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NEONATAL DIABETES MELLITUS AND ITS TYPES

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A. ABSTRACT

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. 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. 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. Neonatal diabetes mellitus is a rare form of diabetes that occurs within the first 6 months of life. Our bodies need insulin to help our cells make energy. Infants with this condition do not produce enough insulin, which increases blood glucose levels.

Neonatal diabetes is often mistaken as type 1 diabetes, which is much more common. But type 1 diabetes usually occurs in children older than 6 months.

- Half of babies diagnosed with neonatal diabetes have a lifelong condition. This is called permanent neonatal diabetes mellitus. It occurs in 1 in 260,000 babies in some areas of the world.
- For the other half, the condition disappears within the first twelve weeks of life: but it can reoccur later. This is called transient neonatal diabetes mellitus.

Fetuses with neonatal diabetes do not grow as well in the womb, and these newborns may be small for their gestational age. This is called intrauterine growth restriction.

B. Story of resistance in diabetes mellitus

Genetic and environmental factors contribute majorly to the development of insulin resistance. Concordance in identical twins with DM: 70-90%. If either of the parents have DM: 25% chance developing DM. If both parents have DM: 40% chance of developing DM. HLA association with TYPE 1 DM is higher than that of TYPE 2 DM.

The starting point for all resistance is METABOLIC SYNDROME aka Syndromic Neonatal Diabetes. In Indian patients this is regarded as diabesopathy/ diabesity/ adiposopathy. Single most important parameter in metabolic syndrome in one of the parents: Centripetal obesity.

Genetic forms of resistance

1) Resistance due to mutation in insulin receptors : Rabson-mendenhall syndrome, Type A insulin resistance
2) Antibody against insulin receptor: Type B resistance
3) PCOS : Type C resistance

Type a resistance is characterized by

- Young girl
- Hyperandrogenemia
- Acanthosis nigricans
- Insulin resistance

Type C Resistance is characterized by

- Type A + PCOS + obesity
- Type C is aka HAIR AN Syndrome

C. Hyperglycemia in 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. The prevalence of high glucose levels in preterm infants is 25-75 percent. 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. 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. There is some evidence of insufficient pancreatic insulin secretion and relative insulin resistance in hyperglycemic and non-hyperglycemic critically ill preterm neonates. 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 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. 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.

D. Gene related monogenic neonatal diabetes mellitus

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;	Insulin

			cardiac defect	
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.

E. Types of ndm (Neonatal diabetes mellitus)

There are two types of NDM: permanent neonatal diabetes mellitus (PNDM), a lifelong condition, and transient neonatal diabetes mellitus (TNDM), a form of diabetes that disappears during the infant stage but may reappear later in life.

1) Permanent neonatal diabetes mellitus

Clinical characteristics: Permanent neonatal diabetes mellitus (PNDM) is characterized by the onset of hyperglycemia within the first six months of life (mean age: 7 weeks; range: birth to 26 weeks). The diabetes mellitus is associated with partial or complete insulin deficiency. Clinical manifestations at the time of diagnosis include intrauterine growth restriction,

hyperglycemia, glycosuria, osmotic polyuria, severe dehydration, and failure to thrive. Therapy with insulin corrects the hyperglycemia and results in dramatic catch-up growth. The course of PNDM varies by genotype.

Diagnosis/testing: Persistent hyperglycemia (plasma glucose concentration >150-200 mg/dL) in infants younger than age six months establishes the diagnosis of PNDM. Molecular testing is recommended: identification of pathogenic variant(s) in *ABCC8* or *KCNJ11* can guide treatment.

Management

Treatment of manifestations: Start rehydration and intravenous insulin infusion promptly after diagnosis. When the infant is stable and tolerating oral feedings begin subcutaneous insulin therapy. Children with pathogenic variants in *ABCC8* or *KCNJ11* can be treated with oral sulfonylureas; all others require long-term insulin therapy. High caloric intake is necessary for appropriate weight gain. Pancreatic enzyme replacement therapy is required for those with exocrine pancreatic insufficiency.

Prevention of secondary complications: Aggressive treatment and frequent monitoring of blood glucose concentrations to avoid acute complications such as diabetic ketoacidosis and hypoglycemia and reduce the long-term complications of diabetes mellitus.

Surveillance: Lifelong monitoring of blood glucose concentrations at least four times a day; periodic developmental evaluations. After age ten years, annual screening for chronic complications of diabetes mellitus including urinalysis for microalbuminuria and ophthalmologic examination for retinopathy.

Agents/circumstances to avoid: In general, avoid rapid-acting insulin preparations (lispro and aspart) as well as short-acting (regular) insulin preparations (except as a continuous intravenous or subcutaneous infusion) as they may cause severe hypoglycemia in young children.

