ORIGINAL ARTICLE

Identification of First Case of Neonatal Diabetes in Singapore and Successful Conversion from Insulin to Sulphonylurea

Rashida Vasanwala, *MD (Paeds), MRCPCH (UK)*, Fabian Yap, *MMed (Paeds) MRCP (Paeds), FAMS*, Song Hai Lim, *MRCPCH (UK),* Pei Kwee Lim, *RSCN, CDE*, Soo Ting Lim, *MN, CDE* Angela Hui, *RN, BN*

Department of Paediatric Medicine, KK Women's and Children's Hospital, Singapore

ABSTRACT

Introduction: To date Neonatal Diabetes Mellitus (NDM) has not been reported in Singapore. Neonatal diabetes is a rare (1 in 100,00–300,000 live births) insulin-requiring form of diabetes with well defined subgroups, permanent neonatal diabetes (PND) and transient neonatal diabetes (TND), each accounting for approximately 50% of patients. Genotyping NDM identifies the exact unique molecular aetiology of very early onset insulin requiring diabetes and has the potential to dramatically alter the management of the patient, who would otherwise be insulin dependent for life.

Method: We identified a child who presented at 3 and half months of age with diabetic ketoacidosis and determined the phenotypic and genotypic characteristics. Blood samples for molecular genetic analysis were sent to Royal Devon and Exeter Foundation Trust, UK. We determined her Continuous Glucose Monitoring profiles after initiation of sulphonylurea therapy.

Results: The patient was diagnosed as a heterozygous for a missense mutation R201H, in the *KCNJ11* gene. Results confirmed a diagnosis of permanent neonatal diabetes due to a mutation in the Kir6.2 subunit of the K_{ATP} channel. We initiated sulphonylurea therapy and subsequently ceased insulin treatment successfully. Currently 2 years old, this patient is no longer insulin dependent.

Conclusion: This is the first case report of neonatal diabetes in Singapore. It describes the importance of correct identification of the case, and successful conversion of therapy from insulin to sulphonylureas with optimal blood glucose control. We emphasise the need for medical practitioners to consider molecular testing for all patients who present with diabetes below 6 months of age as this will facilitate accurate diagnosis and appropriate therapy.

Keywords: genetic analysis, neonatal diabetes, sulphonylurea

INTRODUCTION

Neonatal diabetes mellitus (NDM) is a rare, insulin-requiring form of diabetes characterised by the onset of diabetes in a neonate or infant below six months of age. Children with NDM have non-autoimmune diabetes mellitus caused by an abnormality in one of a number of genes. These include mutations in the genes (*KCNJ11* and *ABCC8*) encoding the two protein subunits (Kir6.2 and SUR1, respectively) of the ATP-sensitive potassium channel and in the (*INS*) gene encoding insulin[1–12]. They account for 31% (*KCNJ11*), 12% (*INS*) and 10% (*ABCC8*) of cases in the large Exeter cohort[13].

Unlike classical juvenile diabetes, it is possible for NDM to resolve spontaneously a condition known as transient neonatal diabetes mellitus (TND). It is also possible for some children with permanent forms of the disease, known as permanent neonatal diabetes mellitus (PND), to switch from insulin injection to oral sulphonylurea treatment. As these observations have important management implications for the child with NDM and because

NDM has not been reported in Singapore, we report this first case and characterise its phenotype and genotype.

METHODS

Case Identification

We identified this case who presented with features suggestive of early onset diabetes. Clinical data was extracted from the case notes. The following investigations were performed — blood gases, blood/urine for ketones, C-peptide levels, and Glutamic acid Decarboxylase (GAD) and Islet Cell antibody (ICA) levels. A Continuous Glucose Monitoring System (CGMS) was used to analyse the blood glucose trends after introduction of sulphonylurea.

Mutational Analysis

Molecular genetic analysis was performed at the molecular genetics laboratory in Exeter, United Kingdom.

Informed consent was obtained from the parents.

