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Three cases of permanent neonatal diabetes mellitus: genotypes and management outcome

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ABSTRACT Neonatal diabetes mellitus (DM) is defined as insulin-requiring DM in the first six months of life. Unlike type 1 DM, it is a monogenic disorder resulting from a *de novo* mutation in the genes involved in the development of the pancreas, β-cell mass or secretory function. The majority of neonatal DM cases are caused by a heterozygous activating mutation in the *KCNJ11* or *ABCC8* genes that encode the Kir6.2 and SUR1 protein subunits, respectively, in the K_{ATP} channel. Sulphonylurea, a K_{ATP} channel inhibitor, can restore insulin secretion, hence offering an attractive alternative to insulin therapy. We report three cases of neonatal DM and their genetic mutations. Two patients were successfully switched over to sulphonylurea monotherapy with resultant improvement in the quality of life and a more stable blood glucose profile. Patients with neonatal DM should undergo genetic evaluation. For patients with *KCNJ11* and *ABCC8* gene mutation, oral sulphonylurea should be considered.

Keywords: ABCC8 gene mutation, KCNJ11 gene mutation, neonatal diabetes mellitus, sulphonylurea therapy
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INTRODUCTION

Neonatal diabetes mellitus (DM) is defined as insulin-requiring DM that occurs in the first six months of life, and this disorder can be transient or permanent.[1] It is rare, with an incidence for any type of neonatal DM being one in 160,949 live births.[2] The incidence of permanent neonatal DM ranges from 1:215,000 to 1:260,000 live births in Europe.[3,4] So far, there has been no published data regarding the incidence of neonatal DM in Malaysia. Here, we report three cases of permanent neonatal DM that were seen in our centre over a period of 18 months from January 2008 to June 2009.

CASE REPORTS

Case 1

MWY was one of the first non-identical twin sisters who was conceived by *in vitro* fertilisation from non-consanguineous parents. She was born at 36 weeks of gestation via lower-segment Caesarean section, with a birth weight of 1.92 kg. She was not dysmorphic and there was no respiratory distress at birth. She was well until 2.5 months of age, when she presented with a one-week history of cough followed by lethargy and tachypnoea for a day. At presentation, MWY was in severe respiratory distress, with metabolic acidosis and hyperglycaemia. She was intubated and treated for bronchopneumonia. She was commenced on insulin infusion on admission and ventilated for seven days. However, she remained insulin-dependent despite the resolution of bronchopneumonia, even though there was no family history of DM. Investigations revealed negative pancreatic autoantibodies and a normal pancreas on ultrasonography. Genetic studies conducted when the patient was eight months old revealed a heterozygous missense mutation *G47V* in exon 2 of the insulin gene (*INS*), resulting in the substitution of valine for glycine at codon 47. At 28 months of age, she weighed 11.5 kg. She received multiple daily injections of insulin at 0.6 units/kg/day, and the most recent HbA1c was 7.1% with no episodes of hypoglycaemia.

Case 2

CYS was delivered via emergency Caesarean section at term for unstable lie. He had a birth weight of 3.1 kg. He was not dysmorphic and was thriving well until three months of age, when he presented with ten episodes of vomiting and lethargy for one day. There was no fever or diarrhoea. His mother complained that she had to change his diapers frequently over the previous one week due to the large amount of urine passed. There was severe hyperglycaemia and metabolic acidosis on admission. CYS was treated empirically for sepsis and started on insulin infusion. However, all cultures were negative and he was subsequently started on multiple injections of insulin at 0.6 IU/kg/day. His DM was well controlled, with HbA1c of 6.5%. There was no family history of the disease. Investigation was negative for pancreatic autoantibodies, and a normal pancreas was identified on ultrasonography. Genetic studies revealed heterozygous activating mutation *V252A* in the *KCNJ11* gene. CYS was successfully weaned off insulin and switched to oral glibenclamide therapy over a three-day period at the age of 13 months using the inpatient protocol described by Pearson et al.[5] He was thriving well with a weight of 12 kg at the age of 22 months and required oral glibenclamide at 0.3 mg/kg/day. The most recent HbA1c was 5.9%, with no episodes of hypoglycaemia.

