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MINIREVIEWS

Infantile onset diabetes mellitus in developing countries - India

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Abstract

Infantile onset diabetes mellitus (IODM) is an uncommon metabolic disorder in children. Infants with onset of diabetes mellitus (DM) at age less than one year are likely to have transient or permanent neonatal DM or rarely type 1 diabetes. Diabetes with onset below 6 mo is a heterogeneous disease caused by single gene mutations. Literature on IODM is scanty in India. Nearly 83% of IODM cases present with diabetic keto acidosis at the onset. Missed diagnosis was common in infants with diabetes (67%). Potassium channel mutation with sulphonylurea responsiveness is the common type in the non-syndromic IODM and Wolcott Rallison syndrome is the common type in syndromic diabetes. Developmental delay and seizures were the associated co-morbid states. Genetic diagnosis has made a phenomenal change in the management of IODM. Switching from subcutaneous insulin to oral hypoglycemic drugs is a major clinical breakthrough in the management of certain types of monogenic diabetes. Mortality in neonatal diabetes is 32.5% during follow-up from Indian studies. This article is a review of neonatal diabetes and available literature on IODM from India.

Key words: Infants; Diabetes mellitus; Monogenic diabetes; Co-morbid state; Mortality

Core tip: The clinical presentation of infantile onset diabetes mellitus (IODM) as syndromic and non-syndromic forms from South India is discussed in this article. Associated co-morbid states, mortality pattern, difficulty in the management and need for genetic evaluation among this group of infants are also discussed. Identification of this form of monogenic diabetes by clinical evaluation and appropriate genetic evaluation to identify the subtypes helps in the management of these infants to improve the overall morbidity and mortality. Reported mortality in IODM is high from South India.

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INTRODUCTION

Infantile onset diabetes mellitus (IODM) is a rare form of diabetes with onset at less than one year of age. Onset of diabetes in the first 6 mo of life is termed neonatal diabetes[1]. The majority of neonatal diabetes cases are monogenic. However, recent reports have suggested evaluation for monogenic diabetes among those with onset in later infancy (onset between 6 mo and 1 year), too[2]. The two phenotypes of neonatal diabetes include transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM). The reported incidence of neonatal diabetes varies from 1 in 200000 to 1 in 400000[3]. Infants with PNDM continue to require insulin for maintaining euglycemia. TNDM usually resolves by 18 mo of age. In a study from Chennai in India, the incidence of infantile onset diabetes was 7.9% among all diabetic children in a pediatric diabetic clinic[4]. Another hospital based retrospective study from South India revealed the incidence to be 7%[5]. A recent international cohort study used comprehensive genetic testing to identify causal mutations which were found in nearly 80% of samples in neonatal diabetes[6]. This indicates that genetic diagnosis results in a phenomenal change in the management of infantile onset diabetes.

Genetics of TNDM

Among the neonatal diabetes cases, 50%-60% of affected neonates are due to TNDM based on the Western literature[7,8]. However, in a study from Chennai in India, TNDM only accounted for 5% of all neonatal DM cases[4]. TNDM is commonly due to a developmental defect in the pancreatic beta cell function. The common genetic defect (60%-70%) is due to mutations on chromosome 6q24[3,9,10]. The cause seems to be a defect in maternal methylation, most often due to recessive mutations in the *ZPF57* (Zinc Finger Protein) gene[11]. There are three types of abnormalities leading to overexpression of the paternal allele at this locus: (1) a paternally inherited duplication; (2) paternal uniparental disomy (UPD); and (3) an epimutation resulting in a complete loss of methylation of the maternal allele on chromosome 6q24[12,13]. Mutations in *KCNJ11* (Potassium channel subfamily J member 11) and *ABCC8* (ATP binding cassette transporter subfamily C, member 8) leading to about 20%-25% of TNDM cases[13-16]. Rarely mutations in *HNF 1B*, insulin gene and solute carrier 2 family 2 gene (*SLC2A2*) can result in neonatal diabetes. TNDM remits permanently or may relapse later during adulthood. Thus, TNDM may be a permanent beta cell defect with variable expression during growth and development. The clinical presentation includes hyperglycemia, dehydration, and failure to thrive with or without ketoacidosis. The associated features in chromosome 6q24 mutations include macroglossia (35%), umbilical hernia (14%) or more rarely cardiac and brain developmental defects. Infants with TNDM resulting from a K_{ATP} channel mutation are often heavier than patients with chromosome 6q24 induced TNDM at birth, are diagnosed with diabetes later, remit later and relapse earlier[17]. Chromosome 6q24 induced TNDM should be treated with insulin. Relapse due to UPD chromosome 6 mutation or *ABCC8* mutation in puberty responds well to sulphonylurea therapy[18,19]. Relapsing diabetes due to 6q24 related diabetes has been successfully treated with dipeptidyl peptidase 4 inhibitor[20]. The majority (> 90%) of TNDM cases due to *ABCC* 8/*KCNJ11* mutation respond to sulphonylurea therapy[21]. Infants born with TNDM harbour a greater risk of developing type 2 diabetes later in the life[22]. There were only few studies, and most were case reports about TNDM in the Indian literature[23-29]. Rarely encountered is type 1 diabetes in infancy especially in the non-syndromic diabetes with onset in later part of infancy[30].

