

## NEONATAL DIABETES MELLITUS- A REVIEW

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### ABSTRACT

Diabetes presenting within first six months of life is classified as neonatal diabetes, which is one of the rarest form of diabetes. It is a developmental disorder of insulin production that resolves postnatally. The heterogeneity of presentation is a diagnostic challenge but with advent of genetic testing it has become easier to get an accurate diagnosis, start required treatment, and provide genetic counselling to the family.

**Key-words:** Neonatal diabetes, Mutant gene, Hyperglycemia.

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### INTRODUCTION

Diabetes presenting within first six months of life is classified as neonatal diabetes. It is one of the rarest form of diabetes with reported incidence 1 in 450,000 live births.<sup>1,2</sup> Kitzelle<sup>3</sup> in 1852 first described the disease in his son. Hutchinson *et al*<sup>4</sup> were the first to distinguish the permanent (PNDM) from relapsing transient (TNM) forms of congenital or neonatal diabetes. TNM is a developmental defect of insulin secretion that resolves spontaneously and represents 50% to 60% of cases of neonatal diabetes though some affected infant may develop type 2 diabetes mellitus later on in life.

Neonatal diabetes mellitus presents with hyperglycemia, failure to thrive, dehydration and in few rare cases diabetic ketoacidosis, within the first few months

of life. There are no clinical features that can predict whether a neonate with diabetes will eventually have permanent or transient disease. This review describes the clinical features, molecular causes and management of both subtypes of neonatal diabetes.

### PATHOGENESIS

**Transient neonatal diabetes mellitus:** TNM is a developmental disorder of insulin production that resolves postnatally. Almost half of cases of neonatal diabetes have TNM.<sup>1,2</sup> Intrauterine growth retardation (IUGR) is usually seen in TNM. The pathogenetic defect in TNM is decrease in insulin secretion which can be either from delayed maturation of pancreatic  $\beta$  cells or its dysfunction. In more than 90% of TNM

, causative genes have been identified. The majority of cases are due to abnormalities in the 6q24 region but some cases have been caused by mutations in *KCNJ11* and *ABCC8*, respectively.

The abnormalities of chromosome 6 include paternal isodisomy through genomic imprinting and partial duplications of the long arm of the paternal chromosome 6.<sup>5,6</sup> Abnormal methylation patterns have been documented in some TNDM patients where chromosome 6 abnormalities was not present. Two candidate genes are considered: one is the gene encoding transcription factor *ZAC* (*LOT1*) that regulates cell cycle arrest and apoptosis and also the Pituitary Adenylate Cyclase Activating Polypeptide Receptor 1 (*PACAP1*) being a potent insulin secretagogue, and the other is the *HYMAI* gene (hydatiform mole-associated and imprinted—also called *PLAGL1*, for pleomorphic adenoma of the salivary gland gene like 1).<sup>7</sup>

**Permanent diabetes mellitus:** The pathogenesis of PNDM can be classified into genetic mutations affecting islet development or reduced  $\beta$  cell mass or  $\beta$  cell dysfunction.

**Abnormal pancreatic development:** *PDX1*, also known as *IPF-1* or insulin-promoter factor 1, is a transcription factor that plays a critical role in the formation of the pancreas by determining the fate and regulating the propagation of both pancreatic exocrine and endocrine precursor cells.<sup>8</sup> A frame shift mutation causes *PDX1* to truncate prematurely and results in pancreatic agenesis. The infant homozygous for the mutation required insulin treatment and pancreatic enzymes

to replace pancreatic function. Whereas those heterozygous for the mutation developed early-onset type 2 diabetes (*MODY4*).<sup>9,10</sup>

*GLIS* subfamily of Kruppel-like zinc finger proteins-3 (*GLIS3*) is expressed in the pancreas mainly in  $\beta$  cells at an early developmental stage. Taha *et al*<sup>11</sup> reported *GLIS3* mutation in two infants in family presenting with congenital diabetes, neonatal hypothyroidism, liver fibrosis, glaucoma, polycystic kidneys, and minor facial abnormalities.

