Transforming lives: transferring patients with neonatal diabetes from insulin to sulphonylureas

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Abstract

Background: Mutations in the *KCNJ11* gene encoding Kir6.2 are the most common cause of neonatal diabetes. Although clinically 'insulin dependent' these patients may respond to oral sulphonylureas. Families' experiences of coping with the condition and the impact of transferring from long-term insulin to sulphonylureas have not been explored.

Aim: This study aims to increase understanding of having a child with neonatal diabetes caused by a mutation in the *KCNJ11* gene.

Method: In-depth interviews were conducted with parents of 11 UK patients with *KCNJ11* gene mutations during 2004–2005. The patients had a median age of 13 years (range 0.5–57 years). Qualitative methodology was used to gain an in-depth understanding of the experiences from diagnosis of diabetes to present day. Interviews were audiotaped, transcribed and subjected to thematic content analysis.

Results: Three key categories were identified: i) difficulties managing diabetes in a baby/young child – highlighting the constant care required and impact on family relationships; ii) recognition and implications of learning difficulties and muscle weakness; iii) impact of transfer from insulin to sulphonylureas – including effect on lifestyle, learning difficulties and glycaemic control.

Conclusion: Having a baby with neonatal diabetes is exhausting and places additional strain on families. Mothers acknowledged feeling overprotective. Before genetic diagnosis learning delay and diabetes had not been related, but had implications for future independent living. Transfer to sulphonylureas greatly improved diabetes control and reduced incidences of hypoglycaemia; this enabled families to normalise the condition and reduced social stigma. Sulphonylurea treatment transformed quality of life for the children and their families, who were able to view the future more positively.

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Key words

Genetic testing; neonatal diabetes; sulphonylureas; KCNJ11; Kir6.2

Background

Neonatal diabetes usually presents within the first three months of life. The can be classified into those with transient neonatal diabetes, who remitted and were able to discontinue insulin treatment; and those with permanent neonatal diabetes, who did not remit and required insulin throughout life.[1] Patients with neonatal diabetes may develop ketoacidosis or severe hyperglycaemia and require insulin treatment from diagnosis. C-peptide is generally undetectable and patients are usually insulin dependent and require replacement insulin doses of approximately 0.9 units/kg/day.[2] However, human leukocyte antigen and autoantibody studies indicate that diabetes diagnosed before the age of six months is rarely due to type 1 diabetes.[3,4] Until 2004 the cause of diabetes for the most patients with neonatal diabetes was unknown.

Heterozygous activating mutations in the *KCNJ11* gene which encodes the Kir6.2 subunit of the β-cell ATP-sensitive potassium channel (K_{ATP}) have recently been identified[5] and cause 30–58% of cases of diabetes diagnosed before six months of age.[6] *KCNJ11* mutations have been found to account both for permanent neonatal diabetes and, less commonly, transient neonatal diabetes.[6] Patients with neonatal diabetes have low birth weight, with a median birth weight of 2550 g at a gestational age of 40 weeks.[1] This reduced birth weight reflects the reduced fetal insulin secretion *in utero*. In addition to diabetes, 30% of patients also have neurological features ranging from mild developmental delay, +/- muscle weakness to developmental delay, epilepsy and neonatal diabetes (DEND) syndrome.[2]

Identifying a *KCNJ11* mutation is important as sulphonylureas can act as an effective replacement for insulin in approximately 90% of

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Individual with Kir6.2	Age diagnosed (weeks)	Age at time of interview (years)	Treatment now	Learning difficulties/ muscle weakness present	Parent interviewed	Relationship comments
A	1	0.5	Sulphonylureas	Not known	Mother	Child of H
B	1	1	Sulphonylureas	No	Mother and father	C's sibling
C	6	3	Sulphonylureas	No	Mother and father	B's sibling
D	2	5	Sulphonylureas	Yes	Mother	
E	16	11	Sulphonylureas	Yes	Mother	Child of J
F	6	13	Sulphonylureas	No	Mother	
G	15	18	Sulphonylureas	Yes	Mother	
H	5	28	Insulin	Yes	Mother	Mother of A transfer unsuccessful
I	156	31	Sulphonylureas	No	Father	Father of B and C
J	11	42	Insulin	Yes	Mother	Mother of E transfer unsuccessful
K	20	57	Insulin	Yes	Mother	Transfer not appropriate

Table 1. Characteristics of individuals with *KCNJ11* mutations, details of relationships and parents interviewed

these patients by restoring insulin secretion from the β-cells.[6] In the pancreas the K_{ATP} channel is composed of Kir6.2 and sulphonylurea receptor-1 (SUR1) subunits. Defects in the Kir6.2 subunit of the K_{ATP} channel due to a *KCNJ11* mutation results in a failure of channel closure by ATP, however sulphonylureas promote insulin secretion in these cases by binding to the SUR1 subunit and closing the K_{ATP} channel.

