Importance of genetic testing and recognition of neonatal diabetes: A case report

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Permanent neonatal diabetes (PND) – a rare form of monogenic diabetes – is diagnosed within the first 6 months of life. PND may be caused by mutations in the genes encoding the Kir6.2 (*KCNJ11*) or SUR1 (*ABCC8*) subunits of the adenosine triphosphate-sensitive potassium (K_{ATP}) channels in pancreatic beta-cells. Sulphonylureas can bind to the K_{ATP} channels allowing the release of insulin from these cells. In this article, the authors present the case of an individual who was diagnosed with type 1 diabetes at the age of 6 weeks and immediately commenced insulin treatment, but switched to sulphonylurea therapy at the age of 26 years, following genetic testing confirming mutation in the *KCNJ11* gene. His HbA_{1c} level improved from 10.1% (87 mmol/mol) prior to treatment transfer to 6.5% (48 mmol/mol) at 3 months following transfer; this level remained constant at 12 months.

Permanent neonatal diabetes (PND) is a rare form of diabetes characterised by a diagnosis within the first 6 months of life (Zung et al, 2004; Hattersley and Ashcroft, 2005). A molecular basis can be defined in approximately 60% of people with PND. Mutations in the *KCNJ11* gene encoding the Kir6.2 subunit of the beta-cell adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel are the most common genetic cause of PND (Edghill et al, 2008).

People with neonatal diabetes caused by K_{ATP}-channel mutations are usually born with a low birth weight, with the majority weighing less than the 10th percentile for gestational age as a result of reduced insulin-mediated growth in utero. The majority of mutations in the *KCNJ11* gene are spontaneous and, therefore, there is usually no family history (Slingerland et al, 2006).

There is a spectrum of features associated with K_{ATP}-channel mutations. Isolated diabetes occurs in 80% of cases with these mutations, but neurological features described as DEND (developmental delay, early-onset generalised epilepsy and neonatal diabetes) syndrome are present in the remaining 20% (Slingerland et al, 2006).

Article points

1. Permanent neonatal diabetes caused by inhibition of the adenosine triphosphate-sensitive potassium channel in the beta-cells can be treated with sulphonylureas.
2. The 26-year-old male discussed in this study was diagnosed with type 1 diabetes at the age of 6 weeks and treated with insulin thereafter.
3. After genetic testing revealed that the man had an activating *KCNJ11* mutation, he agreed to switch treatment from insulin to sulphonylurea.
4. At 3 months after treatment transfer, the man's HbA_{1c} level had reduced from 10.1% (87 mmol/mol) to 6.5% (48 mmol/mol).

Key words

- Genetic testing
- Kir6.2 mutation
- Monogenic diabetes
- Neonatal diabetes

Authors' details can be found at the end of this article.

Page points

1. The 26-year-old, white male reported to have been diagnosed with type 1 diabetes at the age of 6 weeks and treated with insulin thereafter.
2. Genetic testing revealed that the individual had an activating *KCNJ11* mutation.
3. Prior to treatment conversion, the man had been taking insulin lispro injections 6 units three times daily with meals and once-daily insulin glargine 28 units at night; his HbA_{1c} level was 10.1% (87 mmol/mol).
4. As the man's blood glucose levels were not well controlled, glibenclamide 10 mg/day (0.1 mg/kg/day) was initially added to his insulin doses. Over the next few days, insulin doses were reduced.

Mutations in the *KCNJ11* gene inhibit K_{ATP}-channel closure in response to increased levels of ATP, thereby preventing membrane depolarisation and insulin secretion. Treatment with sulphonylureas, which bind to the SUR1 receptor of the K_{ATP} channel, allows insulin to be released from the pancreatic beta-cell (Zung et al, 2004). Therefore, many people with neonatal diabetes who have previously been dependent on insulin can now be successfully treated with sulphonylureas (Sagen et al, 2004; Pearson et al, 2006).

In September 2008, Agnieszka conducted an audit of the Broomfield Hospital Diabetes Centre database, which revealed 11 individuals to have been diagnosed with type 1 diabetes within the first 6 months of life. These people were contacted and invited to undergo further investigation to ascertain whether they had a monogenic form of diabetes. Of the 11 people contacted, only one was confirmed to have diabetes diagnosed at <6 months of age. A case report of this individual is presented here.

Case history

This 26-year-old, white male had previously been considered to have type 1 diabetes and "mild cerebral palsy". In January 2000, at the age of 17, he had been referred to the adult diabetes clinic having formerly been under paediatric care. Unfortunately, his early medical notes could not be traced; however, he reported to have been diagnosed with diabetes at the age of 6 weeks and treated with insulin thereafter. The man was born at 40 weeks' gestation by normal delivery, with a low birth weight. Neither his parents nor any other family members have diabetes.

