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Neonatal Diabetes Mellitus: A Focused Review on Beta Cell Function Abnormalities

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Neonatal diabetes mellitus, or congenital diabetes mellitus, is a rare genetic disorder caused by abnormal β cell function and other causes. The symptoms of hyperglycemia that occur in neonatal diabetes. The symptoms of hyperglycemia that occur in neonatal diabetes may be transient or persistent. The most frequent genetic cause of neonatal diabetes characterized by abnormal β cell function is abnormalities at the 6q24 locus. Another possible cause is mutations in the *ABCC8* or *KCNJ11* genes, which code for potassium channels in pancreatic β cells. This underscores the importance of rapid genetic diagnosis following neonatal diabetes diagnosis and highlights the critical timing of sulfonylurea use.

Key words: Neonatal diabetes mellitus, Gene, 6q24, K_{APT} channels

REVIEW ARTICLE

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INTRODUCTION

Neonatal diabetes mellitus, also known as congenital diabetes mellitus, is a rare genetic disorder with an incidence of approximately 1 in 10,000 live births [1,2]. Neonatal diabetes is defined as diabetes diagnosed within the first six months of life [3]. Although diabetes generally arises from complex interactions between environmental and genetic factors, neonatal diabetes arises specifically from genetic defects [2]. Neonatal diabetes is primarily associated with abnormalities in the development and secretion of insulin-producing cells in the pancreas, or with dysfunction of pancreatic β cells. The most frequent genetic causes of neonatal diabetes characterized by abnormal β-cell function include abnormalities at the 6q24 locus and mutations in the *ABCC8* or *KCNJ11* genes, which code for potassium channels in pancreatic β cells [1,2].

Other genetic anomalies have been reported, which are associated with pancreatic development, abnormalities in β cell differentiation, and apoptosis [4]. Neonatal diabetes is classified based on insulin dependency into the transient (temporary) and permanent [3] forms. In the transient form, treatment can be discontinued at any time from the first few weeks up to age five years, whereas the permanent form requires lifelong treatment. The clinical differences between transient and permanent neonatal diabetes are not always associated with distinct molecular mechanisms. Abnormalities at the 6q24 locus are solely associated with transient neonatal diabetes, whereas mutations in *ABCC8*, *KCNJ11*, and *INS* are linked to both permanent and transient forms [5-7]. Other genetic factors are also associated with permanent neonatal diabetes [4]. At birth, 62% of neonates have a birth weight below the 10th percentile, underscoring the critical role of insulin secretion in fetal growth [3]. In patients with transient diabetes, the condition recurs at the onset of puberty in 86% of cases, likely due to insulin resistance

associated with puberty [8]. No differences were observed among the genetic groups, and neonatal diabetes can be accompanied by neurological disorders and developmental defects [9]. Genetic analysis can diagnose monogenic diabetes in nearly 83% of patients before six months of age [10]. Genetic diagnosis is essential as it influences treatment options and can predict potential diabetes-related complications or illnesses. Genetic analysis should be performed for all children in the following cases: those diagnosed with diabetes within six months of birth; those aged six months to 1 year who exhibit extra-pancreatic features and lack evidence of pancreatic autoimmunity; and those with multiple autoimmune disorders, unusual family history, and associated congenital disabilities. Testing should not be delayed until other symptoms or potential remission [11]. Furthermore, it is crucial to ascertain whether sulfonylureas can be successfully introduced [12].

GENETIC ASPECTS (ABNORMAL β CELL FUNCTION)

Abnormalities at the 6q24 locus (*PLAGL1* and *HYMAI*)

