A diagnosis of monogenic neonatal diabetes can improve treatment and glycaemic control

Maggie Shepherd, Julie Cropper, Sarah Flanagan, Sian Ellard, Andrew Hattersley

Neonatal diabetes presents before 6 months of age, and previously required lifelong treatment with insulin. However, recent advances in genetic knowledge have led to the identification of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel mutations that prevent insulin release from the beta-cell and cause neonatal diabetes. In these infants, sulphonylurea therapy enables K_{ATP} channel closure and insulin release, leading to improved glycaemic control and quality of life. This article highlights known genetic causes of neonatal diabetes and describes the clinical characteristics and successful use of sulphonylurea therapy. A case study is presented to illustrate these issues. Genetic testing for those diagnosed before 6 months of age (irrespective of their current age) is available free of charge (www.diabetesgenes.org).

There have been recent dramatic changes in the diagnosis and treatment of diabetes presenting in the first 6 months of life. It is now known that this form of diabetes, which develops in the neonatal period, is often caused by a change in a single gene (monogenic) and is not type 1 diabetes (Slingerland and Hattersley, 2005; Edghill et al, 2006).

These major changes have resulted from the identification of neonatal diabetes as a condition that is frequently caused by mutations in the *KCNJ11* or *ABCC8* genes, which encode the Kir6.2 and SUR1 subunits of the beta-cell adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel (Gloyn et al, 2004; Babenko et al, 2006; Proks et al, 2006).

People with neonatal diabetes due to K_{ATP} channel mutations have previously been dependent on lifelong insulin injections as the mutated channels fail to close in response to ATP. This prevents depolarisation of the beta-cell membrane and influx of calcium^{2+} ions, with the result that insulin is not released from the beta-cell. However, in most cases these individuals can transfer to sulphonylurea therapy, which closes the K_{ATP} channel by binding to the SUR1 subunit, thereby allowing

Article points

1. Neonatal diabetes presents before 6 months of age, and until recently was treated with lifelong insulin injections. It is now known that this form of diabetes is not type 1 diabetes but is likely to have a genetic cause.
2. The majority of neonatal diabetes is caused by adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel mutations, which prevent the release of insulin from beta-cells.
3. Most of those affected can transfer from insulin injections to sulphonylurea tablets, leading to improved glycaemic control and quality of life.

Key words

- K_{ATP} channel mutations
- Monogenic diabetes
- Neonatal diabetes
- Sulphonylurea

Author details are given at the end of the article.

Page points

1. Neonatal diabetes occurs in 1 in 100–200 000 live births.
2. K_{ATP} channel mutations account for around 40% of permanent neonatal diabetes and 25% of transient neonatal diabetes.
3. The majority of mutations occur spontaneously so there is often no family history of diabetes.
4. There is a spectrum of features associated with K_{ATP} channel mutations: 80% have isolated diabetes and 20% have diabetes and neurological features.

the release of insulin (Gribble and Reimann, 2003). Thus, many of those who were previously dependent on insulin can now be treated successfully with sulphonylureas (Sagen et al, 2004; Babenko et al, 2006; Pearson et al, 2006; Rafiq et al, 2008).

Genetic causes of neonatal diabetes

Neonatal diabetes is found in 1 in 100–200 000 live births (Stanik et al, 2007; Slingerland et al, 2009). As the majority of mutations occur spontaneously there is often no family history of diabetes (Edghill et al, 2007).

K_{ATP} channel mutations account for around 40% of permanent neonatal diabetes (PND) and 25% of transient neonatal diabetes (TND) (Flanagan et al, 2007; Edghill et al, 2008). These mutations will be the focus of this article as the majority of those affected are able to transfer from insulin injections to sulphonylurea tablets.

Mutations in the gene encoding insulin account for 12% of PND cases (Støy et al, 2007; Edghill et al, 2008) and people with these mutations require ongoing insulin treatment. The aetiology in 40% of people with PND remains unknown, suggesting that other genetic causes are still to be identified. The genetic basis of TND is known in approximately 95% of cases (Flanagan et al, 2007), with chromosome 6q24 abnormalities the most common cause (Gardner et al, 2000).

