



# Glibenclamide controls ketosis-prone diabetes in a 38-year-old woman with Kir6.2 mutation

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## Introduction

Neonatal diabetes is defined as diabetes diagnosed within six months of birth. It is broadly classified into transient and permanent, the transient type spontaneously resolving in weeks to months.

Until recently, the aetiology was largely unknown and the treatment was limited to replacement with insulin. Recent research has shown that several heterozygous activating mutations in the *KCNJ11* gene on chromosome 11p15.1, encoding the Kir6.2 subunit of the pancreatic ATP sensitive potassium ( $K_{ATP}$ ) channel, play a role in the pathogenesis of permanent neonatal diabetes.<sup>1</sup> Such mutations account for 30–58% of cases of permanent neonatal diabetes.<sup>1–7</sup> The majority of these are de-novo mutations, although approximately 10% of cases have shown a familial transmission with autosomal dominant inheritance. Some patients with *KCNJ11* mutations have neurological features that are part of a discrete neurological syndrome termed developmental Delay, Epilepsy and Neonatal Diabetes (DEND).<sup>8</sup>

The  $K_{ATP}$  channel is a critical regulator of beta-cell insulin secretion. The insulin secretion is initiated by closure of the  $K_{ATP}$  channels and inhibited by their opening. The closure of the channel is mediated by increased ATP production in the presence of glucose. In neonatal diabetes, the mutated  $K_{ATP}$  channel does not close in response to increased ATP and thus insulin secre-

## ABSTRACT

Monogenic forms of diabetes, where there is a single gene defect causing diabetes, are rare, accounting for about 1–2% of all cases of diabetes in young people. Neonatal diabetes is one form of monogenic diabetes. It usually presents within six months of birth and can be permanent or transient. Several mutations in the *KCNJ11* gene lead to permanent neonatal diabetes by interfering with insulin release from islet cells. These patients can be treated with sulphonylureas as they facilitate insulin secretion by acting on the mutated pancreatic potassium channel.

We report the case of a patient with *KCNJ11* S3C mutation, who is the oldest patient with neonatal diabetes to have successfully transferred from insulin to sulphonylureas. She was diagnosed with diabetes at the age of four and was treated as having type 1 diabetes mellitus. Her glycaemic control was always sub-optimal; she had had several admissions with diabetic ketoacidosis. Her daughter who developed diabetes at six weeks was found to have neonatal diabetes, which led to her genetic testing. Our patient was also diagnosed with the same *KCNJ11* mutation as her daughter. At 38 years of age, after outpatient assessment, she was started on glibenclamide and in three weeks came off insulin completely, achieving good glycaemic control with glibenclamide. Her HbA<sub>1c</sub> improved from 10% pre-transfer to 5.9% in four months. Copyright © 2009 John Wiley & Sons.

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## KEY WORDS

monogenic diabetes; Kir6.2; *KCNJ11* mutation; neonatal diabetes

tion does not occur. Sulphonylureas can close the  $K_{ATP}$  channel by an ATP-independent mechanism enabling release of insulin.<sup>9</sup>

## Case report

Our patient is a 38-year-old Caucasian woman who has been attending our diabetes centre for more than a decade. Her early medical records cannot be traced, but her mother recalls that her birth weight was 3 kg. She was healthy and there was no delay in her attaining her developmental milestones. A routine test prior to a squint operation at the age of four had shown that her urine contained glucose. Soon afterwards, she was diagnosed with diabetes. According to her

mother, she was treated with tablets twice a day until starting insulin aged six at a local hospital. She continued to wet her bed and failed to gain weight, so that a year later she was referred to Birmingham Children's Hospital. She has remained on insulin ever since, albeit with poor glycaemic control (HbA<sub>1c</sub> 9–13.6%), with at least two hospital admissions with ketoacidosis.