RESULTS

The patient was identified and diagnosed as a case of neonatal diabetes mellitus. She presented at 3 and half months of age with history of fever and vomiting for 2 days. A full septic workup which included lumbar puncture, urine and blood cultures and sensitivities was done. She was noted to have a high anion gap metabolic acidosis (pH 7.24, PCO_2 18, PO_2 56, BE-17, HCO_3 7.5), a blood glucose of 20 mmol/l, urine ketones 2+, urine sugar 4+, blood ketones 2.8mmol/l. In view of the hyperglycaemia, metabolic acidosis and ketonaemia, a diagnosis of early onset diabetic ketoacidosis was made. Treatment was started with the diabetic ketoacidosis protocol. The patient was also treated for possible sepsis.

She was started on 10% deficit replacement for dehydration with dextrose saline solution and intravenous insulin infusion 0.1units/kg/hour. The insulin infusion was reduced to 0.05units/kg/hour following a drop in the blood glucose levels to 8 mmol/L feeds were commenced 2 days later and the insulin regime was converted to subcutaneous injections of insulatard and novorapid. Her metabolic acidosis and ketonaemia, improved and her blood sugars remained stable. The blood and urine cultures were all negative; her HbA1c was 14.5%, C-peptide 0.7, Insulin 1mU/l, and GAD & ICA antibodies were negative.

A clinical diagnosis of probable neonatal diabetes was entertained and confirmed by molecular genetic testing. The patient was diagnosed as heterozygous for a missense mutation R201H, in the *KCNJ11* gene. Results confirmed a diagnosis of permanent neonatal diabetes due to a mutation in the Kir6.2 subunit of the K_{ATP} channel. Both of her parents were tested for the mutation, and were negative. It is therefore likely that the R201H mutation has arisen de novo. The possibility of having another affected child cannot be excluded.

She was discharged with subcutaneous insulatard injections at a dose of 2.5 units 3 times a day (8 am, 4 pm, 12 midnight), with instructions to add Novorapid 0.5 units if the blood glucose was more than 18 mmols/L. After 6 weeks of discharge she was admitted for initiation of sulphonylurea therapy and CGMS monitoring. The insulatard was switched to twice daily dosing (2.5 units) and glibenclamide was started at 0.2mg/kg/day twice a day, given at 6:00–8:00 am and 6:00–8:00 pm. Within one month of initiation of glibenclamide therapy her insulatard was weaned off. Currently she is 2 and half year's old and is on twice daily glibenclamide (dose of 0.12mg/kg/day) with good glycaemic control. Transfer to sulphonylurea therapy had been successful for all patients with this mutation and hence, sulphonylurea therapy was introduced successfully and she is no longer insulin dependent[13].

Fig. 1 shows the CGMS trends over 3 days after introduction of sulphonylurea and Fig. 2 shows the trend for HbA1c and C-peptide.

DISCUSSION

This is the first case report of neonatal diabetes in Singapore. It demonstrates the successful conversion of a child with permanent neonatal diabetes from insulin to sulphonylurea therapy with optimal blood glucose control. The outcome illustrates the importance of diagnosing neonatal diabetes correctly as it has implications for future treatment and prognosis.

This case of neonatal diabetes with the R201H mutation, in the *KCNJ11* gene represents the most common permanent neonatal diabetes causing mutation. Activating mutations in the Kir6.2 pore-

