

## Clinical Profile and Outcome of Infantile Onset Diabetes Mellitus in Southern India

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**Objective:** To study the etiology, clinical presentation and outcome of infantile onset diabetes mellitus (IODM).

**Design:** Descriptive cohort study. Retrospective study from 1999-2007 and prospective from 2008-2012.

**Setting:** The diabetic clinic at a Pediatric tertiary care referral institute in Chennai.

**Methods:** All infants diagnosed to have diabetes at less than one year of age were studied. Study variables were age at onset, gender, mode of presentation, birth weight, initial blood glucose, serum HbA1c, serum c-peptide levels, outcome at initial presentation, insulin requirement, associated co-morbid conditions, genetic analysis and outcome at the end of the study or until they were followed up.

**Results:** 40 infants with infantile onset diabetes were studied, constituting 8% of all children with onset of DM at less than 12 years of age. 67.5% of these children presented with diabetic keto acidosis (DKA), only 30% had a provisional diagnosis of DM or

DKA at first physician contact. 63% of IODM with onset less than 6 months and 30% with onset more than 6 months were of low birth weight. Nearly 85% of the study group had low C-peptide levels. 84.5% of IODM with onset less than 6 months and 55% of those with onset more than 6 months were monogenic. Wolcott Rallison syndrome was the commonest type encountered. Genetic diagnosis aided switching over from insulin to oral sulphonylurea in 5 children with *KCNJ11* and *ABCC8* mutations. Missed diagnosis, recurrent admissions for metabolic instability and developmental delay were common problems in IODM. Mortality at 12.5 year follow up was 32.5%.

**Conclusions:** IODM with onset at less than 6 months is predominantly monogenic and low birth weight is more common. 55% of IODM were misdiagnosed at onset. Developmental delay is the common co morbid condition in IODM. Genetic diagnosis aids change of therapy to oral sulphonylurea.

**Keywords:** India, Infantile onset diabetes, Monogenic diabetes, Neonatal diabetes.

**PII: S097475591200932**

Infantile Onset Diabetes Mellitus (IODM) is an uncommon form of diabetes. Diabetes Mellitus (DM) in the first 6 months of life is usually monogenic and is referred to as neonatal diabetes, and recent studies have suggested extending the screening for monogenic diabetes into later part of infancy [1]. Hospital-based incidence has been reported to be 1 in 125 type I DM patients [2]. Pediatric hospital based studies reveal the incidence of IODM as high as 1 in 7 children [3]. The reported incidence of neonatal diabetes mellitus varies from 1 in 89,000 to 1 in 4,00,000 live births [4-6]. Neonatal diabetes can be either transient or permanent. Transient neonatal diabetes is usually associated with abnormalities of chromosome 6 and *KCNJ11* and *ABCC8* [7]. Transient DM usually resolves before 18 months of age but may reappear in early childhood [8]. Incidence of permanent neonatal diabetes mellitus (PNDM) is 1 in 90,000 to 1 in 2, 10,000 and these infants present with persistent hyperglycemia

which requires long term insulin therapy [8]. This paper reports on 40 infants with IODM. To the best of our knowledge this is the only study on IODM with a follow up and genetic evaluation.

*Accompanying Editorial: Pages 737-8*

### METHODS

This descriptive study was conducted between January 2008 and April 2012 at the diabetic clinic of Institute of Child Health and Hospital for Children, a major teaching hospital in Chennai, India. The objective was to study the presentation and outcome of IODM. Data collection was retrospective from 1999 to 2007 and prospective from 2008 to 2012. For the purpose of this study, children with onset of diabetes at less than one year of age were considered as infantile onset and they were sub classified as neonatal if the onset was less than 6 months of age. (fasting C-peptide levels <0.5 pmol/mL was considered

poor pancreatic reserve). Data on infants treated as DKA where the hyperglycemia persisted for <72 hours or infants who were treated as DKA but died without confirmation by estimation of serum c-peptide levels or serum insulin levels or HbA1c at hospitalization were not included. Study parameters included age at onset, gender, mode of presentation, provisional diagnosis at admission, birth weight, initial blood glucose, serum HbA1c, serum c-peptide levels, outcome at initial presentation, insulin requirement, associated co-morbid conditions, genetic analysis and outcome at the end of the study or until they were followed up.

Data were analyzed using Epi Info statistical software and proportions were calculated. The study was undertaken after the approval of the institutional ethical and scientific review board. Informed consent was obtained from caregivers of all prospective subjects.

