Impact of misdiagnosis in HNF1A diabetes: A case study

Maggie Shepherd

Maturity-onset diabetes of the young (MODY) accounts for 1–2 % of diabetes in the UK but is frequently misdiagnosed as type 1 diabetes. Identifying the different subtypes of MODY by molecular genetic testing is important as this has implications for treatment, for example, those with HNF1A MODY are particularly sensitive to the hypoglycaemic effect of sulphonylureas and experience improved glycaemic control and quality of life with this treatment (Shepherd et al, 2003; Shepherd and Hattersley, 2004). This article presents data from qualitative in-depth interviews with an 18-year-old male who was misdiagnosed with type 1 diabetes at the age of 16 years and with his mother who had been diagnosed with type 2 diabetes. The impacts of recurrent hypoglycaemia, molecular genetic testing and treatment change are described from the family's perspective. The use of non-genetic tests to aid differential diagnosis and the potential impact misdiagnosis has on relationships with healthcare professionals are also discussed.

Article points

1. Maturity-onset diabetes of the young (MODY) is frequently misdiagnosed as type 1 diabetes.
2. Those with HNF1A MODY are particularly sensitive to the hypoglycaemic effect of sulphonylureas and have improved glycaemic control and quality of life with this treatment.
3. This article presents data from qualitative in-depth interviews with an 18-year-old male who was misdiagnosed with type 1 diabetes at the age of 16 years, and his mother who also has diabetes.

Key words

- Maturity-onset diabetes of the young (MODY)
- Misdiagnosis
- HNF1A

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Maturity-onset diabetes of the young (MODY) is estimated to account for 1–2 % of diabetes cases (Owen and Hattersley, 2001); approximately 20 000–40 000 cases in the UK. It is characterised by three key features: a young age of onset with at least one family member being diagnosed below the age of 25 years; non-insulin dependence; and an autosomal–dominant pattern of inheritance (Stride and Hattersley, 2002). However, in the literature and in the author's experience MODY is misdiagnosed initially in up to 90 % of cases (Gilliam et al, 2007). It is frequently misdiagnosed as type 1 diabetes and treated immediately with insulin due to its presentation with marked hyperglycaemia in slim adolescents and young adults (Lehto et al, 1997, Møller et al, 1998; Hathout et al, 1999; Lambert et al, 2003). Misdiagnosis also occurs due to inadequate investigation of the family's medical history and unfamiliarity with the inheritance of MODY or unawareness of the different types of MODY.

To date, six genes have been identified that are known to cause MODY. Mutations in the hepatocyte nuclear factor 1-alpha (HNF1A) gene account for approximately 65 % of MODY cases in the UK (Frayling et al, 2001). Those with HNF1A MODY are known to have a low renal

threshold for glucose and are particularly sensitive to the hypoglycaemic effects of sulphonylureas (Menzel et al, 1998; Pearson et al, 2000; Pearson et al, 2003). Identifying the different subtypes of MODY by molecular genetic testing is important as it can have implications for treatment (Stride and Hattersley, 2002). Those with HNF1A MODY can be treated successfully with small-dose sulphonylureas, with which they report increased quality of life and improved HbA_{1c} levels when transferred from insulin (Shepherd et al, 2003; Shepherd and Hattersley, 2004).

In people with established type 1 diabetes, autoantibodies can help define the aetiology of the disease and provide markers to aid classification (Schmidt et al, 2005). Differential diagnosis of diabetes is clearly important, yet the use of non-genetic tests to aid accurate diagnosis, such as islet cell antibodies (ICA) and glutamic acid decarboxylase (GAD) antibodies are not performed routinely. Results may also be considered inconclusive in some cases as approximately 20 % of people with type 1 diabetes may be antibody negative and testing for a range of antibodies is recommended to enhance disease prediction (Zimmet, 1996; Schmidt et al, 2005).