Genetic counselling: The mode of inheritance of PNDM is autosomal dominant for mutation of *KCNJ11*, autosomal dominant or autosomal recessive for mutation of *ABCC8* and *INS*, and autosomal recessive for mutation of *GCK* and *PDX1*.

Individuals with autosomal dominant PNDM may have an affected parent or may have a *de novo* pathogenic variant. Each child of an individual with autosomal dominant PNDM has a 50% chance of inheriting the pathogenic variant.

The parents of a child with autosomal recessive PNDM are obligate heterozygotes and therefore carry one pathogenic variant. Heterozygotes for pathogenic variants in *GCK* and *PDX1* have a mild form of diabetes mellitus known as *GCK*-familial monogenic diabetes (formerly known as MODY2) and *PDX1*-familial monogenic diabetes (formerly known as MODY4). At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier (or of having familial monogenic diabetes), and a 25% chance of being unaffected and not a carrier.

Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant(s) in the family are known.

Diagnosis

Suggestive findings

Permanent neonatal diabetes mellitus (PNDM) **should be suspected** in individuals with the following laboratory and radiographic features.

Laboratory features

- Persistent hyperglycemia (plasma glucose concentration >150-200 mg/dL) in infants younger than age six months
- Features typical of diabetes mellitus (e.g., glucosuria, ketonuria, hyperketonemia)
- Low or undetectable plasma insulin and C-peptide relative to the hyperglycemia
- Low fecal elastase and high stool fat in infants with pancreatic aplasia or hypoplasia

Note: Measurement of hemoglobin A1c is not suitable for diagnosing diabetes mellitus in infants younger than age six months because of the higher proportion of fetal hemoglobin compared to hemoglobin A.

Radiographic features

Pancreatic hypoplasia identified on ultrasound, CT, or MRI examination

Note: Visualization of the pancreas in neonates may be difficult; biochemical evidence of pancreatic insufficiency (e.g., low fecal elastase, high stool fat) may help with the diagnosis in these infants.

Establishing the diagnosis: The diagnosis of PNDM **is established** in an infant with diabetes mellitus diagnosed in the first six months of life that does not resolve over time. Molecular testing is recommended: identification of pathogenic variant(s) in one of the genes.Molecular genetic testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Serial single-gene testing

Individuals with one parent with diabetes mellitus:

- Sequence analysis of *KCNJ11* first.
- If no *KCNJ11* pathogenic variant is found, sequence analysis of *ABCC8* and *INS*
- Individuals whose parents both have diabetes mellitus: sequence analysis of *GCK* and *PDX1*
- Individuals without a family history of diabetes mellitus:

- Sequence analysis of *ABCC8* and *KCNJ11* first (as identification of pathogenic variants changes management)
- If no pathogenic variants are identified, sequence analysis of *GCK* and *INS*

Individuals with pancreatic insufficiency or agenesis without extra-pancreatic abnormalities: Sequence analysis of *PDX1* first. If no pathogenic variants are identified, consider sequence analysis of *PTF1A* [Houghton et al 2016]. Individuals with syndromic PNDM: the extrapancreatic characteristics should guide genetic testing (see Genetically Related Disorders and Differential Diagnosis).

Note: Deletion/duplication analysis of *GCK*, *INS*, *PDX1*, and *PTF1A* (and for genes associated with syndromic PNDM) should be considered when sequencing is negative, as homozygous deletions in these genes can be associated with permanent neonatal diabetes mellitus.

Molecular Genetic Testing Used in Permanent Neonatal Diabetes Mellitus

Gene	Proportion of Permanent Neonatal Diabetes Mellitus Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants Detectable by Method	
		Sequence analysis	Gene-targeted deletion/duplication analysis
ABCC8	19%	100%	None reported
GCK	4%	100%	None reported
INS	20%	>99%	1 family
KCNJ11	30%	100%	None reported
PDX1	<1%	100%	None reported
Unknown		NA	

2) Transient neonatal diabetes mellitus

Clinical characteristics: 6q24-related transient neonatal diabetes mellitus (6q24-TNDM) is defined as transient neonatal diabetes mellitus caused by genetic aberrations of the imprinted locus at 6q24. The cardinal features are: severe intrauterine growth restriction, hyperglycemia that begins in the neonatal period in a term infant and resolves by age 18 months, dehydration, and absence of ketoacidosis. Macroglossia and umbilical hernia may be present. 6q24-TNDM associated with a multilocus imprinting disturbance (MLID) can be associated with marked hypotonia, congenital heart disease, deafness, neurologic features including epilepsy, and renal malformations. Diabetes mellitus usually starts within the first week of life and lasts on average three months but can last longer than a year. Although insulin is usually required initially, the need for insulin gradually declines over time. Intermittent episodes of hyperglycemia may occur in childhood, particularly during intercurrent illnesses. Diabetes mellitus may recur in adolescence or later in adulthood. Women who have had 6q24-TNDM are at risk for relapse during pregnancy.

