RESEARCH PAPER

Neonatal Diabetes: A Case Series

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Background: Neonatal diabetes mellitusis a rare disorder with an incidence of 1 in 2,60,000 live births. **Methods**: Retrospective analysis of clinical and genetic profile of children admitted with neonatal diabetes mellitus in a tertiary-care hospital in Chennai, India over 11 years. **Results**: Ten children were diagnosed with neonatal diabetes of whom 9 had permanent neonatal diabetes mellitus. The age range at onset was from 3 days- 5 months. Of the 9 children, *KCNJ11* gene mutation was positive in one, *and ABCC* 8 and *INS* gene mutation in two children each. Children with *KCNJ11* and *ABCC 8* gene mutations were switched over to oral sulfonyl urea therapy. **Conclusion**: Few genotypes causing NDM can be managed effectively with oral sulfonyl ureas.

Keywords: *Diabetes mellitus, Genetics, Permanent, Transient.*

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Monogenic diabetes results from the inheritance of a mutation or mutations in a single gene [1], and accounts for 1-5% of all childhood diabetes [2]. Neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY) are the two main forms of monogenic diabetes. NDM first occurs in newborns and young infants; MODY usually first occurs in children or adolescents but may be mild and not detected until adulthood. Most patients with monogenic diabetes are incorrectly diagnosed as either type 1 or type 2 diabetes. Identifying this entity correctly not only helps to initiate appropriate treatment but also helps us to explain the other associated clinical features and offer genetic counseling to the family for subsequent pregnancies [3]. An earlier study from Chennai [4] had reported 28 children with neonatal diabetes (0.05%) and 12 children with diabetes onset between 6 months to 1 year of age out of 506 diabetic children registered in their institute. The common gene mutations reported in their series were *ABCC8 f*ollowed with *EIF2AK3* and *KCNJ11*. We describe the clinical features and follow-up of children with neonatal diabetes from an urban children's hospital in Chennai, India.

METHODS

A retrospective analysis of case records of children admitted with neonatal diabetes mellitus in the Department of Pediatrics and Endocrinology of Kanchi Kamakoti CHILDS Trust hospital, Chennai from January 2004 to December 2014 were analyzed. The study was approved by the institutional review board. A diagnosis of neonatal diabetes mellitus was established in infants who had their onset of diabetes within the first 6 months of life and presented with features of polyuria, polydipsia, weight loss, DKA and had their fasting blood sugar >126 mg/dL with HbA1C >6.5%. The case records of infants with neonatal diabetes mellitus were analyzed for birth weight, the age at onset of symptoms, the clinical features, laboratory investigations (FBS, HbA1C values), Genetic mutation testing results, treatment and follow-up details. We collected 3 mL of whole blood in EDTA tube from the proband and their parents, and sent it to Royal Devon and Exeter NHS Foundation Trust laboratory, Exeter, UK for genetic analysis. Molecular genetic testing included gene sequencing by PCR technique. All infants were treated with subcutaneous insulin at 05 -0.8 U/kg/day and were followed up.

RESULTS

During the study period, a total of 137 children were diagnosed as Type 1 diabetes mellitus as per WHO diagnostic criteria and 10 (5 boys) were diagnosed as neonatal diabetes mellitus. The age range at onset was from 3 days to 160 days. Six children were born to parents with consanguineous marriage and none had history of diabetes in their first degree relatives. All were born at term and six were born with a birth weight <2.5 kg. Diabetic ketoacidosis was the mode of presentation in 3 (30%) children *(INS,EIF2AK3* and *NEUROD1* gene). Glutamic