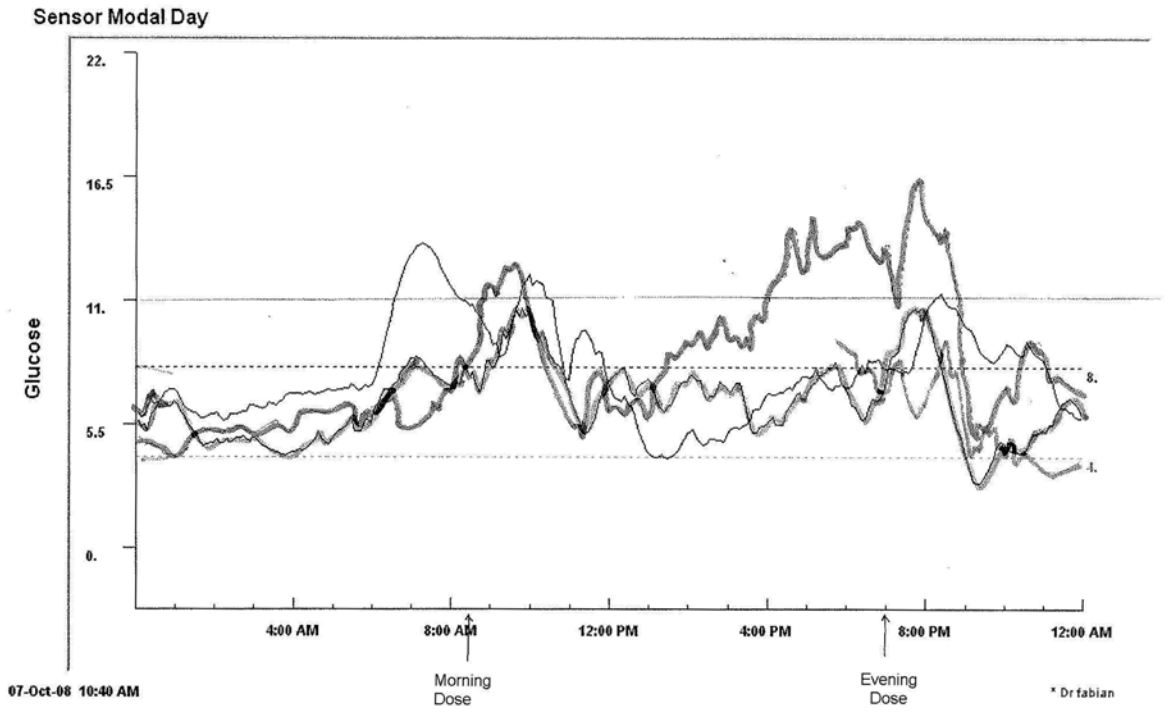

Fig 1. CGMS post sulphonylurea blood glucose trend over three days.

CGMS: Shows the trend of blood glucose over three days on twice daily dose of glibenclamide. Most of the readings are between 5 to 11 mmol/L, with an average of 5.5 mmol/L.