Diagnosis: The diagnosis of 6q24-TNDM is established in a proband with transient neonatal diabetes mellitus and DNA methylation analysis demonstrating relative hypomethylation within the 6q24 differentially methylated region (DMR). 6q24-TNDM is caused by overexpression of the imprinted genes at 6q24 (*PLAGL1* and *HYMAI*). The DMR (i.e., *PLAGL1* TSS alt-DMR) is present within the shared promoter of these genes. Normally, expression of the maternal alleles of *PLAGL1* and *HYMAI* is silenced by DMR methylation and only the paternal alleles of *PLAGL1* and *HYMAI* are expressed. Additional molecular genetic testing can establish the underlying genetic mechanism, which is required for genetic counseling. Three different genetic mechanisms resulting in twice the normal dosage of *PLAGL1* and *HYMAI* (and thus causing 6q24-TNDM) are (1) paternal uniparental disomy of chromosome 6, (2) duplication of 6q24 on the paternal allele, and (3) hypomethylation of the maternal *PLAGL1* TSS alt-DMR, resulting in inappropriate expression of the maternal *PLAGL1* and *HYMAI* alleles.

Maternal *PLAGL1* TSS alt-DMR hypomethylation may result from an isolated imprinting variant or as part of MLID. Biallelic *ZFP57* pathogenic variants account for almost half of TNDM-MLID.

Management

Treatment of manifestations: Rehydration and IV insulin are usually required at the time of diagnosis; subcutaneous insulin is introduced as soon as possible and used until blood glucose levels stabilize. Later recurrence of diabetes may require diet modifications alone, oral agents, or insulin.

Prevention of secondary complications: Prompt treatment of dehydration to avoid sequelae.

Surveillance: Periodic glucose tolerance tests (abnormalities suggest future recurrence); monitoring of growth and development.

Agents/circumstances to avoid: Factors that predispose to late-onset diabetes or risk factors for cardiovascular disease.

Evaluation of relatives at risk: Screening for diabetes mellitus in relatives who have inherited a paternal

6q24 duplication or who are at risk of having inherited two *ZFP57* pathogenic variants.

Molecular Genetic Mechanisms for 6q24-Related Transient Neonatal Diabetes Mellitus

Locus	Genes of Interest	Imprint	Parental origin of imprint	Disease Mechanism
6q24	*PLAGL1*, *HYMA1*	Methylated [1]	Maternal	Hypomethylation, paternal UPD, or paternal duplication

1 In unaffected individuals, the maternally derived methylated copy is not expressed.

Types of tndm

Type	OMIM	Gene	Locus	Description
TNDM1	601410	ZFP57, PLAGL1	6p22.1, 6q24.2	
TNDM2	610374	ABCC8	11p15.1	Due to the mutations of the other subunit of the K_{ATP} channel, SUR1, which is encoded by the ABCC8 gene.[2]
TNDM3	610582	KCNJ11	11p15.1	

F. Genetically related (Allelic) disorders

***ABCC8, GCK,* and *KCNJ11*.** Pathogenic variants in *ABCC8*, *GCK* and *KCNJ11* are known to be associated with familial hyperinsulinism (FHI). FHI is characterized by hypoglycemia that ranges from severe, difficult-to-manage neonatal-onset disease to childhood-onset disease with mild symptoms and difficult-to-diagnose hypoglycemia. Neonatal-onset disease manifests within hours to one to two days after birth; childhood-onset disease manifests during the first months or years of life. FHI caused by pathogenic variants in either *ABCC8* or *KCNJ11* (FHI-K_{ATP}) is most commonly inherited in an autosomal recessive manner and less commonly in an autosomal dominant manner. FHI caused by pathogenic variants in *GCK* is inherited in an autosomal dominant manner. Infants with GCK-related FHI tend to be large for gestational age at birth and may present in early infancy (range: 2 days to 30 years).

ABCC8* and *KCNJ11

Common variants in *ABCC8* and *KCNJ11*, particularly p.Glu23Lys in *KCNJ11*, have been associated with type 2 diabetes mellitus [Hani et al 1998, Gloyn et al 2001, Hansen et al 2001, Hart et al 2002, Gloyn et al 2003, Nielsen et al 2003, Florez et al 2004].

Activating pathogenic variants in *ABCC8* and *KCNJ11* with less severe effects on channel function have been found to cause TNDM that is similar to the biphasic course seen in the 6q24-related TNDM phenotype. Typically, infants with TNDM caused by K_{ATP} channel pathogenic variants present before age six months, then go into remission between ages six and 12 months and are likely to relapse during adolescence or early adulthood [Gloyn et al 2005, Flanagan et al 2007].