Neonatal diabetes resulting from abnormalities in the 6q24 locus (MIM#601410 and 603044) encompasses paternal uniparental disomy of 6q24 (pUPD6), partial duplication of paternal 6q24, and relaxation of the maternal 6q24 imprinted locus [13]. This locus contains a CpG island with differential methylation depending on parental origin. Methylation downregulates the gene transcription of methylated alleles [13]. Overexpression of imprinted genes located at 6q24, such as *PLAGL1* (pleiomorphic adenoma gene-like 1) and *HYMAI* (hydatidiform mole-associated and imprinted) transcript, is believed to be associated with disease manifestations [14,15] (Table 1). *PLAGL1* is a transcription factor that encodes a protein involved in the regulation of cell cycle arrest and apoptosis, as well as in the induction of the receptor one gene for the potent insulin secretagogue human pituitary adenylate cyclase-activating polypeptide (PACAP1). Diabetes resulting from abnormalities at the 6q24 locus typically occurs before one month of age in 93% of cases, and before three months in 100% of cases. Intrauterine growth restriction was observed across all genetic groups, with a higher percentage found in patients with 6q24 abnormalities than in those with *ABCC8* or *KCNJ11* mutations. Reports indicate that 97% of patients with 6q24 locus abnormalities experience remission before one year of age [16]. Additionally, patients with 6q24 locus abnormalities can experience developmental defects (such as macroglossia, umbilical hernia, cardiac malformations, renal and urinary malformations, non-autoimmune anemia, and hypothyroidism with glands in situ) and neurological disorders [16].

Mutations of the K_{ATP} Channel Genes (*ABCC8* and *KCNJ11*)

The ATP-sensitive potassium channel (K_{ATP} channel) (MIM *600509 and *600937) is critical in stimulating insulin secretion in response to glucose in pancreatic β cells. Under low blood glucose conditions, K_{ATP} channels are activated and remain open, maintaining a hyperpolarized resting membrane potential. When blood glucose levels rise, glucose is taken up into β cells, entering the glycolytic pathway and increasing intracellular ATP concentration. This leads to the closure of K_{ATP} channels, resulting in potassium accumulation within the cell, ultimately causing membrane depolarization. Depolarization activates voltage-dependent calcium channels, allowing Ca^{2+} ions to enter β cells, facilitating the exocytosis of secretory vesicles, and releasing insulin into the bloodstream. ATP channels comprise a tetrameric protein structure formed by two subunits encoded by *KCNJ11* and *ABCC8* [17,18]. Even in individuals with a normally structured pancreas, activation mutations in either of these genes can disrupt the structure or function of K_{ATP} channels, leading to neonatal diabetes. These mutations cause the K_{ATP} channel to remain permanently open, thereby failing to regulate membrane potential in response to rising glucose levels, which ultimately results in impaired insulin secretion. Mutations in the *ABCC8* and *KCNJ11* genes man-

Table 1. Genetic causes of neonatal diabetes mellitus

Abnormality point	Gene	Gene function	Tansmission mode	Type of diabetes
6q24 locus methylation	*PLAGL1, HYMAI*	Transcription factor regulation of cell cycle arrest and apoptosis	Genetic aberrations of the imprinted locus at 6q24	Mostly transient, rare permanent
K_{ATP} Channel	*ABCC8, KCNJ11*	K_{ATP} channel/insulin secretion	AD	Permanent, transient, DEND
Pro-insulin	*INS*	Hormone	Rare AR	Transient, permanent
Glucokinase	*GCK*	Glucose metabolism	AD, AR	Heterozygous: MODY2 Homozygous: permanent

AD, autosomal dominant; AR, autosomal resessive; DEND, Developmental delay Epilepsy and Neonaral diabetes.

ifest in approximately 30% of cases before one month of age and between 1 and 6 months of age in 66% of cases [3]. In patients with *ABCC8* or *KCNJ11* mutations, remission may persist until five years of age [3,19]. Approximately 25% of these patients experience neurological disorders ranging from severe epilepsy to cognitive developmental delays, commonly referred to as DEND syndrome (developmental delay, Epilepsy, and Neonatal Diabetes) [20] (Table 1). Furthermore, when patients undergo detailed neuro-psychomotor and neuropsychological assessments, attention deficits or language disorders, including dyslexia, are observed in 100% of cases [3].

Mutations of the Insulin Gene (*INS*)

Mutations in the insulin gene (*INS*) (MIM *176730) predominantly involve heterozygous mutations affecting the structure of pro-insulin and are inherited in an autosomal dominant manner [21,22]. Pro-insulin with structural abnormalities is degraded within the cell, leading to severe endoplasmic reticulum (ER) stress and eventual β cell death. This process has been documented in mouse models and human studies, and reports suggest that INS mutations may influence β cell growth and development through chronic ER stress rather than solely leading to cell death [23-26]. Some mutations alter protein expression and are primarily inherited in a recessive manner within consanguineous families. These mutations have been shown to affect the expression of the insulin promoter directly or are influenced by mutations in factors that enhance its activity [27] (Table 1). Rare recessive *INS* mutations may lead to remission at a median age of 12 weeks. However, most *INS* mutations are dominant and do not lead to remission.