## RESULTS

Over a period of 12.5 years from 1999 to 2012, 506 children aged less than 12 years were registered in our diabetic clinic with diabetes Mellitus (DM), of whom 40 children (19 males) were IODM i.e., diagnosed at age less than one year (7.9% of the total clinic diabetic population). Age at diagnosis ranged from 3 days to 12 months (median 3.75 months). 27(67.5%) infants presented with diabetic keto acidosis (DKA) at the onset. Only 13 infants were initially diagnosed to have either diabetes or diabetic keto-acidosis. Revision of diagnosis was made with blood glucose values in 22 infants while 5 infants were screened for diabetes based on parental suspicion because the siblings were known to have diabetes.

14 infants with IODM (30%) were born of consanguineous marriage. 27.5% of the mothers reported previous miscarriage or death of a sibling in infancy.

**TABLE I** CLINICAL PRESENTATION OF INFANTILE ONSET DIABETES

| Initial presentation  | Number (%) |
|-----------------------|------------|
| Fever                 | 24 (60%)   |
| Polyuria              | 20 (50%)   |
| Breathlessness        | 18 (45%)   |
| Vomiting              | 18 (45%)   |
| Altered sensorium     | 16 (40%)   |
| White genital patches | 4 (1%)     |
| Poor feeding          | 3 (0.75%)  |
| Irritability          | 3 (0.75%)  |
| Sticky urine          | 3 (0.75%)  |
| Seizures              | 2 (0.5%)   |

Fever and polyuria were the commonest presenting symptoms (**Table I**). Evaluation for fever or hepatomegaly was a common mode of incidental diagnosis. Candidiasis of the external genitalia was the primary reason for medical attention in three infants. Sticky urine with flies and ants around the urinated floor was the primary reason for parental suspicion of diabetes in three infants.

Birth weight of the infants ranged from 1.6 to 3.5 kg (mean  $2.39 \pm 0.48$ ) and 50% of the babies were low birth weight (<2.5 kg). Neonatal diabetes was encountered in 28 infants (70%). The initial blood glucose ranged from 236 mg/dL to 950 mg/dL (mean 477 mg/dL). Among the 25 infants who had C-peptide evaluation, 21(84%) had poor pancreatic reserve while 3 were in the normal range. High C-peptide was seen in one infant with Berardinelli Seip Congenital Lipodystrophy (BSCL). Mean HbA1c at diagnosis was  $9.4 \pm 2.4\%$ .

Among the children with neonatal diabetes (*i.e.* onset <6 months of age), prevalence of low birth weight was higher than those with onset above 6 months of age ( $P=0.04$ ) (**Table II**).

Among the 40 infants, 2 died at initial presentation, 5 were referred back to the referring institute after initial stabilization and were not followed in our diabetic clinic. 33 infants were followed up for variable duration ranging from 30 days to 12.5 years. During follow up, 4 (10%) infants (3 female) had complete remission of DM (ability to maintain euglycemia without insulin). One infant with *ABCC8* mutation remitted at 6 months but was restarted on insulin at 9.7 years of age due to persistent hyperglycemia. Following genetic analysis, she was successfully switched

**TABLE II** COMPARISON BETWEEN INFANTS WITH ONSET OF DIABETES BEFORE AND AFTER 6 MONTHS OF AGE

| Parameters                         | Diabetes onset <6 mo of age (n=28) | Diabetes onset between 6-12 mo of age (n=12) |
|------------------------------------|------------------------------------|--|
| M:F ratio                          | 1:1.2                              | 1:1  |
| Birth weight <2.5 kg               | 63%                                | 30%*   |
| Mean initial blood glucose (mg/dL) | 478                                | 477  |
| Presentation as DKA                | 60.7%                              | 75%  |
| Mean insulin dose                  | 1.19 <sup>#</sup>                  | 1.4 <sup>#</sup>                             |
| Mortality at presentation          | 3.6%                               | 8.3%   |
| Overall mortality                  | 21.42%                             | 41.6%  |
| Monogenic DM                       | 16/19= 84.2%                       | 5/9=55.5%                                    |

\* $P=0.04$ ; <sup>#</sup>units/kg/day.

over to oral sulphonylurea at 10 years. The second child remitted at 5 months of therapy and is off insulin for 17 months with a HbA1c of 5.4 and has normal growth and development. The third child with *ABCC8* mutation remitted at 4.5 months of age and is off insulin for 5.5 years with HbA1c of 6.4%. The fourth child remitted at 4 months of therapy and is off insulin for 14 months and tested negative for *ABCC8*, *KCNJ11* and *INS*.

