. Unlicensed administration is currently achieved by parents through crushing and extemporaneous dilution of the tablets. However, the crushed tablets are poorly soluble in water, which may lead to variations in the dosage actually received by the child. To resolve this problem, a sulphonylurea suspension called AmglidiaRhas demonstratable efficacy in this indication.

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