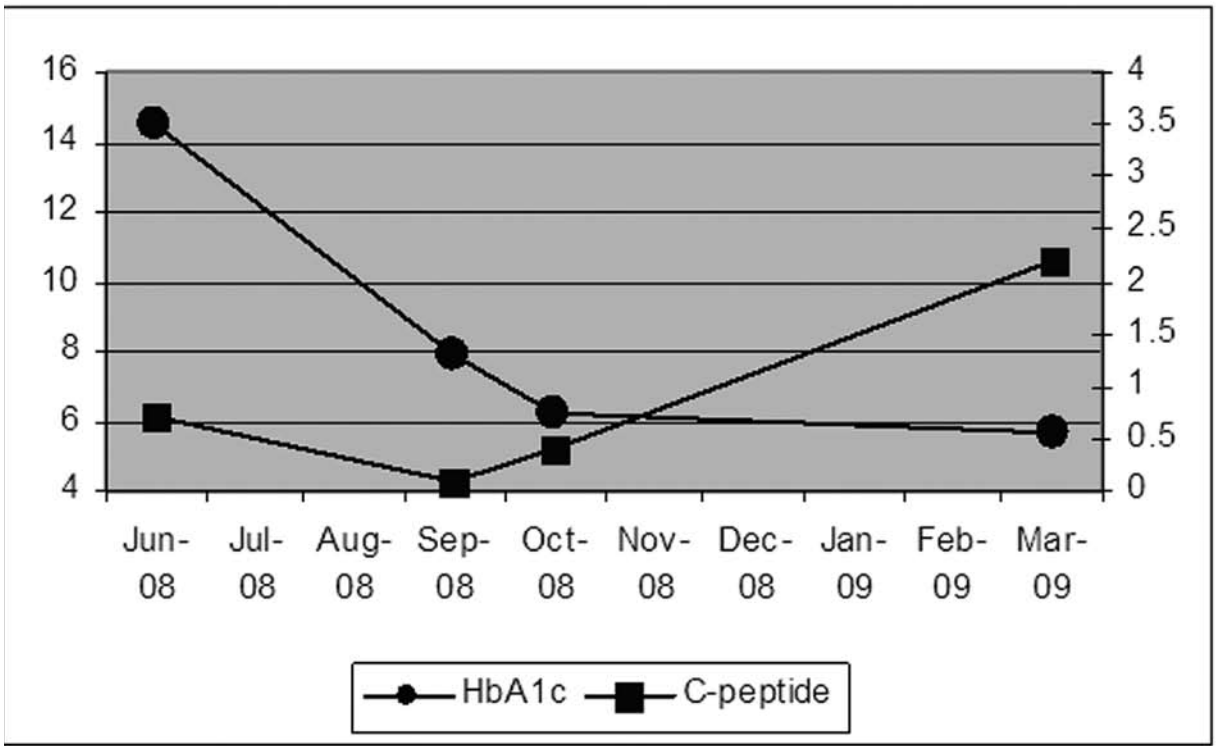

Fig 2. Trends for HbA1c and C-peptide.

Graph shows the trends of HbA1c and C-peptide, and the points of introduction of glibenclamide and taking off insulin treatment completely. HbA1c has been maintained at 6% on glibenclamide therapy and the C-peptide levels have progressively increased.

encoding gene (*KCNJ11*) have been identified in both transient and permanent neonatal diabetes mellitus[14]. These mutations are familial or more often sporadic in nature. Under physiological conditions K_{ATP} channel closure is a central step in glucose-stimulated insulin release. *KCNJ11*-activating mutations result in reduced channel sensitivity to ATP, in the presence of glucose. This favours an open channel state and membrane hyperpolarisation, translating into impaired insulin release and neonatal diabetes mellitus seen in the absence of β-cell auto-antibodies[14].

KCNJ11-activating mutations, such as the R201H polymorphism which is the most common permanent neonatal diabetes mellitus-causing mutation, results in ATP-insensitive channels that respond to sulfonylurea with channel closure and insulin release[14]. These drugs stimulate insulin secretion by binding to, and closing the K_{ATP} channels. Sulphonylureas bypass beta-cell metabolism but subsequently stimulate the same chain of events as glucose. This ability to successfully inhibit K_{ATP} channel activity by an ATP-independent mechanism, and thus bypass nucleotide-dependent channel gating, forms the basis for the clinical application of these drugs in patients with neonatal diabetes. Recently, the efficacy of therapeutic amendment from insulin to sulfonylurea-based treatment was assessed in cases of neonates with diabetes owing to Kir6.2 mutations[15]. Ninety per cent of subjects had a successful therapeutic response to an oral sulfonylurea, such as glyburide. These patients usually have minimal, if any, detectable circulating insulin levels and require exogenous insulin to prevent hyperglycaemia and ketoacidosis. Sulfonylurea was not only effective in achieving an acceptable level of glycated haemoglobin, a parameter used to assess glycaemic control, but they also sustained the euglycemic response in patients with Kir6.2 mutations. Other studies have also independently established the success of sulfonylureas in achieving a clinical response in patients with diabetes due to Kir6.2 mutations affecting the ATP sensitivity of the channel[16,17].

The clinical application of these drugs in patients with neonatal diabetes due to mutations affecting the ATP sensitivity of the channel is reflected in this case. After initial diagnosis, the patient was started on insulin and the dose was rapidly weaned with successful introduction of glibenclamide. Good glycaemic control was achieved on glibenclamide as illustrated by the HbA1c trends in Fig. 2. Oral sulfonylurea treatment thus forms an attractive alternative to lifelong exogenous injections of insulin in these patients.