Aged 18, she gave birth to a daughter, who developed diabetic ketoacidosis at six weeks after birth with associated cerebral oedema, requiring a prolonged period of intensive care which left her severely disabled. As part of a national initiative for defining genetic causes of diabetes in children diagnosed within

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six months of birth, this daughter was found to have *KCNJ11* S3C mutation. This led us to test our patient and she was found to have the same mutation as her daughter. We explained to her that patients with a similar mutation causing diabetes have been successfully transferred from insulin therapy to oral antidiabetic therapy.<sup>10</sup>

We agreed with the patient to follow the Exeter outpatient transfer protocol to attempt transfer from insulin to glibenclamide in several weeks.<sup>11</sup> She was on a basal bolus regimen with insulin detemir (Levemir) and insulin aspart (NovoRapid) at a total dose of 40 units/day (0.8 units/kg/day). Whilst continuing with this insulin regimen, glibenclamide 5mg bd (0.1mg/kg/day) was added. However, her transfer to glibenclamide was much more rapid than we expected. After a week, her insulin detemir was reduced and by two weeks her total dose of insulin had fallen by half to 18 units/day with no increase in glibenclamide. Three weeks after starting the transfer, she came off insulin completely and glibenclamide was doubled to 10mg bd (0.2mg/kg/day). After a further three weeks and continuing hypoglycaemia when active, glibenclamide was reduced to 7.5mg bd. By four months she only needed glibenclamide 7.5mg daily to maintain excellent glycaemic control (HbA<sub>1c</sub> 5.9%). Sixteen months after transfer, her diabetes remains well-controlled on only 2.5mg bd of glibenclamide (HbA<sub>1c</sub> 6.7%).

Fasting glucose, C-peptide and insulin were measured at baseline, prior to transfer. This biochemical picture was consistent with exoge-

nous insulin replacement, with no detectable endogenous insulin production. Fasting glucose, C-peptide and insulin repeated four months after transfer indicated good endogenous insulin production (Table 1).

### Discussion

Although neonatal diabetes is a rare entity, it accounts for almost all cases of diabetes diagnosed before six months. All patients diagnosed with diabetes within six months of birth should be tested for both *KCNJ11* and *ABCC8* mutations as they are present in over 50% of cases and, if found, can radically change management.<sup>10</sup> Our patient's daughter satisfied the criterion and was found to have a *KCNJ11* mutation, which in turn led us to test our patient for the same mutation. The majority of mutations are spontaneous, but this family falls into the 10% where the mutation could be transmitted as an autosomal dominant inheritance.

Our patient's daughter remained on insulin as her grandmother, who is her main carer, felt that it would be more convenient to manage the diabetes with insulin, especially with her granddaughter's swallowing difficulties. Her disabilities are thought to be a result of her severe diabetic ketoacidosis rather than the neurological findings associated with DEND.

This case has several unique features. This is the oldest reported patient with diabetes caused by *KCNJ11* mutation to have successfully transferred from insulin to sulphonylurea. Interestingly, in spite of her very poor glycaemic control over a long period, she has no evidence of micro- or macrovascular complications. Her

### Key points

- All patients diagnosed with diabetes within six months of birth should be screened for *KCNJ11* mutations. Such patients should be referred to the Exeter team ([www.diabetesgenes.org](http://www.diabetesgenes.org))
- Children diagnosed later may have these mutations
- Transfer from insulin can be attempted safely at any age, even after years of insulin injections

current dose of glibenclamide is unusually low at 0.1mg/kg/day, compared to the median dose 0.5mg/kg/day of glibenclamide (30mg daily in a 60kg adult) from the Exeter series.<sup>11</sup> It is also unusual as this patient was diagnosed at four years of age, well outside the usual six-month period, and the diagnosis would not have been suspected if her daughter had not been tested.

In patients with *KCNJ11* mutations, sulphonylureas offer a safe and effective alternative to insulin. Our case illustrates that children diagnosed later may have these mutations and may have neonatal diabetes. This case also highlights the fact that transfer from insulin can be attempted safely even after years of insulin injections – 32 years in our patient's case. Early recognition of this recently identified monogenic diabetes would avoid a lifetime of insulin injections.

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### Conflict of interest statement

There are no conflicts of interest.

### References

References are available at [www.practicaldiabetesinternational.com](http://www.practicaldiabetesinternational.com).

**Table 1.** Fasting pre- and post-transfer glucose, insulin, C-peptide and HbA<sub>1c</sub> four months apart

	Glucose (mmol/L)	Insulin (pmol/L)	C-peptide (pmol/L)	HbA <sub>1c</sub> (%)
<b>Pre-transfer</b>				
Basal bolus insulin 40 U/d	7.1	495	<91	10.0
<b>4 months post-transfer</b>				
Glibenclamide 7.5mg/d	5.3	27	595	5.9

Row 1: Exogenous insulin treatment – high insulin levels but undetectable C-peptide.  
Row 2: Sulphonylurea treatment (off exogenous insulin) – decreased fasting insulin, but elevated levels of C-peptide confirming release of insulin from beta cells.



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