Clinical characteristics (*Box 1*)

Neonatal diabetes

Neonatal diabetes is defined as diabetes diagnosed within the first 6 months of life. Analysis of pancreatic autoantibodies and human leukocyte antigen genotypes indicates that individuals diagnosed with diabetes before 6 months have monogenic diabetes and not type 1 diabetes (Iafusco et al, 2002; Edghill et al, 2006). Most infants with neonatal diabetes present with symptomatic hyperglycaemia and may present in diabetic ketoacidosis (Hattersley and Ashcroft, 2005). While PND requires lifelong treatment, TND resulting from a K_{ATP} channel mutation will typically remit by a median of 35 weeks, with most of those affected having a relapse of diabetes in late childhood (Flanagan et al, 2007).

Box 1. Characteristics of neonatal diabetes.

- Diagnosed before 6 months of age.
- May be transient or permanent.
- Adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel mutations are common.
- Usually have low birth weight (often below 10th centile).
- Eighty per cent have isolated diabetes.
- Twenty per cent have diabetes and neurological features.
- Majority (with *KCNJ11* or *ABCC8* mutations) can successfully transfer from insulin injections to sulphonylurea tablets.

Birth weight

Infants with neonatal diabetes usually have a low birth weight (median 2.65 kg), with the majority below the 10th centile for gestational age due to reduced insulin-mediated growth in utero (Edghill et al, 2008). However, they show rapid catch-up growth after treatment is started (Hattersley and Ashcroft, 2005; Slingerland and Hattersley, 2005).

Other features

There is a spectrum of features associated with K_{ATP} channel mutations. Isolated diabetes is the most common phenotype, occurring in 80% of cases (Hattersley and Ashcroft, 2005).

Neurological features are present in approximately 20% of those with a K_{ATP} channel mutation. They present either as DEND syndrome (developmental delay, epilepsy <12 months and PND) or more frequently as intermediate DEND (iDEND) with mild developmental delay and permanent neonatal diabetes (Hattersley and Ashcroft, 2005). The developmental delay includes muscle weakness, a delay in motor function and learning difficulties (Gloyn et al, 2004).

The neurological features are explained by the expression of mutated K_{ATP} channels in nerves, muscle and brain. The severity of the mutation determines the clinical presentation: mutations with the greatest impact on the closing of the channel by ATP cause DEND or iDEND syndrome (Proks et al, 2004).

Transfer from insulin to sulphonylurea in neonatal diabetes

For those with neonatal diabetes, identification of a K_{ATP} channel mutation has revolutionised therapy and transformed their lives and those of their families (Hattersley and Ashcroft, 2005; Shepherd, 2006). Ninety per cent of those with *KCNJ11* neonatal diabetes have successfully discontinued insulin therapy and all show improved HbA_{1c} levels (8.1% [65 mmol/mol] on insulin, 6.4% [46 mmol/mol] on sulphonylureas; $P<0.001$; Pearson et al, 2006).

The median dose of glibenclamide initially required for those with *KCNJ11* mutations is 0.45 mg/kg/day (range 0.05–1.5 mg/kg/day (Pearson et al, 2006), while those with *ABCC8* mutations require a lower median dose (0.26 mg/kg/day (Rafiq et al, 2008). Glucose values fluctuate less, as well as being lower (Zung et al, 2004), and improved glycaemic control is maintained over 12 months despite reducing doses of sulphonylureas (Pearson et al, 2006). Although relatively high doses are required, the only reported side-effects appear to be transitory diarrhoea (Codner et al, 2005) and tooth discoloration (Kumaraguru et al, 2009).

Recent (unpublished) data indicate that of 122 people with a K_{ATP} channel mutation in whom treatment change was attempted, 111 (91%) successfully transferred from insulin to sulphonylureas. The majority of those in whom transfer was unsuccessful had the more severe DEND syndrome or were middle-aged or older adults when transfer was attempted. Transfer is more successful in children than in adults, but is worth attempting at any age.

Improvements in neurological function

Improvements in motor and cognitive function have been reported in people with iDEND, which have coincided with glibenclamide introduction (Slingerland et al, 2006; 2008). This may be explained by the binding of glibenclamide to mutated K_{ATP} channels in the muscle, peripheral nerves and brain.