CONCLUSION

This recent advance in the field of neonatal diabetes illustrates how the molecular understanding of some monogenic forms of diabetes may lead to an unexpected change of treatment in children. This is a spectacular example of a pharmacogenomic approach improving the quality of life of our young patients. The challenge ahead is to identify these cases early, so as to facilitate accurate diagnosis and tailor therapy accordingly. We emphasise the need for medical practioners to consider molecular testing for all patients who present with diabetes below 6 months of age as this will facilitate accurate diagnosis and appropriate therapy.

REFERENCES

1. Flanagan SE, Edghill EL, Gloyn AL, Ellard S, Hattersley AT. Mutations in KCNJ11, which encodes Kir6.2, are a common cause of diabetes diagnosed in the first 6 months of life, with the phenotype determined by genotype. Diabetologia. 2006;49(6):1190–7.
2. Edghill EL, Dix RJ, Flanagan SE, Bingley PJ, Hattersley AT, Ellard S, et al. HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. Diabetes. 2006;55(6):1895–8.
3. Slingerland AS. Monogenic diabetes in children and young adults: challenges for researcher, clinician and patient. Rev Endocr Metab Disord. 2006;7(3):171–85.
4. Flanagan SE, Patch AM, Mackay DJ, Edghill EL, Gloyn AL, Robinson D, et al. Mutations in ATP-sensitive K+ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. Diabetes. 2007;56(7):1930–7.
5. 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(5):456–66.
6. Støy J, Edghill EL, Flanagan SE, Ye H, Paz VP, Pluzhnikov A, et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proc Natl Acad Sci U S A. 2007;104(38):15040–44.
7. Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. Nat Genet. 1997;15(1):106–10.
8. Delepine M, Nicolino M, Barrett T, Golamaully M, Lathrop GM, Julier C. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. Nat Genet. 2000;25(4):406–9.
9. Njolstad PR, Sovik O, Cuesta-Munoz A, Bjorkhaug L, Massa O, Barbetti F, et al. Neonatal diabetes mellitus due to complete glucokinase deficiency. N Engl J Med. 2001;344(21):1588–92.
10. Vaxillaire M, Dechaume A, Busiah K, Cavé H, Pereira S, Scharfmann R, et al. New ABCC8 mutations in relapsing

neonatal diabetes and clinical features. Diabetes. 2007;56(6):1737–41.

11. Polak M, Dechaume A, Cavé H, Nimri R, Crosnier H, Sulmont V, et al. Heterozygous missense mutations in the insulin gene are linked to permanent diabetes appearing in the neonatal period or in early infancy: a report from the French ND (Neonatal Diabetes) Study Group. Diabetes. 2008;57(4):1115–9.
12. Edghill EL, Flanagan SE, Patch AM, Boustred C, Parrish A, Shields B, et al. Insulin mutation screening in 1044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. Diabetes. 2008;57(4):1034–42.
13. Sagen JV, Raeder H, Hathout E, Shehadeh N, Gudmundsson K, Baevre H, et al. Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2: patient characteristics and initial response to sulfonylurea-urea therapy. Diabetes. 2004;53(10):2713–8.
14. Gloyn AL, 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(18):1838–49.
15. Pearson ER, Flechtner I, Njolstad PR, Malecki MT, Flanagan SE, Larkin B, et al. Switching from insulin to oral sulfonylurea in patients with diabetes due to Kir6.2 mutations. N Engl J Med. 2006;355(5):467–77.
16. Zung A, Glaser B, Nimri R, Zadik Z. Glibenclamide treatment in permanent neonatal diabetes mellitus due to an activating mutation in Kir6.2. J Clin Endocrinol Metab. 2004;89(11):5504–7.
17. Rafiq M, Flanagan SE, Patch AM, Shields BM, Ellard S, Hattersley AT. Effective treatment with oral sulfonylurea in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. Diabetes Care. 2008;31(2):204–9.