TABLE 1 CLINICAL AND GENETIC PROFILE OF CHILDREN WITH NEONATAL DIABETES MELLITUS

Case No	*Age at diagnosis*	*Sex*	*Clinical features*	*Consan-guinity*	*Birth-weight*	*Genetic analysis*	*Diagnosis*	*Treatment*	*Follow-up*
1	3 d	F	Hyperglycemia, Macroglossia, umblicalhernia	No	2 kg	Complete loss of methylation at the TND differentially methylated region on chromosome 6q24.	TNDM	Insulin × 5 mo, then offinsulin	16 mo of age, off insulin, doing well
2	60 d	M	Polyuria, poor weightgain	No	2.4 kg	Heterozygous missense mutation (R201C) in the *KCNJ11*gene.	PNDM	Insulin Initially, Glibenclamide (0.5mg/kg)	5 y, On Glibenclamide, doing well
3	160 d	M	Polyuria, seizures	No	2.5 kg	Novel heterozygous frame-deletionc.3808_3813delA*ACTCC* in exon 31 of the *ABCC8* gene.	PNDM	Insulin Initially, Glibenclamide (0.5mg/kg)	3 y, On Glibenclamide, doing well
4	14 d	F	Polyuria, seizures	2 degree	3.6 kg	Homozygous splicing mutation, IVS16+1G>A, in intron 16 of the *ABCC8* gene; Father and mother carriers.	PNDM	Insulin Initially, Glibenclamide	3 y, on Glibenclamide, (0.5mg/kg) doing well
5	45 d	M	Polyuria, poor weightgain	2 degree	2.4kg	Heterozygous missense mutation, Y108D, inexon 3 of the *INS*gene.	PNDM	Insulin	3 y, On insulin, doing well
6	90 d	F	Polyuria, FTT, DKA	No	2.3 kg	Homozygous novel mutation. c-218A>C/c.-218A>C, in the promoter of the *INS* gene; Mother carrier.	PNDM	Insulin	5 y, On insulin, doing well
7	20 d	F	Poor feeding, lethargy, fever	3 degree	1.7 kg	Homozygous for a novel missense mutation, R176 Q in exon 2 of the *PDX1 (IPF1)* gene.	PNDM	Insulin	8 y, on insulin, doing well
8	150 d	M	DKA (5 Months), Hepatitis (1,2 y), short stature (2 y)	2 degree	3 kg	Homozygous for a novel missense mutation, R587Q, in exon 10 of the *EIF2AK3* gene; Father and mother carriers.	PNDM-Wolcott Rallison syndrome	Insulin, liver supportive	Died at 4 yrs of age due to MODS
9	137 d	F	Polyuria, FTT, Anemia (8mo), Retinitispigmentosa (7mo), cochlear implant (2 y)	3 degree	2.8 kg	Heterozygous novel missense mutation, G105 E in exon 2 of the *SLC19A2* gene.	PNDM-TRMA	Insulin, Thiamine	10 ys, on insulin+thiamine, Doing well
10	60 d	M	DKA, Right focal seizure, inferior cerebellar vermis hypoplasia	2 degree	2.4 kg	Homozygous for a frame shift mutation c.235_236 insT, in the *NEUROD1*gene. Father and mother carriers.	PNDM	Insulin	20 mo on insulin, has mild motor developmental delay

F- Female; M-Male; FTT- Failure to thrive; DKA- Diabetic ketoacidosis; TNDM-Transient neonatal Diabetes mellitus; PNDM-permanent Neonatal Diabetes mellitus.

acid decarboxylase and islet cell autoantibodies were negative in all children. The mean blood sugar was 499 mg/dL. Of the 10 children, one child had transient neonatal diabetes mellitus and nine had permanent neonatal diabetes mellitus. The child with transient neonatal diabetes presented with hyperglycemia on D3 of life, required insulin for 5 months, and mutation analysis revealed complete loss of methylation on chromosome 6 q24. She is off insulin and at her 16 month follow-up, she is growing well. Of the nine children with permanent neonatal diabetes mellitus, *KCNJ11* gene mutation was positive in 1, *ABCC 8* gene and *INS* gene mutation in 2 each, *PDX1* gene mutation in 1, *NEURO D1* mutation in 1, *EIF2AK3* mutation in 1 and *SLC19A2* gene mutation in 1 child. Children with *KCNJ11* gene mutation and *ABCC 8* gene mutation were treated with oral sulfonyl urea and others were treated with Insulin. On follow up, the child with Wolcott Rallison Syndrome died and other patients are growing well without problems. The details are shown in ***Table* I**.