To date 95 patients have been identified with *KCNJ11* mutations throughout the world. At least 44 patients worldwide have successfully transferred from insulin injections to sulphonylureas with improvements in glycaemic control.[6] Families' experiences in coping with neonatal diabetes and treatment changes have not previously been described.

Aims

To increase understanding of families' experiences of having a child with neonatal diabetes caused by *KCNJ11* gene mutations.

Methods

The approach was qualitative, as this is the most appropriate means of capturing 'lived experience' and it facilitated a deep understanding of the reality of living with diabetes, the impact of genetic testing and treatment changes. In-depth interviews were used to gain understanding of the families' experiences from diabetes diagnosis to present day. English-speaking families living in the UK who had a child diagnosed with a *KCNJ11* gene mutation between 2004 and 2005 were approached by letter, following initial contact by their local physician or genetic diabetes nurse.[7] Ethical approval was obtained and information sheets and consent forms were enclosed with the letter. Mothers were contacted initially as the main caregivers, however, where available, fathers were also approached. All interviews were conducted by

the same experienced qualitative researcher (MS).

Interviews were conducted with 11 parents (nine mothers and two fathers) of 11 patients, identified with *KCNJ11* mutations (Table 1). Of the 11 patients, 10 were diagnosed <22 weeks of age and at the time of interview patients were between 0.5 and 57 years. In three families the individual with the *KCNJ11* mutation also had a child with the same mutation and in these cases the individual was interviewed about their own experiences of diabetes and the diagnosis of their child. One of the families had two siblings who had both inherited the mutation.

Some patients with *KCNJ11* mutations also have a degree of learning difficulty. As no previous research had been conducted in this area it was considered important to include those able to provide informed consent. Sensitivity was used to determine inclusion of these participants' and questions worded appropriately. Interviews were conducted face-to-face at the family home or, for reasons of practicality due to the geographical distances involved, by telephone. All interviews were tape recorded and transcribed verbatim. Broad questions were asked relating to experiences of diabetes diagnosis, glycaemic control, genetic testing and consequences of treatment change. Thematic analysis was used; this involves the researcher searching the data for related categories with similar meaning, which are then grouped together and themes inferred and generated from the data. Data from the transcripts was open-coded initially, then further focused coding took place, categories formed and theoretical interpretations developed. Codes and categories were compared/contrasted within and across the families.

Results

Three main themes were identified: i) the difficulties of managing diabetes in a baby/young child; ii) recognition and implications of learning difficulties and muscle weakness; iii) impact of transfer from insulin to sulphonylureas.

Difficulties of managing diabetes in a baby/young child

The mothers described having little respite from the constant care that a small child with diabetes required. Levels of anxiety were particularly evident shortly after diagnosis and were related to the fact that many of the babies had been critically ill:

The first month I had her home neither of us could sleep, we had the cot jammed up against the side of the bed, we just lay there watching her, seeing that she was OK.
J's mother

Dramatic fluctuations in blood glucose levels also contributed to the need for continuous supervision:

It was absolutely exhausting because he would go from one extreme to the other, one minute his blood glucose would be 20 and then it would be 2.
D's mother

This highlighted the need to be persistently alert for problems developing in children who were too young to recognise signs of hypoglycaemia themselves. Consequently mothers acknowledged feeling overprotective towards their child with diabetes and frequently chose not to leave them with others:

I wouldn't leave her with anybody, I was with her 24/7.
C's mother

Many of the mothers found it distressing to leave their child for short periods of time even with family members:

I remember when I'd left her with Mum, I'd gone off to do a food shop, if there was a queue at the checkout I used to get a panic attack, thinking 'I've got to be back soon', things like that were traumatic.
G's mother

When families did feel able to leave their child for short periods finding someone to look after them was difficult due to others' concerns about the condition:

Nobody would come and baby-sit for us then, everybody was frightened.
I's father

The diagnosis of neonatal diabetes consequently impacted on relationships between parents:

I didn't want anyone else to look after him, not even my husband in case things weren't right.
F's mother

Mothers also felt unable to direct adequate attention to other siblings as a result of the time needed to look after their baby with diabetes:

I felt as if I was neglecting my other son.
D's mother

Having a baby with diabetes created a significant additional burden of responsibility, which was usually taken on by the mothers as part of their nurturing role. The impact on everyday life was significant in terms of the time and attention required to look after the child with diabetes. This often led to exhaustion, over-protectiveness and feelings of guilt contributing additional stresses to family life.