Genetics of PNDM

Children with PNDM have their onset in early infancy and continue to be hyperglycemic, which needs lifelong insulin therapy. The genetic defect involves mutation of genes involving the pancreatic B cell development, function, apoptosis and insulin molecule. Nearly 40% of the defects are in the genes regulating the K_{ATP} (potassium ATP) channel. As early as 1997 mutations leading to PNDM have been described. The first is pancreatic agenesis due to mutations in *IPF*/pancreatic and duodenal homeobox 1 (*PDX1*). Between 2004 and 2007 the mutations of *KCNJ11*, *ABCC8* and *INS* genes were identified for PNDM. *KCNJ11* and *ABCC8* mutations account for nearly 40%-50% of all PNDM cases[31]. PNDM can be nonsyndromic or syndromic (associated with other systemic features). The five genes in which mutations in nonsyndromic PNDM occur include *KCNJ11* (approximately 30% of NDM cases), *ABCC8* (approximately 19%), *INS* (approximately 20%), *GCK* (approximately 4%), and *PDX1* (< 1%)[32]. The mode of inheritance of PNDM is autosomal dominant for mutations in *KCNJ11*, autosomal dominant or autosomal recessive for mutations in *ABCC8* and *INS*, and autosomal recessive for mutations in *GCK* and *PDX1*.

K_{ATP} CHANNEL MUTATION

Glucose sensing and insulin release from beta cells are a complex process. Glucose enters through GLUT receptors and generates energy in the form of ATP. This increased ratio of ATP to ADP results in closing of the potassium channels and depolarization. This activates the calcium channels and influx of calcium into cells, leading to release of insulin by exocytosis. The potassium channel subunit Kir 6.2 (potassium inward receptor) and SUR (sulphonylurea receptor 1) are encoded by genes called *KCNJ11* and *ABCCC8*. Mutations in these two genes are common in PNDM. The majority of these children respond to sulphonylurea, which acts on the potassium channels,

keeps them open and prevents depolarization[33]. These channels are present in non-pancreatic tissues like the brain, heart and skeletal muscles and this explains the associated co-morbid states like developmental delay, muscle weakness and seizures in DEND syndrome [developmental delay, epilepsy, neonatal diabetes mellitus (NDM)][34,35]. A number of patients with K_{ATP} channel mutations present with a milder phenotype without epilepsy [termed intermediate DEND (iDEND] syndrome[36-38]. Infants or children with Kir mutation respond well to sulphonylurea therapy, which is preferred than insulin as sulphonylurea therapy is associated with improvement of other systemic features along with glycemic control[39]. Among the published data from South India, out of the 9 identified mutations, 7 were due to *KCNJ11* and *ABCC8* mutations and successful switch was done in these children following genetic reports except one child with *ABCC8* mutation induced hyperinsulinemic hypoglycemia[40].

INSULIN

Insulin gene defects lead to defective folding of insulin in the endoplasmic reticulum and this affects the insulin release. They may present as NDM or MODY[41]. These infants do not have any extra-pancreatic features. The heterozygous form presents during the first 6 mo of age and 50% have keto acidosis. The more severe form with homozygous mutation presents much earlier and have low birth weight. Management includes insulin, prevention of hyperglycemia through diet and use of insulin sensitizers like metformin. Sulphonylureas are not effective. Insulin gene mutations leading to neonatal diabetes have been described even in Indian infants[40,42,43].

