RESEARCH BRIEF

Neonatal Diabetes: A Case Series

Ramaswamy Ganesh, Natarajan Suresh, Thiruvengadam Vasanthi and *KG Ravikumar

From Departments of Pediatrics and **Endocrinology, Kanchi Kamakoti CHILDS Trust hospital* and *The CHILDS Trust Medical Research Foundation, Chennai, Tamil Nadu, India.*

Correspondence to: *Dr Ramaswamy Ganesh, Consultant Pediatrician, Kanchi Kamakoti CHILDS Trust hospital, Chennai 600 034, India. ganeped79@rediffmail.com*

PII: S097475591600020

ABSTRACT

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 1, *ABCC* 8 and *INS* gene mutation in 2 each, *PDX1* gene mutation in 1, *NEURO D1* mutation in 1, *EIF2AK3* mutation in 1, and *SLC 19A2* gene mutation was seen in one child. 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,

INTRODUCTION

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] has 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 tertiary care 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 this study period a total of 137 children were diagnosed as Type 1 diabetes mellitus (DM) 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 of consanguineous marriage and none had history of DM in their first degree relatives. All were born at term and 6 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 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. Children with *KCNJ11* gene mutation and *ABCC 8* gene mutation were treated with oral sulfonyl urea (Glibenclamide 0.5 -1mg/kg/day) and others were treated with Insulin. On follow up, child with Wolcott Rallison Syndrome died and other patients are growing well without problems. The details are shown in ***Web 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 DM.

***Acknowledgements*:** Prof Sian Ellard, Consultant Molecular Geneticist, Peninsula Medical School (Royal Devon and Exeter NHS Foundation Trust, Exeter) and Professor Karen Temple, Wessex Regional Genetics laboratory, University of Southampton School of Medicine for carrying out the molecular Genetic work-up.

Contributors: RG, NS, TV: reviewed literature, drafted manuscript and were involved in patient management; KGR: reviewed manuscript for intellectual content and will act as the guarantor.

Funding: None; *Competing interest*: None stated.

What This Study Adds?

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

REFERENCES

1. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue KC. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatric Diabetes. 2009;10:33-42.
2. National diabetes information clearing house. Monogenic Forms of Diabetes: Neonatal Diabetes Mellitus and Maturity-onset Diabetes of the Young. Available from: *www.diabetes.niddk.nih.gov*. Accessed February 24, 2012.
3. Slingerland AS. Monogenic diabetes in children and young adults: Challenges for researcher, clinician and patient. Rev Endocr Metab Disord. 2006;7:171-85.
4. Varadarajan P, Sangaralingam T, Senniappan S, Jahnavi S, Radha V, Mohan V. Clinical profile and outcome of infantile onset diabetes mellitus in southern India. Indian Pediatr. 2013;50:759-63.
5. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, *et al.* Activating mutations in the gene encoding the ATP-sensitive potassium channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med. 2004;350:1838-49.
6. Hattersley AT, Ashcroft FM. Activating mutations in Kir6.2 and neonatal diabetes: new clinical syndromes, new scientific insights, and new therapy. Diabetes. 2005; 54:2503-13.
7. Gloyn AL, Reimann F, Girard C, Edghill EL, Proks P, Pearson ER, *et al.* Relapsing diabetes can result from moderately activating mutations in KCNJ11. Hum Mol Genet. 2005;14:925-34.
8. Colombo C, Delvecchio M, Zecchino C, Faienza MF, Cavallo L, Barbetti F. Transient neonatal diabetes mellitus is associated with a recurrent (R201H) KCNJ11 (KIR6.2) mutation. Diabetologia. 2005;48:2439-41.
9. Pearson ER, Flechtner I, Njolstad PR, Malecki MT, Flanagan SE, Larkin B, *et al.* Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med. 2006;355:467-77.
10. Babenko AP, Polak M, Cave H, Busiah K, Czernichow P, Scharfmann R, *et al.* Activating mutations in the *ABCC8* gene in neonatal diabetes mellitus. N Engl J Med. 2006;355:456-66.