Although many cases of DEND do not respond to sulphonylurea therapy (Pearson et al, 2006), there have been two reports of people with DEND responding with improved neurological function: one person's epilepsy and psychomotor development improved (Shimomura et al, 2007) and a second showed improved verbal performance, visual naming ability, verbal learning and long-term memory (Gurgel et al, 2007). These data indicate that sulphonylurea therapy should be attempted in all those with K_{ATP} channel mutations.

The case study presented in *Box 2* illustrates the issues discussed above.

Box 2. Case study.

Claire was born in 1986 at 40 weeks' gestation, with a birth weight of 2.8 kg. She presented with diabetes at 16 weeks of age and was immediately treated with insulin. Her HbA_{1c} level ranged from 6.5% to 14.0% (48 to 130 mmol/mol) with frequent hypoglycaemic episodes. Insulin regimens varied from twice daily to four times daily. There was no family history of diabetes and no record of learning difficulties, although she was socially disadvantaged and did not do well at school.

In 2005, at 19 years of age, Claire was identified through the Yorkshire Register of Diabetes as having been diagnosed with diabetes before 6 months of age. Genetic testing was performed and a *KCNJ11* mutation was found; at this time, Claire was 26 weeks pregnant. As this mutation is inherited in a dominant pattern, the fetus was at 50% risk of inheriting the same mutation and developing neonatal diabetes. The growth of the baby was monitored and was considered normal at 28 weeks. The baby was delivered by caesarean section at 33 weeks because of pre-eclampsia, a weak, unreactive cardiotocograph, a transverse presentation and hyperglycaemia in Claire. Paul was born weighing 2.96 kg and cord blood was taken; he was found not to have inherited the *KCNJ11* mutation and was therefore unaffected.

Claire's weight was 65.6 kg, her BMI was 23 km/m^2 and total daily insulin dose was 0.7 units/kg. Islet cell and glutamic acid decarboxylase antibodies were negative. Her blood glucose level was fluctuating from hypoglycaemia to 30 mmol/L; her HbA_{1c} level was 11.4% (101 mmol/mol).

Claire was transferred to glibenclamide therapy but stopped it after she developed a facial rash. She was switched to gliclazide and is now on 480 mg gliclazide in the morning and 640 mg in the evening. Based on her latest weight of 63.6 kg, she requires around 17.6 mg/kg/day (equivalent to approximately 1.1 mg/kg/day of glibenclamide). Her glycaemic control and quality of life have both improved dramatically, she feels happy and well on her current treatment, and her last HbA_{1c} level (February 2010) was 7.3% (56 mmol/mol).

Conclusion

The majority of referrals for genetic testing for neonatal diabetes come from paediatricians. Consequently, adults with PND are probably still underdiagnosed and more effort should

Page point

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Page points

1. Diabetes teams should check their patient databases for records of people diagnosed before 6 months of age and refer them for genetic testing, irrespective of their current age.
2. Genetic testing is clinically important as these individuals are likely to have improved glycaemic control and quality of life on sulphonylurea tablets compared with insulin injections, and some show an improvement in neurological features.

be made to identify these individuals as many will benefit from sulphonylurea treatment.

Diabetes teams should check their patient databases for records of people diagnosed with diabetes before 6 months of age and refer them for genetic testing, irrespective of their current age. Genetic testing is clinically important as these individuals are likely to have improved glycaemic control and quality of life on sulphonylurea treatment compared with insulin therapy, and some show an improvement in neurological features. ■

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Genetic testing: Important information.

- Genetic testing for neonatal diabetes is offered free of charge by the Molecular Genetics Department at the Royal Devon and Exeter NHS Foundation Trust for anyone diagnosed with diabetes before 6 months of age (irrespective of current age).
- Individuals diagnosed between 6 and 12 months will also be tested, although the chances of identifying a genetic cause of diabetes in this age group is much lower (approximately 5% vs 65% of those diagnosed before 6 months).
- More information and details of the samples required for testing can be found at: www.diabetesgenes.org.

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