GLUCOKINASE

Glucokinase (GCK) is the glucose sensor of the cell. It is essential for phosphorylation of the glucose molecule that enter the cells. Mutations lead to defective glycolytic activity, and thereby the cascade leading to insulin release is affected. Homozygous infants present with NDM. They need lifelong insulin therapy. Heterozygotes may present later as MODY 2 (maturity onset diabetes in young). A homozygous *GCK* mutation has been described in an infant from Chennai[4,43]. Although *GCK* mutations in neonates do not respond well to sulphonylurea, there are a few case reports suggesting a role for glibenclamide along with insulin in children with homozygous *GCK* mutations[44,45].

PDX1

The homozygous form presents as PNDM and has both pancreatic exocrine and endocrine dysfunctions. The heterozygous form present as MODY 4[46].

Syndromic causes of PNDM are due to mutations in *GATA6*, *PTF1A*, *FOXP3*, *GLIS3*, *RFX6*, *NEUROD1*, *NEUROG3*, *HNF1B*, *PAX6*, *SLC19A2* and *WFS1* genes.

MUTATIONS IN *GATA6* GENE

This is the most common cause for pancreatic agenesis. Extra-pancreatic features are common and include structural heart defects, biliary tract and gut anomalies, and other endocrine abnormalities. Inheritance is autosomal dominant, but in most reported cases the mutations have arisen *de novo*[47].

PANCREATIC TRANSCRIPTION FACTOR 1, A SUBUNIT

This factor is essential for pancreatic development and function as well as cerebellar development. Other than pancreatic hypoplasia, cerebellar hypoplasia, microcephaly and respiratory distress may also develop[48].

FOXP3 GENE

The dysfunction of the transcription factor FOXP3 may result in X-linked-IPEX syndrome (immune dysregulation, polyendocrinopathy and enteropathy). Although autoimmune diabetes is uncommon in infancy, most of the autoimmune children may be due to *FOXP3* mutations[49]. The IPEX syndrome gene on the X chromosome, which codes for a forkhead domain-containing protein known as "scurfin", is required for immune homeostasis. These children present with intractable diarrhea with villous atrophy, exfoliative dermatitis, autoimmune hypothyroidism, hemolytic anaemia and recurrent infections. They may test positive for islet cell auto-antibodies.

GLI SUBFAMILY OF KRUPPEL-LIKE ZINC FINGER PROTEIN-3

This transcription factor is involved in various processes in multiple tissues. These infants present with multi-system involvement like diabetes, congenital hypothyroidism, congenital glaucoma, renal cysts and dysmorphic facies[50].

Other causes for syndromic neonatal diabetes include the following: *MNX1* (motor neuron and pancreas homeobox I) mutations - neonatal diabetes with developmental delay, neurogenic bladder, sacral agenesis, and imperforate anus; *NKX2* (NK homeobox 2) mutations - neonatal diabetes with developmental delay, hypotonia, hearing impairment, cortical blindness and short stature; *RFX6* mutations - pancreatic hypoplasia, intestinal atresia, and gall bladder hypoplasia[51]. Pancreatic exocrine function is normal. Inheritance is autosomal recessive; *NEUROD1* mutations - cerebellar hypoplasia, sensorineural deafness, and visual impairment[52]. Pancreatic exocrine function is normal and the inheritance is autosomal recessive; *NEUROG3* mutations - congenital malabsoptive diarrhea and the exocrine

pancreatic function may be affected[53]. Inheritance is autosomal recessive; *HNF-1β* mutations - hypo plastic pancreas and renal abnormalities. The inheritance is autosomal recessive with incomplete penetrance; *PAX 6* mutations - central nervous system phenotype such as microcephaly and panhypopituitarism. The ocular phenotype includes aniridia, keratopathy, optic nerve defects, cataracts, microphthalmia and anophthalmia. Wolfram syndrome - DM with optic atrophy, diabetes insipidus and/or deafness, usually presents a little later in life although it can present in the neonatal period. Optic atrophy and diabetes may present in the first decade of life while diabetes insipidus and deafness present later in the 3rd or 4th decade[32]; *SLC19A2* (soluble carrier family 19, member 2; thiamine transporter) mutations. Recessive mutations lead to NDM, thiamine responsive megaloblastic anemia and deafness. They may have cardiac manifestations. This is also called Rogers syndrome and is inherited as an autosomal recessive disorder[54,55]; *SLC2A2* (soluble carrier family 2 member 2) mutations - Fanconi bickel syndrome. DM with hepatomegaly, glycosuria, proteinuria, hypophosphatemic rickets are the presenting features[56]. *EIF2AK*3 (eukaryotic translation initiation factor 2 alpha kinase 3) mutations - Wolcott-Rallison syndrome. Infants with *EIF2AK* mutations present with neonatal diabetes, liver failure, growth retardation, epiphyseal dysplasia, developmental delay, hypothyroidism and renal failure. Higher mortality has been reported among these children. This is more common in infants born of consanguinity. Mortality is predominantly due to liver cell failure in these children[4,40].