His early treatment involved twice-daily insulin; however, at the age of 16 years he was switched to a four-times-daily insulin regimen as a result of poor glycaemic control (HbA_{1c} level range 9–14% [75–130 mmol/mol]). He continued with sporadic attendance at the diabetes clinic and his glycaemic control remained poor.

In 2005, at the age of 23, he was referred back to his GP having repeatedly missed his follow-up appointments with the diabetes specialist team over a 4-year period. In addition, he was diagnosed with depression and overdosed on insulin twice. He also had several admissions to hospital presenting with diabetic ketoacidosis. In July 2006, he was diagnosed with retinopathy.

Treatment transfer

Genetic testing revealed that this man had an activating *KCNJ11* mutation. It was explained to him that other people with *KCNJ11* PND had successfully undergone treatment transfer from insulin injections to sulphonylurea tablets. He agreed, with the support of the genetic diabetes nurse (GDN), to follow the Exeter Outpatient Protocol (see www.diabetesgenes.org) and attempt treatment transfer from insulin to glibenclamide. The GDN provided support and advice throughout the process of transfer.

Prior to conversion, the man had been taking insulin lispro 6 units three times daily with meals and once-daily insulin glargine 28 units at night. At this time, his weight was 60 kg and HbA_{1c} level was 10.1% (87 mmol/mol). As his blood glucose levels were not well controlled, glibenclamide 10 mg/day (0.1 mg/kg/day) was initially added to his insulin doses. According to the protocol, the daily dose of glibenclamide should not exceed 1.0 mg/kg/day.

Over the next 3 days, his insulin doses were reduced to once-daily insulin lispro 3 units with his evening meal only and once-daily insulin glargine 10 units at night. Two days later, the glibenclamide dose was increased to 15 mg/day (0.2 mg/kg/day), insulin lispro was discontinued and the insulin glargine dose was reduced to 6 units/day.

Key information about neonatal diabetes testing.

- People diagnosed with diabetes before 6 months of age should have genetic testing, whatever their age now.
- Confirmation of neonatal diabetes caused by a *KCNJ11* mutation may lead to successful treatment transfer from insulin to sulphonylurea.
- All clinics could conduct a simple audit to help identify people diagnosed with diabetes before 6 months of age.
- More information about neonatal diabetes and genetic testing can be found at www.diabetesgenes.org.

Table 1. Pre-transfer and 3, 6 and 12 months post-transfer HbA_{1c} levels and glibenclamide doses.

	Pre-transfer	Post-transfer		
		3 months	6 months	12 months
HbA_{1c} (% [mmol/mol])	10.1 (87)	6.5 (48)	5.8 (40)	6.8 (51)
Glibenclamide dose (mg/day)	–	40	55	45
Insulin regimen	Insulin lispro 18 units/day with meals and insulin glargine 28 units at night	Nil	Nil	Nil

At 3 weeks after the transfer, he stopped insulin completely and glibenclamide doses were gradually increased to 40 mg/day (0.6 mg/kg/day). At 8 weeks after transfer, glibenclamide doses were increased to 55 mg/day (0.9 mg/kg/day); at this time, his blood glucose levels ranged 4.1–7.6 mmol/L.

At 3 months after the transfer, his HbA_{1c} level was 6.5% (48 mmol/mol); this decreased within 6 months to 5.8% (40 mmol/mol) (*Table 1*). His glibenclamide doses were subsequently reduced. At the time of writing (12 months following transfer) he was taking glibenclamide 45 mg/day (0.7 mg/kg/day) and had an HbA_{1c} level of 6.8% (51 mmol/mol) (*Table 1*).

In addition to improvements in glycaemic control, the man also described improvements in his quality of life (QOL):

> ***"I could not believe what was happening. At first I thought they had found a cure for diabetes, but then they explained the faulty gene to me. I feel like a new person now, like I have got my life back."***

Conclusion

Recognition of PND is important as the majority of people with a K_{ATP}-channel mutation can successfully undergo treatment transfer from insulin to sulphonylureas. Such transfer may be attempted at any age, even after many years of receiving insulin injections (Jose et al, 2009). A correct diagnosis of PND, confirmed by molecular genetic testing, can predict the clinical course of diabetes and explain other associated clinical features. Most importantly, it guides the treatment, allows appropriate genetic counselling and improves QOL. ■

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Page points

1. At 3 weeks after the treatment transfer, the man stopped insulin completely and glibenclamide doses were gradually increased to 40 mg/day (0.6 mg/kg/day).
2. At 3 months after the transfer, the man's HbA_{1c} level was 6.5% (48 mmol/mol); this decreased within 6 months to 5.8% (40 mmol/mol). At 12 months, he was taking glibenclamide 45 mg/day (0.7 mg/kg/day) and had an HbA_{1c} level of 6.8% (51 mmol/mol).
3. In addition to improvements in glycaemic control, the man also described improvements in his quality of life.