**Reduced  $\beta$  cell mass:** Wolcott-Rallison syndrome is an autosomal recessive disorder characterized by onset in infancy (often within the neonatal period) along with spondyloepiphyseal dysplasia. Other features included hepatomegaly, mental retardation, renal failure and early death.<sup>12</sup> The mutation in eukaryotic translation initiation factor 2\_ kinase 3 (*EIF2AK3*; also called *PERK*) gene which is present in chromosome 2p12 and acts as a regulator of protein synthesis causes this syndrome.<sup>13</sup>

**Insulin defect:** Stoy *et al*<sup>14</sup> found that mutations in the insulin (*INS*) gene and its precursors can also cause PNDM. Ten recessive mutations had been found so far.<sup>15</sup> which have been linked with abnormal cleavage and folding of preproinsulin and proinsulin.

***IPEX syndrome and FOXP3 gene:*** *IPEX* syndrome is an X-linked disorder associated with exfoliative dermatitis, intractable diarrhea with villous atrophy, hemolytic anemia, autoimmune thyroid disease and neonatal onset diabetes.<sup>16</sup> The syndrome is considered to have

autoimmune cause with involvement of FOXP3 gene which encodes scurf protein. The mutation leads to overexpression of CD4/CD25 lymphocytes which causes destruction of pancreatic beta cells leading to PNDM.<sup>17</sup>

**β cell dysfunction:** KCNJ11 gene encodes the Kir6.2 subunit of the pancreatic ATP-sensitive potassium channels (KATP) present in pancreatic β cells. The activation of these channels is responsible for insulin release. Structurally, these channels are made up of an octameric complex with two kind of subunits: four regulatory sulfonylurea receptors (SUR) embracing four pore forming inwardly rectifying potassium channels (Kir). Gloyn *et al*<sup>18</sup> were the first to report the identification of six heterozygous, missense activating mutations in KCNJ11 that were associated with PNDM in 29 cases, mainly from the International Society for Pediatric and Adolescent Diabetes (ISPAD) Rare Diabetes Collection. These mutations lead to a permanent opening of the potassium channel leading to insulin secretory defect. There is a phenotypic heterogeneity due to different expression of KCNJ11 gene in the central nervous system (CNS) and skeletal muscle.<sup>19,20</sup> The clinical presentation vary from severe developmental delay and muscle weakness to dysmorphic features along with diabetes. DEND (delayed development, epilepsy, NDM) syndrome is the most serious presentation and patients without epilepsy are classified as intermediate (iDEND).<sup>21</sup> *ABCC8* gene expresses SUR1 subunit of the pancreatic KATP channel. The activating mutations in *ABCC8* are known to cause neonatal diabetes but it has been found that these over-active channels

retain sulfonylurea sensitivity.<sup>22</sup> GCK is another gene implicated which expresses enzyme glucokinase. Glucokinase is “glucose sensor” of beta cell and mutation in GCK gene has been implicated in MODY 2. The homozygous mutations have been found to cause classical PNDM.<sup>23</sup>

***“Transient” and permanent neonatal diabetes: a common molecular mechanism?***

The clinical difference between a transient and a permanent form of neonatal diabetes is not always accounted for by a different molecular mechanism. The mutations in the SUR1 and Kir6.2 subunit have been found in association with both transient and permanent neonatal diabetes. Of note is that mutations in Kir6.2 have been found mostly in association with very early forms of diabetes, usually before 6 months of age, whereas the phenotypic variability of SUR1 mutations is broader.<sup>21,22</sup>