The course of PNDM varies by genotype. Pancreatic agenesis/hypoplasia caused by homozygous mutations in *PDX1* results in severe insulin deficiency and exocrine pancreatic insufficiency. The morbidity and mortality vary according to the co-morbid conditions of the infant. Rarely congenital hyperinsulinemia can present with neonatal diabetes with ABCC8 mutations and is refractory to insulin therapy as in congenital lipodystrophy[57].

CLINICAL PRESENTATION OF NDM

Clinical features of TNDM and PNDM are indistinguishable. NDM often presents with hyperglycemia incidentally identified during evaluation for intercurrent illness or may present with keto acidosis. Rarely candida infection of the genitalia can be a presenting feature. A higher incidence of consanguinity was encountered in the study of 12 children with infantile diabetes from Chennai, India. Initial presentation as diabetic keto acidosis (DKA) was encountered in 83% of the study group. Mortality at 1-year follow-up was 16.6%[5]. Another study by Varadarajan *et al*[4] from South India revealed 67.5% of infants with ketotic onset. The median age at diagnosis was 3.75 mo. Based on the study published from South India only 32% of infants were diagnosed to have diabetes or DKA at presentation. Missed diagnosis was common in infants with diabetes (67.5%). Infantile onset diabetes present with a history of polyuria, polydipsia, irritability, vomiting, seizures, breathlessness, poor feeding, white discharge from genitals, or sticky urine. Low birth weight and monogenic diabetes were more common in those infants with onset at less than 6 mo of age in comparison with those with onset beyond 6 mo. Sixty-three percent of infants with onset in the first 6 mo of life were of low birth weight. Eighty-five percent of infants with onset less than 6 mo were identified to be monogenic in comparison to 55% if the onset was more than 6 mo. This study revealed Wolcott Rallison to be most common type of monogenic diabetes[4]. This is similar to the study by Ganesh *et al*[5] where 50% of the study group had Wolcott Rallison syndrome. Among the non-syndromic type KCNJ11/8 was common and among the syndromic type Wolcott Rallison syndrome was common. Ten percent (4 out of 40) of infants had transient NDM with remission of hyperglycemia in the first few months and one of them relapsed at 9.7 years of age. Children with Wolcott Rallison syndrome had a higher mortality than any other group. Hepatic failure was the most common cause of death. Co-morbid states encountered in infants with diabetes include developmental delay, seizures, hepatic involvement, hypothyroidism, optic atrophy, hepatomegaly, short stature and rickets. The mean insulin requirement was 1.19 units/kg per day in those with onset less than 6 mo or 1.4 units/kg per day in those with onset more than 6 mo. Among those children with *KCNJ11* or *ABCC8* mutation the response to oral sulphonylurea is excellent and better metabolic control has been documented even during follow-up. Other than glibenclamide, glyburide has also been tried in children with *KCNJ11* or *ABCC8* mutation. Relapsing NDM in older children do respond well to sulphonylurea without need for insulin therapy. Despite the advances of diagnosis and management of IODM, day-to-day problems exist in the management in developing countries. One of the problems of concern is the assessment of glycemic control among infants who are on 2-3 hourly breast feeds or demand feeds. Difficulty in dispensing very low doses of insulin is a problem in developing countries. Delivering insulin less than 1 unit is difficult as there are no diluents available in developing countries. Dilution with normal saline have been used in such situations but the evidence for the same to be effective is lacking. Currently available insulin pens to dispense 0.5 units may be useful in such infants. The psychological trauma to the family members and lack of adequate support in the community through a structured diabetic care team makes day-to-day management of diabetes difficult in these infants. Frequent hospitalization, glycemic fluctuations, poor weight gain and co-morbid conditions were other problems reported in studies from South India[4]. Literature reveals continuous subcutaneous infusion of insulin as a useful intervention, although

affordability and cost are limiting factors in developing countries. Limited availability of genetic studies in India may cause delay in the diagnosis of monogenic diabetes. Reported mortality in infantile onset diabetes is very high in developing countries. The mortality at 1-year follow-up was 16%[5]. However, another study of 40 infants with diabetes from South India had revealed a mortality of 32.5% over a 12-year period[4]. Cerebral edema, sepsis, acute respiratory distress syndrome, disseminated intravascular coagulation, hypoglycemia, refractory cardiac failure, septic shock, renal failure and hepatic failure were the causes of mortality in infantile onset diabetes.