Aims and Methods

The aim was to gain insight into the experiences of a young person's journey to a diagnosis of MODY, including issues relating to diagnosis, genetic testing and treatment changes. In-depth qualitative interviews were conducted by the author with a 16-year-old male who was initially misdiagnosed as having type 1 diabetes and his mother. To protect his identity, he will be referred to as Harry. Audio tapes of the interviews were transcribed verbatim and subjected to thematic analysis.

Case study

Harry presented with polydipsia and polyuria at the age of 16 years. He was admitted to an emergency medical unit with the characteristics shown in *Table 1*, initiated on insulin and informed that he had type 1 diabetes.

The family were already familiar with diabetes as the young person's mother had been diagnosed with type 2 diabetes 5 months previously at the age of 43 years. She had a BMI of 23 and was treated with diet modification. She previously had gestational diabetes in all three pregnancies and was treated with insulin during her second pregnancy. In addition, Harry's maternal aunt, maternal grandfather and six other family members on the maternal side were known to have diabetes.

At Harry's diagnosis, his mother had suspicions that his diabetes was 'different' and presented the family tree to his diabetes team. She said: 'We told them straight away of our family history. When they said he'd got type 1…we'd actually taken in a drawn-up family tree, but they didn't do anything about it, they just said: "He's type 1."'

Harry's mother was aware that 'Some sort of diabetic testing of a genetic nature had happened in the family.' This was approximately 16 years previously, but she still advised Harry's doctor that MODY was present in other family members.

Treatment

Harry was started on a insulin aspart / insulin protamine mix, 8 units in the morning and 6 units in the evening. Doses were gradually increased to 22 units per day (0.3 units/kg) but he had great difficulty stabilising his blood glucose levels despite eating regularly and gaining dietary advice and support in adjusting his insulin doses. He explained: 'The blood glucose levels were all over the place. They'd be 18 one time and then half an hour later, it was down to 5…I didn't get any warnings, they were just nasty, one minute I'd be kicking a football around and the next minute I'd be flat out on the floor'.

Harry was transferred to a basal–bolus regime 5 months after diagnosis and his doses were increased to a maximally tolerated 32 units of insulin per day (0.45 units/kg). However, owing to recurrent hypos, these doses were reduced to 14 units per day (0.2 units/kg) over the following 2 months.

Impacts

The family's reaction to the diagnosis of type 1 diabetes was fairly typical. His mother described her 'shock, devastation and total heartbreak.'

The family had a traumatic time dealing

Page points

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2. Differential diagnosis of diabetes is clearly important, yet the use of non-genetic tests to aid accurate diagnosis such as islet cell (ICA) and GAD antibodies are not performed routinely.
3. This paper describes the case of a 16-year-old boy, who was initially misdiagnosed as having type 1 diabetes.
4. Harry was started on a insulin aspart/insulin protamine mix, 8 units in the morning and 6 units in the evening. Doses were gradually increased to 22 units per day (0.3 units/kg) but he had great difficulty stabilising his blood glucose levels despite eating regularly and gaining dietary advice and support in adjusting his insulin doses.

Table 1. Baseline characteristics at admission to emergency medical unit.

Age	16
Height	1.9 m
Weight	70 kg
BMI	19 kg/m^2
Random BG	11.2 mmol/l
Glycosuria	2 %
Ketones	Negative

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1. This instability in blood glucose levels impacted hugely on Harry's lifestyle. He felt tired and unable to study and gave up his driving lessons.
2. Harry underwent antibody testing 7 months after diagnosis following repeated requests from the family. The antibody tests returned negative, which would normally provide evidence against a diagnosis of type 1 diabetes.
3. The mother eventually contacted the diabetes team at the Royal Devon and Exeter NHS Foundation Trust via their website, who offer molecular genetic testing for MODY.
4. The molecular genetic test, taken 8 months after Harry's initial diagnosis of diabetes, indicated a P447L missense mutation in exon 7 of the HNF1A gene and enabled Harry to stop his insulin.

with Harry's severe hypoglycaemic episodes, which continued while his insulin doses were being reduced, and felt unable to leave him unsupervised. 'We got to the stage where we thought Harry would die because towards the end it got to him being unconscious practically every night and sometimes in the day as well,' Harry's mother said.