Recognition and implications of learning difficulties and muscle weakness

Six of these individuals with *KCNJ11* mutations had a degree of learning difficulty or muscle weakness. In some cases it was the families who identified the problem and alerted healthcare professionals:

He wasn't developing as my other child had … by a year old I was very concerned. They kept saying 'He's been very sick, he'll catch up'. At 18 months I said 'No, this isn't right, there's something wrong with him' and he was assessed.
D's mother

In other cases the effects of muscle weakness had been noticed by the families:

Her co-ordination wasn't great, tricycles she'd find difficult … She wasn't really walking properly until she was 18 months. She was a bit clumsy going up and down steps and she ran awkwardly.
G's mother

Despite clear signs of developmental delay and muscle weakness, one family, whose son developed diabetes over 50 years ago, had not confronted the issues until they attempted to register him at school and described their feelings of devastation:

He was still wearing nappies [at 5 years]*, he couldn't walk … we saw the headmistress, she said 'He'll never be able to do anything, he's mentally handicapped' … The signs were there but we just didn't see that, it wasn't talked about, I know it broke both our hearts.*
K's mother

Difficulties with numeracy were frequently described in these individuals:

She couldn't count at all, she can read and write, she just cannot understand anything to do with figures.
J's mother

These problems were often combined with poor attention spans:

He's doing OK but maths is just a complete nightmare, they said at school that he doesn't concentrate at all.
E's mother

Such difficulties also had an impact on general life skills, for example, managing finances:

If I gave her £10 and said 'Can you get something for £8.99' she wouldn't have realised what change she should have brought me.
G's mother

These difficulties also had implications for gaining and maintaining employment:

The manager of a local supermarket took her on, but because she couldn't operate a till, they paid her off.
J's mother

The majority of the families had identified learning difficulties themselves and had requested assessment, occupational therapy and learning support. Particular problems related to difficulties with numeracy, which could impact on future employment opportunities and independence.

Impact of transfer from insulin to sulphonylureas

Many of the families were thrilled at the possibility of sulphonylureas as an alternative to insulin injections:

I was excited, especially for the youngsters.
I's father talking about his grandchildren B and C

In some cases parents didn't want to raise their hopes about the treatment change:

I was determined I wasn't going to get my hopes up, I was trying not to get too excited about what the repercussions could be.
D's mother

Others were unsure whether tablet treatment would be successful:

This is going to be great if it works.
J's mother

The parents who had diabetes themselves were more concerned that the sulphonylureas should work for their child:

I'd rather it worked on A, I don't know any different.
A's mother

Despite the excitement of transferring to sulphonylureas, families needed substantial support. This reflected the importance that insulin held for the families:

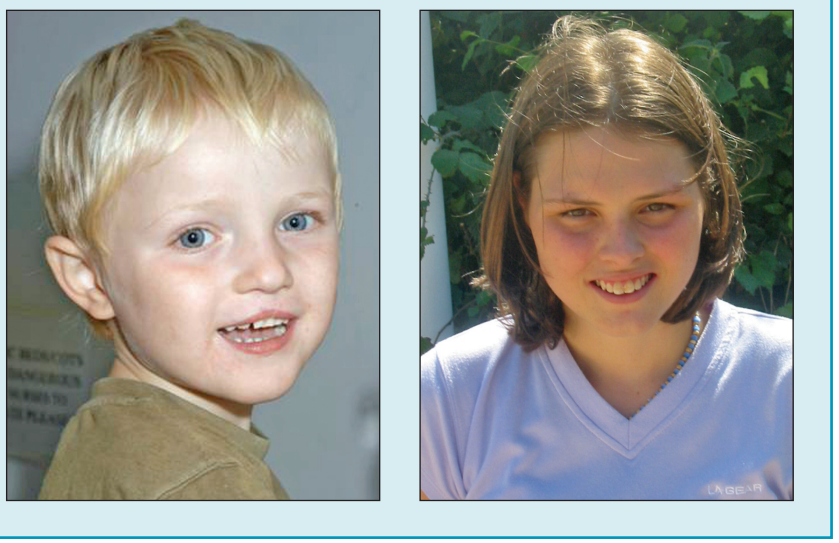
She couldn't get her head around it … she knew she had to have her injections, she knew nothing else, she knew her insulin injections were keeping her alive in effect and so she was very traumatised by it.
G's mother

Consequently some individuals discussed with friends whether the treatment change was something to consider:

It's a big thing to think about … but I talked to my friend about it and she said 'You might as well go for it because it's the only way you'll find out' .
J talking about her own diabetes

Transfer to sulphonylureas removed the daily difficulties of taking insulin and eliminated the stigma often associated with injecting in public:

Obviously people look at you when you start injecting a baby and a toddler, 'What the hell are you doing to those kids?' People would look at me as if I was giving them drugs.
B and C's mother