Comparing the literature about IODM in developed countries, the following needs to be emphasized. TNDM is reported to constitute 40%-60% of IODM cases in Western literature while it is less than 10% from developing countries. The infrequent sequencing for 6q mutations may be a possible explanation. Those with onset between 6 to 12 mo were commonly identified to have *INS* gene mutation in comparison to the *EIF2AK* mutation in developing countries, and a higher rate of consanguinity may be a contributory factor. Comprehensive genetic testing has identified genetic cause in more than 80% of IODM cases in developed countries, while it is much lower in developing countries. Nearly 60%-80% of IODM cases present with DKA in developing countries while no such data are available from developed countries. Developmental delay and neuropsychological dysfunction are common in children with IODM from developed countries while developmental delay and hepatosplenomegaly have been reported from developing countries. Insulin pumps have been used for insulin requiring mutations in developed countries while they have been managed with conventional injections in developing countries like India. Overall mortality in IODM was reported to be 33% in developing countries while no such data on mortality in IODM are available from developed countries.

DIAGNOSTIC APPROACH TO INFANTILE ONSET NEONATAL DIABETES

A low C peptide level and high HBA1c level are supporting lab parameters to confirm infantile onset diabetes from stress induced hyperglycemia in infants. Initial evaluation should include a search for syndromic features. Associated features like hypothyroidism, elevated liver enzymes, skeletal dysgenesis, pancreatic agenesis, enteropathy, developmental delay, anemia, umbilical hernia and macroglossia should be looked for (Table 1). All infants with onset of diabetes at less than one year of age need to undergo genetic evaluation at the earliest for monogenic diabetes. Older children of any age with infantile onset diabetes can undergo genetic work-up as therapy with sulphonylurea at a later age is still useful for good glycemic control and management

Table 1 Diagnostic clues for type of mutation in infantile onset diabetes mellitus

Associated features	Diagnostic possibility of mutation
Umbilical hernia, macroglossia	6q 24
Developmental delay	*KCNJ11, ABCC8, EIF2AK3*
Microcephaly	*PTF 1A*
Hypothyroidism	*EIF2AK3, GLIS 3, FOXP3*
Diarrhea, eczema	*IPEX*
Anemia	*EIF2AK3, SLC19A2*
Hepatomegaly with liver dysfunction	*EIF2AK3*
Cerebellar hypoplasia	*PTF1A, NEUROD 1*
Pancreatic hypoplasia	*RFX 6, HNF1B, PTF1A, GATA6*
Ocular manifestations	*PAX 6*
Rickets, round facies, mild hyperglycemia	*SLC2A2*
No syndromic features	*KCNJ11, ABCC8, INS*
Renal abnormalities	*GLIS3, HNF1B*
Hirsutism, failure to thrive	Insulin resistance syndromes

KCNJ11: Potassium channel subfamily J member 11; *ABCC8*: ATP binding cassette transporter subfamily C, member 8; *EIF2AK3*: Eukaryotic translation initiation factor 2 alpha kinase 3; *PTF*: Pancreatic transcription factor; *GLIS3*: GLI subfamily of Kruppel-like zinc finger protein-3; *SLC2A2*: Solute carrier 2 family 2 gene; *INS*: Insulin.

of other comorbid factors. However, long-term insulin therapy may reduce the available beta cell mass and they may need additional glucose reducing drugs. Hence, an earlier genetic confirmation or therapy with sulphonylurea is warranted. Comprehensive genetic screening has been found to be more useful for early diagnosis than the conventional genetic screening. Conventional genetic tests analyze few genes based on the clinical features. With improved sequencing methods simultaneous analysis of multiple genes is possible. The genetic result predicts the best diabetes treatment and development of associated features. Evaluation with auto-immune antibodies may be warranted in infants with onset of diabetes in late infancy as the chances of type 1 diabetes presenting in late infancy has been reported in the literature.