This instability in blood glucose levels had a huge impact on Harry's lifestyle. He felt tired and unable to study and gave up his driving lessons. 'I had to quit my driving because my blood sugars became so unstable and I didn't know what I was doing, even on the tiniest doses,' Harry commented.

Harry underwent antibody testing 7 months after diagnosis following repeated requests from the family. The antibody tests returned negative, which would normally provide evidence against a diagnosis of type 1 diabetes. Harry's mother commented: 'He'd had the test ... and the result suggested that type 1 was the wrong diagnosis… but the consultant said it just means it's a slowly-developing type 1.' The results did not seem to be interpreted with consideration of additional evidence such as the autosomal–dominant inheritance that supported a possible diagnosis of MODY.

During this period, Harry's mother was desperately searching for answers and turned to the internet for information. When she approached the healthcare team with her findings, she found these were dismissed: 'Mum started looking on the internet and she found the MODY stuff. So she suggested the idea but it got wiped off the table pretty quickly by Dr A who said to carry on with what I was doing.'

Feeling that they were not being listened to or believed led to increasing frustration for the family, particularly the mother who was a nurse and had personal experience of diabetes with her own condition and that of other family members. 'They had a plan of action for a teenager with type 1 and they wouldn't veer away from that,' she said. 'We asked at clinic for genetic testing many times and they said "Well we'll never take him off insulin so what's the point?"'

The mother recognised that her son did not need insulin treatment and wanted to stop it but was concerned about the possible implications and was seeking professional support. She commented: 'I wanted to take him off the insulin, but I know that is such a very, very major thing to do and I was scared…but there was a real feeling that it wasn't doing him any good.'

The mother eventually contacted the diabetes team at the Royal Devon and Exeter NHS Foundation Trust via their website (www.diabetesgenes.org) who offer molecular genetic testing for MODY. She discussed her son's case with the head of the department and organised for a blood sample to be sent from Harry for genetic testing for HNF1A. She immediately felt reassured: 'I was pretty convinced it was MODY. The relief I couldn't ever put into words: that someone was listening; that we knew what to do. The relief is just indescribable.'

The molecular genetic test, taken 8 months after Harry's initial diagnosis of diabetes, indicated a P447L missense mutation in exon 7 of the HNF1A gene resulting in a cytosine to thymine nucleotide change. This result provided confirmation for the family and the professionals involved.

Outcome

The molecular genetic diagnosis enabled Harry to stop his insulin and the family saw an immediate improvement. He explained: 'It was May 2005 that I had the big day where I just didn't take insulin at all. I tested my blood about 48 times over those 24 hours and it just didn't really move. I just felt so much better. I had a completely different perspective on life…I had energy, I played football, I cycled, I went out with some of my friends. It was fantastic.'

Harry was started on a small dose of a sulphonylurea with the support of his GP and the Exeter team and found that his blood glucose levels quickly stabilised and his glycaemic control improved dramatically. He reported that his GP had thoroughly researched MODY and working with the Exeter team initiated Harry on gliclazide 20mg twice daily. Harry's HbA_{1c} dropped to 5.7 % five months later and was 6.2 % a year after transfer to a sulphonylurea.

Transfer to a sulphonylurea and the resulting improvement in glycaemic control dramatically

improved Harry's quality of life; he was able to concentrate on his studies and began driving again. 'I just felt completely different. It was just like being normal again. It's absolutely fantastic. It's a completely new lease of life,' he said.

When he was on insulin, the family found it difficult to consider Harry's future, but following transfer to sulphonylureas, he achieved three A grade A-levels, started a gap year and was applying to university.

'I can't emphasise enough how different it's been. I was looking to fail college and then to go out with As and get into vet school and spend the year doing physical work in the fields with animals, it's fantastic,' Harry explained.

His mother felt able to relax for the first time in 6 months and was delighted at the positive changes in her son. 'He's absolutely brilliant. He's so well, he's so fit, he's doing farm work now in a gap year. I don't worry about him going off to university next year,' she said.