***ABCC8*.** A dominant *ABCC8* pathogenic variant is associated with hyperinsulinemic hypoglycemia in the neonatal period and may lead to diabetes mellitus later in life [Huopio et al 2003]. See Maturity-Onset Diabetes of the Young Overview.

***GCK*.** Dominant inactivating pathogenic variants in *GCK* are associated with *GCK*-familial monogenic diabetes, a mild form of diabetes mellitus presenting later in life.

***INS*.** Heterozygous pathogenic variants in *INS* have been reported in individuals with infancy-onset diabetes, type 1b (antibody negative) diabetes, familial monogenic diabetes and early-onset type 2 diabetes [Støy et al 2010].

***KCNJ11*.** A subset of individuals with biallelic pathogenic variants in *KCNJ11* will present with transient instead of permanent neonatal diabetes mellitus (see Differential Diagnosis).

***PDX1*.** Dominant inactivating pathogenic variants of *PDX1* are associated with *PDX1*-familial monogenic diabetes, a mild form of diabetes mellitus.

G. Differential diagnosis

Permanent neonatal diabetes mellitus (PNDM) vs transient neonatal diabetes mellitus (TNDM)

When diabetes mellitus is diagnosed in the neonatal period, it is difficult to determine if it is likely to be transient or permanent.

6q24-related TNDM is defined as transient neonatal diabetes mellitus caused by overexpression of the imprinted genes at 6q24 (*PLAGL1* and *HYMAI*). The cardinal features are: severe intrauterine growth restriction (IUGR), hyperglycemia that begins in the neonatal period in a term infant and resolves by age 18 months, dehydration, and absence of ketoacidosis. Macroglossia and umbilical hernia are often present. In the subset of children with *ZFP57* pathogenic variants,

other manifestations can include structural brain abnormalities, developmental delay, and congenital heart disease. Diabetes mellitus usually starts within the first week of life and lasts on average three months but can last more than a year. Although insulin is usually required initially, the need for insulin gradually declines over time. Intermittent episodes of hyperglycemia may occur in childhood, particularly during intercurrent illnesses. Recurrence in adolescence is more akin to type 2 diabetes mellitus. Relapse in women during pregnancy is associated with gestational diabetes mellitus.

The two most common causes of transient neonatal diabetes are 6q24-related TNDM and pathogenic variants in *ABCC8* or *KCNJ11*. In 50 children presenting with neonatal diabetes, Metz et al [2002] failed to demonstrate clear clinical indicators to differentiate 6q24-related TNDM from other causes. However, the clinical presentation may be slightly different: neonates with 6q24-related TNDM have more severe IUGR, present earlier, remit earlier, and relapse later than K_{ATP}-related TNMD. The presence of other distinguishing features of 6q24-related TNDM may guide the approach to genetic testing, such macroglossia (seen in 1/3 of individuals) and umbilical hernia [Rubio-Cabezas et al 2014].

H. CONCLUSION

For infants presenting in the first two weeks of life, it is reasonable to test for 6q24- related aberrations first, followed by testing for *KCNJ11* and *ABCC8* pathogenic variants.

For infants presenting from the third week of life onward, it may be more appropriate to test for *KCNJ11* and *ABCC8* pathogenic variants first, followed by testing for 6q24-related aberrations.

In infants presenting between age six and 12 months or later who are antibody negative or have a family history consistent with autosomal dominant inheritance, evaluation for pathogenic variants in *INS* should be considered first.

For infants with associated extra-pancreatic features or consanguineous parents, other genetic analysis may be appropriate.

The incidence of type 1 diabetes mellitus in childhood & adolescence is steadily rising worldwide.

Polydipsia, polyuria, and weight loss are the most common presenting symptoms of diabetes mellitus.

Type 1 diabetes is the commonest type in 90% of affected children, however type 2 diabetes is increasingly happened in children owing to increased rate of obesity.

Insulin therapy is given by subcutaneous injection or by needle or by insulin pump.

The goals of treatment in children are the near-normalization of glucose metabolism and keeping HbA1c <7.5%.

High risk infants require special attention and optimal care to reduce morbidity and mortality. Therefore adequate antenatal care, specialized delivery and early referral for optimal neonatal care will go a long way in averting the series of problems associated with them and help prevent both short term and long term complications.

Tight maternal glycemic control is associated with improved outcomes in infants of diabetic mothers.

Regardless of glycemic control, these infants are at higher risks for birth defects, abnormal growth, metabolic complications and even neurodevelopmental delay as compared to their peers of non-diabetic mothers.

Having a regularly updated management protocol in our Paediatric units will greatly improve the level and quality of care these children receive.

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