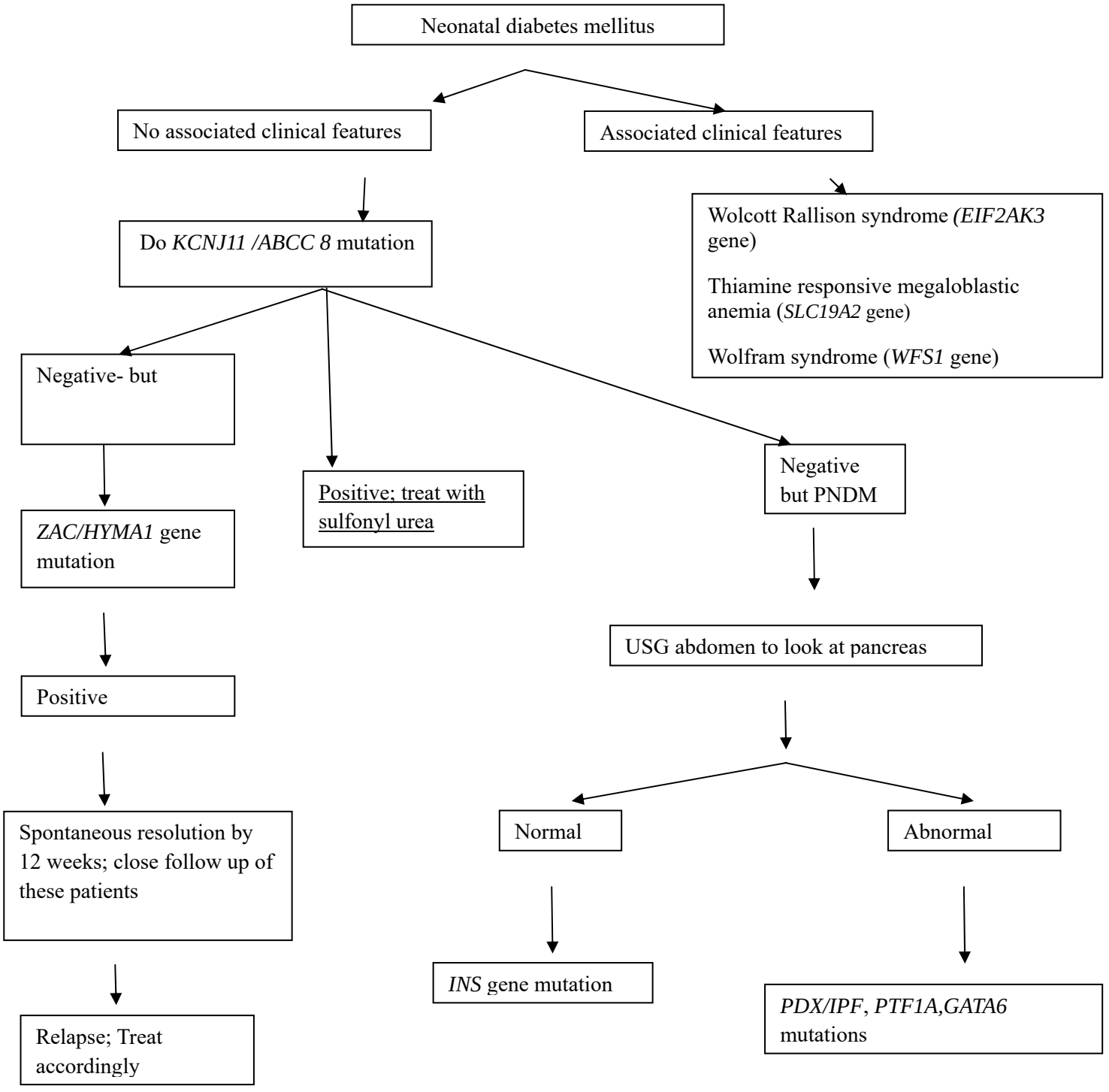

***Fig.* 1:** Proposed genetic testing algorithm for patients with neonatal diabetes

Case No	Age at diagnosis	Sex	Clinical Features	Consanguinity	Birth weight	Genetic analysis	HbA1C at diagnosis	Diagnosis	Treatment	Follow up
1	3 days	F	Hyperglycemia,Macroglossia, umblical hernia	No	2 kg	Complete loss of methylation at the TND differentially methylated region on chromosome 6 q24	15.40%	TNDM	Insulin (1.2 U/kg/day) x 5 months, then off insulin	16 months of age, off insulin,Normal development
2	60 days	M	Polyuria, poor weight gain	No	2.4 kg	heterozygous missense mutation (R201C) in the *KCNJ11* gene	10.20%	PNDM	Insulin (0.5 U/kg/day)Initially, Glibenclamide (0.5 mg/kg)	5 years , On Glibenclamide, doing well,Normal Development
3	160 days	M	Polyuria, seizures	No	2.5 kg	Novel heterozygous frame deletion c.3808_3813delAACTCC in exon 31 of the *ABCC 8* gene.	15.10%	PNDM	Insulin (0.5-0.8 U/kg/day)Initially, Glibenclamide (0.5 mg/kg)	3 years ,On Glibenclamide, doing well,Normal Development
4	14 days	F	Polyuria, seizures	2 degree	3.6 kg	homozygous splicing mutation, IVS16+1G>A, in intron 16 of the *ABCC8* gene. Father & mother carriers	14.20%	PNDM	Insulin (0.5-0.8 U/kg/day) Initially, Glibenclamide (0.5 mg/kg)	3 years,on Glibenclamide, doing well,normal development
5	45 days	M	Polyuria, poor weight gain	2 degree	2.4 kg	heterozygous missense mutation, Y108D, in exon 3 of the *INS* gene.	25.30%	PNDM	Insulin(0.5 U/kg/day)	3 years,On insulin, ,Normal development
6	90 days	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	14.80%	PNDM	Insulin(0.7 U/kg/day)	5 years,on insulin, normal development
7	20 days	F	Poor feeding, lethargy, fever	3 degree	1.7 kg	Homozygousfor a novel missense mutation , R176 Q in exon 2 of the *PDX1(IPF1)* gene.	10.70%	PNDM	Insulin (0.5U/kg/day)	8 years,on insulin,normal development
8	150 days	M	DKA (5 Months), Hepatitis(1.2 years), short stature (2 years)	2 degree	3 kg	Homozygous for a novel missense mutation, R587Q, in exon 10 of the *EIF2AK3* gene. Father & mother carriers	8.40%	PNDM-Wolcott Rallison syndrome	Insulin(0.8 U/kg/day),liver supportives	Died at 4 years of age due to MODS
9	137 days	F	Polyuria,FTT,Anemia (8 months), Retinitis pigmentosa(7months), cochlear implant (2years)	3 degree	2.8 kg	Heterozygous novel missense mutation ,G105E in exon 2 of the *SLC19A2* gene	10.20%	PNDM-TRMA	Insulin(0.7 U/kg/day),Thiamine	10 years,on insulin+ thiamine, global development delay
10	60 days	M	DKA,Right focal seizure , inferior cerebellar vermis hypoplasia	2 degree	2.4 kg	Homozygous for a frameshift mutation c.235_236insT, in the *NEUROD1* gene. Father & mother carriers	11.10%	PNDM	Insulin(0.8 U/kg/day)	20 months 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

Web Table I Clinical and genetic profile of children with neonatal diabetes mellitus