DISCUSSION

Nine children were diagnosed with permanent NDM in the present series. Heterozygous activating mutations in the *KCNJ11* gene, that encodes the KATP channel subunit *Kir6.2*, accounts for 47% of permanent *NDM* [5,6] and a few cases of treatment NDM [7,8]. Similarly mutations in *ABCC8* gene which encodes the SUR1 regulatory subunit of the ATP-sensitive potassium channels in beta cells can cause both permanent and transient neonatal diabetes. In clinical practice it is difficult to differentiate between patients with *KCN J11*or *ABCC8* mutations and oral sulfonyl urea becomes the treatment of choice for diabetes resulting from both these mutations [9,10]. Our patients were switched on treatment from insulin to oral glibenclamide (0.5 mg/kg/day) once the genetic diagnosis was established, and on follow up their glycemic control was good.

The present study describes the clinical and genetic profile of children with neonatal diabetes mellitus. As the molecular genetic testing is expensive, we suggest an algorithm to approach a child with neonatal diabetes for ordering genetic testing in resource limited setting like ours (***Fig.* 1**). Molecular genetic testing has a big impact on management of NDM as switching over to oral sulfonyl urea is required in children with *KCNJ11/ABCC 8* gene mutation. Complete history, thorough clinical examination with a high suspicion and correlation with physical findings may help us to guide further the genotype work up of neonatal diabetes mellitus.

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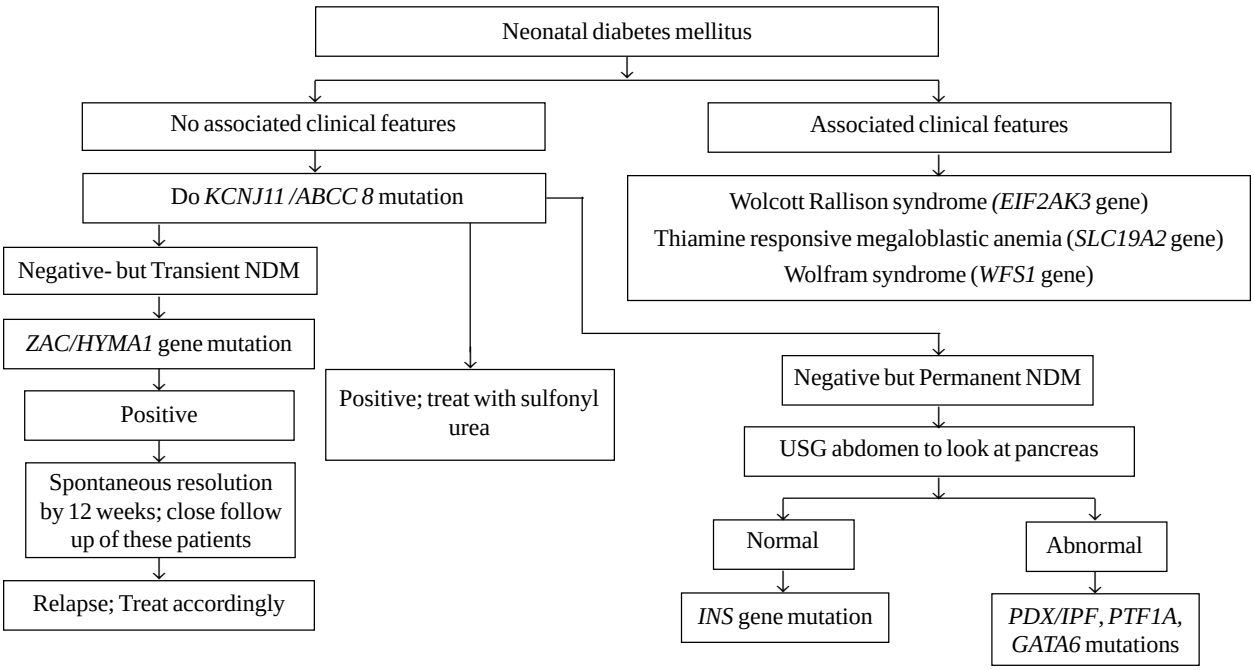

FIG. 1 *Proposed algorithm for ordering genetic mutation testing in patients with neonatal diabetes (NDM).*

WHAT THIS STUDY ADDS?

- The present study reports the molecular genetics of nine children with permanent neonatal diabetes mellitus.

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