Harry's mother underwent genetic testing and it was discovered that her diabetes was not type 2 as previously assumed by the staff caring from her, but HNF1A MODY like her son. Harry's two siblings also underwent predictive genetic testing with the support of their local specialist genetic diabetes nurse. The predictive test was to check whether or not they had also inherited the affected HNF1A gene: if they had, in the author's experience they would be near-certain to develop HNF1A MODY (99 % risk). Neither had inherited the mutated copy of the HNF1A gene, which reassured the family that their risk of type 1 or type 2 diabetes was no more than the general population.

Reflections

The difficulties encountered by this family in pursuing an accurate diagnosis for their son affected their perceptions and relationships with their hospital diabetes team. 'They were nice but didn't seem to want to think outside the box,' Harry said. The family believed that the healthcare professionals had increased knowledge and understanding of MODY from Harry's case but found it difficult to retain faith in their advice following this experience.

However, the family felt strongly that their GP had supported them and their quest for genetic testing from the outset but felt he was unable to pursue this as Harry was under the care of the hospital diabetes team. They also felt their GP had taken the time to find out information about MODY and had supported them in the transfer from insulin to sulphonylureas and remain confident in his care.

Discussion

Diagnosis of diabetes is often difficult to adjust to, but having problematic hypoglycaemia due to unnecessary treatment and continued difficulty convincing healthcare professionals to listen to their suggestions made the diagnosis of diabetes particularly traumatic for this family.

Some professionals may consider molecular genetic testing inappropriate or an unnecessary expense, particularly if treatment change is unlikely. However, genetic tests are recommended where they are likely to be positive and will alter clinical care (Hattersley et al, 2006).

It is appreciated that this account relates only to the perceptions of the patient and his mother and that the views of the professionals involved in this case may be contrary. However, acknowledging patients' stories is important and provides insight into the daily experiences of diabetes. For example, in this case, Harry was clearly very sensitive to small doses of insulin and this has been noted in other patients with HNF1A (Lehto et al, 1997; Pearson et al, 2000). Taking accurate family histories and being aware of the implications of an autosomal–dominant pattern of inheritance is equally important.

Once a diagnosis has been made, many people with diabetes do not have their diagnosis reviewed. In some cases where MODY may be suspected even several years after diagnosis, non-genetic tests may be used to confirm or dispute a diagnosis of type 1 diabetes.

C-peptide measurements at least 5 years after diagnosis are helpful in determining whether or not the individual is producing insulin of their own and, therefore, would be unlikely to have type 1 diabetes. C-peptide measurements are not helpful soon after diagnosis owing to continued production of insulin during the 'honeymoon' period. Between 3 and 30 % of people with

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type 1 diabetes will have absent pancreatic islet autoantibodies when measured at diagnosis and if testing occurs at this time, it can be useful to test for ICA, insulin antibodies and GAD antibodies to increase the chance of a positive result (Sabbah et al, 1999; Hathout et al, 2000; Borg et al, 2002). GAD antibodies are present up to 20 years after diagnosis, making them a useful tool prior to genetic testing. Regrettably, neither antibody nor C-peptide tests are used with great frequency despite their value in clarifying diagnosis.

Conclusion

Molecular genetic testing is appropriate in cases where a diagnosis of MODY is suspected due to a young age of diagnosis; an autosomal–dominant inheritance of diabetes; and non-insulin dependence, particularly when treatment changes may be possible. More information about MODY, genetic testing and the UK genetic diabetes nurses is available from www.diabetesgenes.org (accessed 08.01.2008). ■

Acknowledgements

I would like to thank 'Harry' and his mother for sharing their story. Thanks to Professor Andrew Hattersley and Professor Sian Ellard for their comments on this manuscript. This work has been supported by a Fellowship grant from the National Co-ordinating Centre for Research Capacity Development.