Management of IODM

Adequate hydration of infants with acute presentation in DKA is essential. Infants with DKA may need much more fluids than the management of older children. Associated predisposing factors like sepsis or bronchopneumonia need to be treated for early control of hyperglycemia. Infusions of short-acting insulin in DKA and subcutaneous doses of insulin are the therapy of choice until evaluation for monogenic diabetes. These infants and toddlers may be very sensitive to small doses of insulin and careful watch for hypoglycemia is a must. Avoiding hypoglycemia is essential in these infants as sequelae of hypoglycemia on the developing brain leads to increased morbidity. Short-acting and rapid-acting insulin may sometimes cause hypoglycemia that is difficult to control in infants. Intermediate-acting insulin is preferred to be given as once or twice a day therapy[4]. Initial insulin dose for stabilization may

range from 0.35 units/kg per day to 3 units/kg per day. Insulin pumps have been used successfully in developed countries[58,59], but the initial cost and subsequent maintenance are major issues in using insulin pumps in infants from developing countries like India. If genetic reports suggest mutations in *KCNJ11* or *ABCC8* mutations which are responsive to sulphonylurea, transfer to oral drugs should be undertaken. Earlier identification of sulphonylurea responsiveness (*KCNJ11* and *ABCC8* mutations) is essential as the insulin therapy will only achieve glycemic control. Other systemic manifestations like seizures, muscular involvement, and developmental delay do not respond to insulin therapy. Earlier institution of sulphonylurea is essential to prevent worsening of these co-morbid factors in IODM. Following genetic confirmation, insulin can be switched slowly by outpatient protocols or by rapid inpatient protocols[21,60-66]. The initial median dose for sulphonylurea used to treat patients with K_{ATP} channel mutations is 0.45 mg/kg per day (range, 0.05-1.75 mg/kg per day). The switch over from insulin therapy to sulphonylurea may take more than 6 wk as some infants need very high doses up to 2 mg/kg per day of sulphonylurea[4]. In developing countries like India awaiting genetic reports for sulphonylurea therapy may cause a delay in specific treatment for co-morbid conditions. Studies have been undertaken to assess the risk and benefit of sulphonylurea therapy prior to genetic confirmation. In view of the potential benefit in the neurodevelopmental outcome and glycemic control, one may consider empirical inpatient trial with sulphonylurea if the genetic results are likely to be delayed. However, further studies with a large number of infants are warranted to decide on empirical sulphonylurea therapy[67]. Age at initiation of sulphonylurea showed a linear correlation with the dose required at follow-up. Indeed, all patients required additional glucose lowering medications along with sulphonylurea, if drug therapy was started at the age of 13 years or older[68]. Short-term studies on sulphonylurea therapy in children have been found to be safe without major side effects. Diarrheal episodes and rarely discolouration of teeth have been reported with sulphonylurea. Diarrhea usually disappears with therapy. None of these side effects will affect the continuation of therapy[63,69]. It is imperative to confirm the genetic mutation to decide treatment, to assess prognosis and anticipate the long term-outcome. They need to be followed even after remission as relapse has been reported in early adolescence or adults. The relapse responds well to sulphonylurea therapy.

These children need to be followed for glycemic control, growth pattern, developmental delay, seizures, pancreatic exocrine function, hypothyroidism and other comorbid states depending on the type of mutation. Periodic monitoring for long-term complications is mandatory. Presently there are no guidelines for long-term follow-up for diabetes related complications in these children with IODM, as long-term follow-up studies are lacking. Evaluation of the parental diabetic status and the genetic mutations will help to plan counseling regarding the future conceptions in the family. A neonatal diabetes registry has been established in India where facilities are available to sequence *KCNJ11*, *ABCC8*, *insulin* genes and other syndromic mutations.

CONCLUSION

DKA is the most common presentation of IODM (67%-83%). Low birth weight is common in infants less than 6 mo of age at presentation. Sixty-seven point five percent of IODM cases had a missed diagnosis at presentation. Monogenic diabetes is the most common cause of infantile onset diabetes. *KCNJ11/ABCC8* and *EIF2AK* mutations are the commonly reported non-syndrome and syndromic types, respectively. TNDM was noted in 10% of all infantile onset diabetics in South India. Developmental delay and seizures are major co-morbid factors in IODM. Glycemic control assessment among breast-fed infants and dispensing very small doses of insulin are difficult in IODM in developing countries. Management is by once or twice a day injections of intermediate-acting subcutaneous insulin, and continuous subcutaneous insulin infusions if feasible. Potassium channel mutations *(KCNJ11* and *ABCC8*) are sulphonylurea responsive and infants may need higher doses up to 2 mg/kg per day. Reported mortality during follow-up of IODM is very high (33%) in India.

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