Mutations of the *Glucokinase* Gene (*GCK*)

Glucokinase plays a pivotal role in the first step of glucose metabolism in β cells and acts as a glucose sensor to regulate the amount of insulin secreted. Nonsense mutations of the *GCK* gene (MIM *138079) lead to Maturity Onset Diabetes of the Young type 2 (MODY 2), which typically presents as moderate hyperglycemia [28]. This genetic disorder is transmitted in an autosomal dominant manner; however, homozygous states of these nonsense mutations can result in a complete deficiency of glucokinase-mediated glycolysis, leading to neonatal diabetes [29] (Table 1). Although this is not a frequent cause of neonatal diabetes, it is crucial to check fasting blood glucose levels in both parents, mainly if there is a history of gestational diabetes. If mild glucose intolerance is found in both parents, evaluating mutations in the *GCK* gene is necessary.

THERAPEUTIC ASPECTS

Patients with neonatal diabetes often begin treatment during the neonatal period because of early-onset diabetes and intrauterine growth retardation. The initial treatment aims to rebalance carbohydrate metabolism and begins immediately upon diagnosis. Treatment should establish a balance between calorie and carbohydrate intake necessary to restore average weight (15–18 g/kg/day of carbohydrates) while avoiding excessive intake that could lead to future insulin resistance. Additionally, sufficient insulin-based treatment is required to achieve appropriate metabolic equilibrium. The goal is to normalize blood glucose levels without inducing hypoglycemia by targeting blood glucose levels before (target: 70–120 mg/dL) and after meals (target: 100–145 mg/dL). Both hyperglycemia and hypoglycemia can adversely affect the neurological development of neonates; therefore, it may be beneficial to use diluted insulin or an insulin pump to improve insulin management during the early weeks of life. Blood glucose measurements should accurately reflect capillary blood glucose levels and continuous glucose monitoring sensors may serve as alternatives.

Patients with mutations in the *ABCC8* or *KCNJ11* genes were successfully treated with hypoglycemic sulfonylureas. These sulfonylureas bind to the SUR1 subunit, which regulates potassium channels. In patients with these mutations, the K_{ATP} channels remain sensitive to sulfonylureas in approximately 90% of cases, inhibiting the potassium channels in pancreatic β cells and restoring insulin secretion in response to meals. Sulfonylurea therapy is reportedly safe and effective for controlling blood glucose levels in neonatal patients with diabetes, even before genetic test results are available. Therefore, empirical inpatient trials on sulfonylureas should be considered. Current evidence indicates that treatment with sulfonylureas normalizes HbA1c and significantly reduces the incidence of hypoglycemia while providing better metabolic control than insulin in neonatal diabetes associated with *ABCC8* or *KCNJ11* mutations. Recent studies have also demonstrated that when introduced early in childhood, hypoglycemic sulfonylureas can improve neurological, neuropsychological, and visuomotor impairments [33,34]. Moreover, Garcin et al. showed that sulfonylureas could successfully replace insulin in neonatal diabetes associated with chromosome 6 methylation abnormalities [35]. This underscores the importance of rapid genetic di-

agnosis following the diagnosis of neonatal diabetes and highlights the critical timing for the introduction of sulfonylureas.

CONCLUSION

Neonatal diabetes is a model for rare human genetic disorders and is pivotal for understanding beta cell function abnormalities, including issues related to the 6q24 locus and mutations in genes for the K_{APT} channel, pro-insulin, and glucokinase. Neonatal diabetes is often associated with specific neuropsychological or developmental disorders, necessitating all clinicians treating patients with neonatal diabetes to investigate the occurrence of these clinical symptoms. The treatment options for neonatal diabetes include insulin or sulfonylureas; the use of sulfonylureas is associated with a lower risk of hypoglycemia. Ultimately, it is essential to establish a prompt genetic diagnosis and prioritize the early introduction of sulfonylureas for the management of neonatal diabetes.

CONFLICT OF INTEREST

Not applicable.

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