Two of the patients who were successfully transferred from insulin to sulphonylureas

Stopping insulin enabled families to normalise the condition, minimising the need for disclosure of diabetes in public. In those cases where the child was still young a liquid suspension of sulphonylureas was used:

We couldn't go out because you'd have to find a ladies loo, a babies room to do his injection … but now you can go into a restaurant and people think you're just giving him cough medicine or something.
H's mother talking about her grandchild A

Despite initial concerns amongst families improvements in glycaemic control were frequently reported following transfer from insulin to sulphonylureas:

His control is excellent, a lot better, he's 5.8, 4.2, 7.8, nothing's been over 8.
F's mother

When I had two injections a day my HbA_{1c} was 8, but since I've been on the tablets my last blood test [HbA_{1c}] *was 5.4.*
I talking about his diabetes

Problems with dramatic swings in blood glucose levels and frequent hypoglycaemia were also significantly reduced:

It's made a huge difference, I'm not constantly wondering if he was having a hypo … he's not going from one extreme to the other the whole time.
D's mother

Improvements in concentration and understanding were also observed following treatment change:

The teacher said to me 'We have seen a big difference', because they were doing a maths test last week and he got full marks for that.
E's mother

Consequently transfer to sulphonylureas led to vastly improved quality of life for the patients and their families:

Family life has completely changed. Before we were unable to live the life of a normal family as he had 2–3 hypos a day, now he is more independent, he is generally well and has not had one hypo. I have even had the courage to let him go to a friend's for tea.
D's mother

Increased stability of blood glucose levels and freedom from injections enabled families to allow their children greater independence. It also reduced the social stigma the families had previously experienced.

Discussion

Eight of these patients successfully transferred to sulphonylureas. In one case it was considered inappropriate to try changing treatment as there was no guarantee of success and the patient had severe learning difficulties and valued routine.[8] In two other cases transfer to sulphonylureas was unsuccessful and insulin treatment was continued. In both of these cases the individuals acknowledged feeling disappointed but were grateful that the treatment change had been successful for their child who was also affected.

Most of the interviews were with mothers of those affected. In 4/10 families the parents were separated and fathers were not available for interview; in one case the father was deceased. It could be argued that the views obtained do not wholly represent those of fathers, as they were only interviewed in two cases. Future research aims to include the views of fathers and siblings over 16 years to determine the impact on the family more fully.

These findings in families with *KCNJ11* mutations are similar to those amongst mothers of young children with type 1 diabetes who indicate the need for constant vigilance, concerns about hypoglycaemia and a profound sense of responsibility for managing the disease.[9] The critical nature of the child's condition at diagnosis, young age and

the nature of diabetes produce inordinate amounts of stress and have also been found among parents of an infant or toddler with type 1 diabetes.[10] Diagnosis of childhood diabetes necessitates 'psychosocial transition', where families undertake a major revision of their assumptions about the world.[11] However in families with *KCNJ11* mutations additional psychosocial transition occurs when adjusting to the new genetic information and resulting treatment changes which contradict the families' previously held assumptions about the causes and treatment of their child's diabetes. Stopping insulin in patients who have been on this treatment since diagnosis leads to a re-evaluation of their sense of identity and a substantial period of emotional adjustment may be expected.[12]

Conclusion

Although most families appear to adapt well to a diagnosis of diabetes over time the true impact of insulin treatment on individuals and their families is often underestimated. This is clearly seen in these individuals who have been freed from the difficulties and social stigma often associated with diabetes managed by insulin. Having a baby with neonatal diabetes necessitates constant supervision and can lead to mothers feeling overwhelmed and overprotective towards their child. This places additional strain on these families.

Before the identification of a *KCNJ11* mutation, the learning delay, muscle weakness and diabetes had all been considered distinct entities and had not been related, the molecular genetic diagnosis therefore provided an explanation of all these features for the families. Difficulties with numeracy and poor concentration were frequently reported and have implications for the future prospects and independence of these individuals.

Initial uncertainty regarding the success of sulphonylureas in these families reflects their perception of insulin treatment as essential for survival, particularly as they had been taking insulin since shortly after birth and substantial support was required at the time of treatment change. Transfer to sulphonylureas greatly improved diabetes control and transformed quality of life, allowing the families to normalise the condition, and enabling greater freedom for the individuals. The improvements in both blood glucose control and quality of life as a result of transfer to sulphonylureas has enabled these families to view the future more positively.

Recommendations

Any patient diagnosed with diabetes before the age of six months, whatever their age now, should be referred for molecular genetic testing – details available on www.diabetesgenes.org. Guidelines for transfer of patients with *KCNJ11* mutations from insulin to sulphonylureas are also available on this site.

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Conflict of interest statement:

None

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