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Case 3

TXY was delivered at term via spontaneous vaginal delivery, with a birth weight of 2.5 kg. She was not dysmorphic and was well until five weeks old, when she presented to a peripheral hospital with a three-day history of fever, cough and diarrhoea. She developed one episode of seizure on the day of admission. At presentation, she was in severe respiratory distress with hyperglycaemia and metabolic acidosis. She was intubated and started on insulin infusion, after which there were two further episodes of seizures, described as cycling of limbs, on the second and third days of admission. All septic workup, including blood culture and lumbar puncture, were negative. The patient was extubated after four days and the seizures had stopped since then. She remained insulin-dependent, and there were great difficulties in controlling her DM despite using different insulin regimens. She was subsequently transferred to our centre for further management. There was no family history of DM or neurological disorders. Investigations showed negative pancreatic autoantibodies, and a normal pancreas was identified on ultrasonography. Genetic studies revealed heterozygous activating missense mutation *Q211K* in the exon 5 of the *ABCC8* gene, resulting in substitution of lysine for glutamine at codon 211. TXY was subsequently weaned off insulin and switched to oral glibenclamide over 11 days at the age of 8.5 months by using the same protocol as Case 2. She remained well, achieving a body weight of 10 kg at one year of age and requiring oral glibenclamide 1.1 mg/kg/day. There was marked improvement in her glycaemic control, with a stable blood glucose profile. Her most recent HbA1c was 6.2%, four months after switching to oral sulphonylurea therapy.

DISCUSSION

In contrast to type 1 DM, neonatal DM is a monogenic disorder resulting from a *de novo* mutation in the genes involved in the development of the pancreas, β-cell mass or β-cell secretory function.[6] Clinical presentation of neonatal DM is indistinguishable from type 1 DM where most patients would present with diabetic ketoacidosis,[7] and insulin therapy is indicated at presentation. All our patients presented with diabetic ketoacidosis by three months of age. One of the characteristic features of patients with neonatal DM is low birth weight.[8,9] However, our patient (Case 2) with *KCNJ11* gene mutation was born with a healthy birth weight of 3.1 kg.

MWY had an *INS* gene mutation, which was first reported by Stoy et al.[10] This mutation occurs in a critical region of the preproinsulin molecule, which impairs proinsulin folding. The abnormally folded proinsulin molecules undergo degradation in the endoplasmic reticulum, leading to severe endoplasmic reticulum stress and β-cell death by apoptosis. *INS* gene mutation is the second commonest cause of permanent neonatal DM.[11] There is currently no specific treatment for *INS* gene mutation; however, this is an active area of research[1] and a novel intervention might be available in the future.

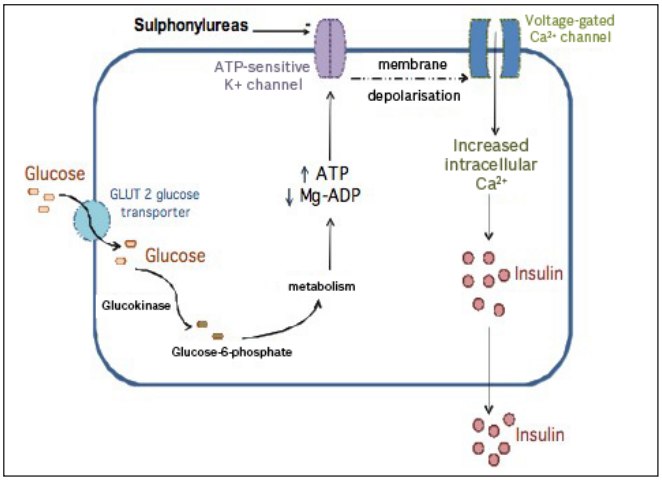

Fig. 1 Diagram shows the role of pancreatic beta cells in insulin secretion. [Adapted from Gloyn et al[9]]