Borg H, Marcus C, Sjöblad S et al (2002) Insulin autoantibodies are of less value compared with islet antibodies in the clinical diagnosis of autoimmune type 1 diabetes in children older than 3 yr of age. *Pediatric Diabetes* **3**: 149–54

Frayling TM, Evans JC, Bulman MP et al (2001) beta-cell genes and diabetes: molecular and clinical characterization of mutations in transcription factors. *Diabetes* **50**: S94–100

Gilliam LK, Pihoker C, Ellard S et al (2007) Unrecognised Maturity onset diabetes of the young (MODY) due to HNF1A mutations in the SEARCH for diabetes in youth study. *Diabetes* **56**: 74

Hathout EH, Cockburn BN, Mace JW et al (1999) A case of hepatocyte nuclear factor-1 alpha diabetes/MODY3 masquerading as type 1 diabetes in a Mexican-American adolescent and responsive to a low dose of sulfonylurea. *Diabetes Care* **22**: 867–8

Hathout EH, Sharkey J, Racine M et al (2000) Diabetic autoimmunity in infants and pre-schoolers with type 1 diabetes. *Pediatric Diabetes* **1**: 131–4

Hattersley A, Bruining J, Shield J et al (2006) ISPAD Clinical Practice Consensus Guidelines 2006-2007. The diagnosis and management of monogenic diabetes in children. *Pediatric Diabetes* **7**: 352–60

Lambert AP, Ellard S, Allen LI et al (2003) Identifying hepatic nuclear factor 1alpha mutations in children and young adults with a clinical diagnosis of type 1 diabetes. *Diabetes Care* **26**: 333–7

Lehto M, Tuomi T, Mahtani MM et al (1997) Characterization of the MODY3 phenotype. Early-onset diabetes caused by an insulin secretion defect. *Journal of Clinical Investigation* **99**: 582–91

Menzel R, Kaisaki PJ, Rjasanowski I et al (1998) A low renal threshold for glucose in diabetic patients with a mutation in the hepatocyte nuclear factor-1alpha (HNF-1alpha) gene. *Diabetic Medicine* **15**: 816–20

Møller AM, Dalgaard LT, Pociot F et al (1998) Mutations in the hepatocyte nuclear factor-1alpha gene in Caucasian families originally classified as having Type I diabetes. *Diabetologia* **41**: 1528–31

Owen K, Hattersley AT (2001) Maturity-onset diabetes of the young: from clinical description to molecular genetic characterization. *Best Practice and Research Clinical Endocrinology and Metabolism* **15**: 309–23

Pearson ER, Liddell WG, Shepherd M et al (2000) Sensitivity to sulphonylureas in patients with hepatocyte nuclear factor-1alpha gene mutations: evidence for pharmacogenetics in diabetes. *Diabetic Medicine* **17**: 543–5

Pearson ER, Starkey BJ, Powell RJ et al (2003) Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet* **362**: 1275–81

Sabbah E, Savola K, Kulmala P et al (1999) Diabetes-associated autoantibodies in relation to clinical characteristics and natural course in children with newly diagnosed type 1 diabetes. The Childhood Diabetes In Finland Study Group. *Journal of Clinical Endocrinology and Metabolism* **84**: 1534–9

Schmidt KD, Valeri C, Leslie RD (2005) Autoantibodies in Type 1 diabetes. *Clinica Chimica Acta* **354**: 35–40

Shepherd M, Pearson ER, Houghton J et al (2003) No deterioration in glycemic control in HNF-1alpha maturity-onset diabetes of the young following transfer from long-term insulin to sulphonylureas. *Diabetes Care* **26**: 3191–2

Shepherd M, Hattersley AT (2004) 'I don't feel like a diabetic any more': the impact of stopping insulin in patients with maturity onset diabetes of the young following genetic testing. *Clinical Medicine* **4**: 144–7

Stride A, Hattersley AT (2002) Different genes, different diabetes: lessons from maturity-onset diabetes of the young. *Annals of Medicine* **34**: 207–16

Zimmet P (1996) Antibodies to glutamic acid decarboxylase in the prediction of insulin dependency. *Diabetes Research and Clinical Practice* **34**: S125–31

For more information about MODY and genetic testing, please visit: www.diabetesgenes.org