***Other syndromes with PNDM:*** Christen *et al*<sup>24</sup> have described two boys with X-linked phosphoribosyl-ATP pyrophosphatase hyperactivity who became diabetic on day one of life along with other features like mental retardation, ataxia and progressive axonal neuropathy. Another syndrome had been described recently in three members of a consanguineous family who developed severe neonatal diabetes and cerebellar hypoplasia. An autosomal recessive inheritance pattern was suggested.<sup>25</sup> It has also been suggested that the maternal enterovirus (echovirus 6) infection in first trimester of pregnancy can lead to autoimmune, neonatal onset diabetes with the presence of anti-insulin and glutamic

acid decarboxylase antibodies at birth or very soon after birth.<sup>26</sup>

**Diagnosis of the "transient" or permanent nature of the neonatal diabetes:** There are no definite phenotypic features to differentiate "transient" diabetes from permanent diabetes and considerable overlap occurs between the two groups, although patients with TNDM are more likely to have intrauterine growth retardation and less likely to develop ketoacidosis than patients with PNDM. TNDM patients are younger at the age of diagnosis of diabetes and have lower initial insulin requirements. Therefore, genetic analysis of chromosome 6 anomalies, the *KCNJ11* and *ABCC8* genes (encoding Kir6.2 and SUR1 respectively) are useful for diagnosing transient from permanent neonatal diabetes mellitus in the neonatal period. 50% of the PNDM cases are linked to potassium channel mutation which has potentially important therapeutic consequences and such patients can be managed with sulfonylureas. Similarly, abnormalities of chromosome 6q24 point towards transient nature of neonatal diabetes with risk of recurrences therefore such patients need strict follow up in future.

**Treatment:** In a clinical setting, insulin is the immediate choice for establishing metabolic control in NDM patients because it will be effective in all cases where an insulin deficit is involved. If diagnosis of diabetes is made before 6 months of age and genetic screening is undertaken, the identification of mutations in *KCNJ11* or *ABCC8* provides an alternative therapeutic strategy. The transfer from insulin injections to oral glibenclamide therapy (0.05-0.15 mg/kg)

seems highly effective and safe in such patients.<sup>27,28</sup> Studies indicate that sulfonylurea therapy provides better long-term metabolic control as assessed by lower blood sugar levels and reduced glycated hemoglobin values.<sup>29,30</sup> Transient gastrointestinal problems and some risk of hypoglycaemic events have been reported. In rest of the cases, insulin therapy is must to obtain satisfactory weight gain and growth in newborns with intra-uterine growth retardation. Very few data are available on the methods of insulin delivery in neonatal diabetes. The intermediate acting isophane or ultralente insulin on a once daily basis has been found to provide reasonable control.<sup>31</sup> Currently the long acting insulin analogs like glargine has not been approved in children of this age. Recently there has been few trials with use of the continuous subcutaneous insulin infusion (CSII) in NDM patients and CSII therapy had been found to be safe, more physiological, more accurate and easier to manage than injections.<sup>32</sup>

**Genetic counselling:** The risk of recurrence is different according to the "transient" or permanent form of the disease and to the different molecular mechanisms identified. In the case of uniparental disomy found in TNDM, none of the allele of the mother is found in the proband, the risk of recurrence does not exist in theory and there is no transmission. Recurrence risk is 25% in the recessive autosomal disorders (*EIF2AK*, *Glis3*, *PTF1A*, and *PDX1* genes). IPEX syndrome is an X linked disorder and mutation in the genes encoding the potassium channel subunits (*KCNJ11* & *ABCC8*) are transmitted in the heterozygous state in a dominant way.

**Prognosis:** In the neonatal period, the prognosis is linked to the severity of the disease, the degree of dehydration and acidosis, as well the rapidity with which the disease is recognized and treated. In the following period, the prognosis is determined by the associated malformations and lesions. Ultimately, the prognosis rely on the metabolic control, as in all the forms of diabetes mellitus, which will determine the timing of appearance of the long standing diabetes complications.

### CONCLUSION

Neonatal diabetes is a rare condition. The heterogeneity of early-onset diabetes, often associated with other clinical symptoms, presents physicians with a challenge. Testing and identification of mutant genes has become an increasingly important tool in the clinician's arsenal, helping to provide an accurate diagnosis, adequate treatment, and appropriate genetic counselling.

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