The most common forms of neonatal DM are caused by heterozygous activating mutation in the *KCNJ11* or *ABCC8* genes that encode the two protein subunits, i.e. Kir6.2 (inwardly rectifying potassium channel) and SUR1 (sulphonylurea receptor), respectively, in the adenosine triphosphate-sensitive potassium (K_{ATP}) channel on the pancreatic β-cells.[1] K_{ATP} channel is an important gateway to the regulation of glucose-mediated insulin secretion. It is an octameric complex consisting of four pore-forming Kir6.2 subunits embraced by four regulatory SUR1 subunits. Once glucose is metabolised in the β-cells, the increased ATP/adenosine diphosphate ratio will cause the closure of the ATP-sensitive K_{ATP} channel, leading to membrane depolarisation, which subsequently activates the voltage-gated calcium channels causing an increase in intracellular Ca^{2+} level; this eventually triggers insulin release from β-cells (Fig. 1).[9] Activating mutation affecting the K_{ATP} channels results in severe inhibition of insulin secretion, manifesting in early infancy as neonatal DM. Sulphonylurea, a K_{ATP} channel inhibitor, binds to the SUR1 subunit and closes the K_{ATP} channel, directly bypassing β-cell metabolism.[12] This drug has been shown to restore insulin secretion, hence offering an attractive alternative to insulin injection.[6]

CYS had a *KCNJ11* gene mutation, which was previously reported by Rica et al.[12] This particular mutation could be associated with both transient and permanent forms of neonatal DM. About 90% of patients with this mutation can be successfully transferred to oral therapy with sustained improvement in glycaemic control,[5] as illustrated in our patient. *ABCC8* gene mutation causing neonatal DM had been reported since 2006.[13] Mutation in TXY was first described by Codner et al.[14] The unusual feature in this case was the presence of seizures, which had not been previously reported. As TXY was already on insulin infusion, the seizures after admission could have been due to undetected hypoglycaemia related to insulin treatment. The cause of seizure on the day of presentation remains unclear, as the subsequent cultures were all negative and there was no documentation of abnormal electrolytes or calcium level from the referring hospital.

According to Rafiq et al, 85% of patients with *ABCC8* gene mutations could be successfully treated with oral sulphonylureas.[15] Despite higher doses of oral glibenclamide (> 1 mg/kg/day), the treatment was well tolerated without hypoglycaemia. In contrast to Rafiq et al's findings,[15] we found that the patient with the *ABCC8* gene mutation needed a higher sulphonylurea dosage and a longer transfer process than the patient with the *KCNJ11* gene mutation. However, there has been no published data regarding the relationship between genotype and the dose of glibenclamide needed. The doses reported in the literature were 0.07–2.80 mg/kg/day.[15]

Glibenclamide (glyburide), glipizide and glimepiride are second-generation sulphonylureas. Glibenclamide was chosen for both our patients (Cases 2 and 3) based on the inpatient transfer protocol of Pearson et al.[5] It was well tolerated by our patients, and the side effects reported include hypoglycaemia, transient nausea, abdominal discomfort and diarrhoea.[15] Glibenclamide is available as a 5-mg tablet, and needs to be diluted to the desired dose based on the patient's body weight. It is taken twice daily, once in the morning and evening, with or immediately after the main meal. There is very limited experience with the use of glibenclamide outside the scope of neonatal DM in paediatric patients. It should not be used in patients with type 1 DM and diabetic ketoacidosis, or in the presence of adrenocortical insufficiency and hepatic or renal impairment.

Insulin therapy is often difficult, especially for infants and young children. It causes wide fluctuations in blood glucose levels with frequent hypoglycaemia and hyperglycaemia, both of which have a negative impact on brain development and DM outcome. It is disheartening for parents to accept the fact that their child needs lifelong insulin injection. Our patients with *KCNJ11* and *ABCC8* gene mutation were successfully switched over to sulphonylurea monotherapy more than six months after the initial clinical diagnosis was made. This was mainly due to the unavailability of genetic testing locally and the initial lack of funding to send the DNA samples to the UK. Oral sulphonylurea therapy is simple, tolerable and more acceptable to the patients' families compared to insulin injection. It has led to a more stable blood glucose profile and improved the quality of life for our patients and their families.

In conclusion, patients with neonatal DM should undergo genetic evaluation. Successful treatment of patients with responsive mutation is not only highly rewarding, but it also significantly improves the patient's diabetic care and quality of life.

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