Based on the clinical features and genetic reports [9], the classification arrived in 21 infants is shown in **Table III**. Amongst the remaining 19 infants, one had pancreatic hypoplasia, seven were negative for *KCNJ11*, *ABCC8* and *INS* and eleven infants did not undergo genetic evaluation. Five IODM's with mutation in *KCNJ11* and *ABCC8* were switched over to sulphonylurea (glibenclamide) successfully (**Table IV**). All are developmentally normal.

WRS was the commonest form of syndromic diabetes in this study group. Of the 9 infants with features suggestive of WRS, 4 were genetically confirmed to have *EIF2AK3* mutation. Four children with WRS had an episode of hepatic failure and recovered. Two of the 9 infants had radiological features suggestive of WRS and associated hypothyroidism was encountered in 5

children. Among the four children with *EIF2AK3* mutation, one died at 3 years of age.

The common co-morbid conditions were hepatosplenomegaly (35%) and developmental delay (51.5%). Less common co-morbid features included short stature, squint, microcephaly, optic atrophy and failure to thrive. Recurrent hospitalization after the initial diagnosis was encountered in all but 7 of the infants followed up at our centre. The reasons for hospitalization were hypoglycemic episodes, DKA and hyperglycemia with intercurrent infections and hepatic failure. Recurrent DKA was a major issue in three infants due to poor compliance with therapy. During follow up, hypoglycemic episodes were encountered in most of the children. Over the period of 12.5 years, 13 out of the 40 infantile onset diabetic children died. Causes of death were DKA with cerebral edema, sepsis, acute respiratory distress syndrome, disseminated intravascular coagulation, hypoglycemia, refractory cardiac failure, septic shock and renal failure.

#### DISCUSSION

The incidence of IODM among all children with diabetes mellitus (<12 years) seen at our centre is 1 out of 13. No

**TABLE III** SYNDROMIC FORMS AND GENETIC MUTATIONS OF IODM

| Types                                      | Predominant clinical features  | Onset <6mo | Onset >6 mo |
|--|--|------------|-------------|
| Wolcott Rallison syndrome                  | Developmental delay, short stature, elevated liver enzymes, hepatic failure, skeletal dysplasia                          | 5          | 4           |
| Berardinelli Seip congenital lipodystrophy | Insulin resistance, failure to thrive, hepatosplenomegaly, lack of subcutaneous fat, coarse facies, hypertriglyceridemia | 1          |             |
| Fanconi Bickel syndrome                    | Round facies, hepatomegaly, rickets  | 1          |             |
| Other Genetic mutations                    | <i>ABCC8</i>   | 5          |             |
|  | <i>KCNJ11</i>  | 2          |             |
|  | <i>GCK</i>   | 1          |             |
|  | <i>INS1</i>  | 1          |             |

**TABLE IV** TRANSFER OF INFANTS FROM INSULIN TO ORAL SULPHONYLUREA THERAPY (GLIBENCLAMIDE)

| No | Genetic mutation | Age at diagnosis of DM (months) | Age at switch over (months) | Glibenclamide dose at switch over | HbA1c before switch over | HbA1c after switch over | Current age (months) |
|----|------------------|---------------------------------|-----------------------------|-----------------------------------|--------------------------|-------------------------|----------------------|
| 1  | <i>ABCC8</i>     | 4                               | 120                         | 0.75 mg/kg/day                    | 9.8                      | 7.6%                    | 122                  |
| 2  | <i>KCNJ11</i>    | 2.73                            | 22                          | 1 mg/kg/day                       | 7.97%                    | 5.1%                    | 46                   |
| 3  | <i>KCNJ11</i>    | 2.83                            | 5                           | 1 mg/kg/day                       | 7.2%                     | 6.9%                    | 15                   |
| 4  | <i>ABCC8</i>     | 1.27                            | 7.5                         | 1.2 mg/kg/day                     | 7.3%                     | 5.9%                    | 14                   |
| 5  | <i>ABCC8</i>     | 2.6                             | 4                           | 1.75 mg/kg/day                    | 14.6%                    | 6.8%                    | 10                   |

gender preponderance was noted in contrast to the existing literature with female preponderance [1, 2]. It is clinically difficult to differentiate between Transient neonatal diabetes mellitus and Permanent diabetes mellitus. PNDM could be nonsyndromic, syndromic or rarely due to pancreatic hypoplasia. Both non syndromic and syndromic PNDM may be due to mutation as previously described [10].

Identification of infants with *ABCC8/KCNJ11* mutation provides an opportunity to switch over from insulin injections to oral sulphonylurea therapy [ 5-7,11-15]. Insulin alone may not be able to reverse the neurological impairment in infantile onset diabetes. But oral sulphonylurea therapy can improve both the glycemc control and neurological status in some of these patients [16]. Rarely type1 DM with onset in infancy has been reported as also the *KCNJ11* mutation beyond 6 months in infancy [17,18].

The prevalence of monogenic diabetes varies from 63% to 78.5% in infants under 6 months and 6.6% to 12.5% in infants between 7-12 months. [19,20].The prevalence was correspondingly 84% and 55% in this study. The increased incidence in infants between 7- 12 months is probably due to the increased occurrence of Wolcott Rallison syndrome and this could probably be explained by the higher incidence of consanguinity.

DKA as the initial presentation was encountered in 67.5% in comparison to 83% in an earlier study from Chennai [3]. Missed diagnosis is common in infantile onset DM (67.5%). Classical symptoms of diabetes were not the presenting complaint in most of the cases. Incidental hyperglycemia was the diagnostic clue in 17 infants. Initial diagnosis in the study group included acute CNS infection, septic shock, urinary tract infection, renal tubular acidosis, bronchopneumonia, bronchiolitis, diarrheal dehydration, metabolic encephalopathy, and hepatomegaly for evaluation. Fever, vomiting and lethargy are common manifestations of IODM [21]. Evaluation of these infants should include family history of consanguinity, examination for dysmorphic features, auto-antibodies for type 1 DM followed by genetic studies. It is essential to evaluate for monogenic diabetes in all antibody negative infants with diabetes mellitus.

Among the 40 infants, mortality at initial diagnosis was 5%. Need for hospitalization exists for most of the diabetic infants during follow up for severe metabolic derangements or intercurrent infection. Children with WRS have hepatomegaly, elevated liver enzymes, short stature, skeletal deformities, and developmental delay with or without hypothyroidism [22]. Hypoglycemic episodes and hepatic failure are common in WRS.

Mortality is reported to be high in WRS [1,3,22]. Infantile onset BSCL is very rare and the infant in this study had hepatosplenomegaly, generalized lack of subcutaneous fat, hirsutism, dyslipidaemia, and dysmorphic facies and died of a rapid fatal course.

Insulin requirement at stabilization for infants ranged from 0.35 to 3 units/kg/day. Intermediate acting insulin is preferred as this prevents hypoglycemia associated with short acting insulin. Use of continuous subcutaneous insulin infusion may be an ideal option to deliver smaller doses of insulin [23]. Dispensing less than one unit of insulin posed difficulty in IODM. Developmental delay and seizures were the common co-morbid conditions. Syndromic associations like Wolcott Rallison syndrome, DEND syndrome [24], consequences of the hypoglycemia and cerebral edema in DKA could explain the high incidence of developmental delay and seizures in IODM. None of the children followed up showed retinopathy or nephropathy. Mortality in IODM over 12.5 year period was 32.5%. A pediatric report of one year follow up of IODM have shown a mortality of 16.6% from Chennai [3]. The limitations of this study include lack of genetic diagnosis in some the infants due to various reasons and being a retrospective study at a referral centre, not all subjects were followed up to the end of the study period.

*Acknowledgments:* Molecular genetic laboratory at Royal Devan and Exeter NHS foundation trust for performing a part of the genetic work up free of cost.

*Contributors:* VP: designed the study and was involved in the data collection; VP, ST, SS and MV: were involved in the study design and data analysis; JS and RV: were involved in the genetic evaluation. All the authors were involved in manuscript preparation.

*Funding:* A part of the genetic investigations for children in this study group was done by the Indian Council of Medical Research through the project "Genetic Analysis of Maturity Onset diabetes of young (MODY) and Neonatal diabetes in India".

*Competing interest:* None stated.

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**WHAT IS ALREADY KNOWN?**

- Indian literature describes few case reports of neonatal diabetes and its outcome.

**WHAT THIS STUDY ADDS?**

- Diagnosis is often missed in infantile onset diabetes mellitus.
- Among the IODM with onset at age <6 months, 85% is monogenic.
- Developmental delay is more common in infantile onset diabetes mellitus and mortality is 32.5%.

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