Identification of MODY: the implications for Holly

Jo Dalton and Maggie Shepherd

Introduction

Maturity onset diabetes of the young (MODY) affects 1–2% of people with diabetes but often goes unrecognised (Shepherd, 2001a). MODY is caused by a mutation in a single gene which is passed down from an affected family member in one generation to the next; each child has a 50% chance of inheriting the affected gene which causes diabetes. Six different genes in which mutations cause MODY are currently identified and account for approximately 89% of people with MODY in the UK. The causal gene has not yet been identified in the remaining 11%. This article discusses the diagnosis of HNF-4α MODY in a girl who had previously been thought to have type 1 diabetes.

Misunderstanding about MODY exists among healthcare professionals. Many consider it to be type 2 diabetes in young people and are unaware or confused about the relevance of a family history of diabetes. The alarming issue about the confusion is that the treatment for type 2 diabetes in adolescents is not the same as the treatment for MODY in the same age group. In early onset type 2 diabetes the patient is often obese and/or has two parents affected with diabetes. In contrast, people with MODY are not usually overweight and typically have one affected parent (see *Table 1*).

A case report

MODY is something that I (JD) knew little about until moving to a new hospital trust where I became aware that some of the paediatric diabetes patients were on very small doses of insulin for their size and age. This could not be explained by a prolonged honeymoon period, and was something that I had not experienced before in my previous posts. My first thought was that these patients and their families must be particularly motivated to maintain near normal blood glucose levels, assisted by a very strict diet. However, having met these patients and families in clinic it became apparent that this was not the case.

One family particularly interested me (*Figure 1*). Holly Benson was 14 years old and was on tiny insulin doses of biphasic insulin lispro (0.14 u/kg of insulin lispro, 4 units pre-breakfast and 4 units pre-evening meal).

I met Holly for the first time in March 2002 and was interested to hear that she never seemed to have hypoglycaemic episodes and had never experienced diabetic ketoacidosis. Even at her diagnosis of diabetes in February, 2000, at the age of 11 years, Holly did not show any ketones in her urine despite presenting with abdominal pain and a random blood glucose of 11–16 mmols/l (laboratory result of 19.8 mmols/l). As she was not ketoacidotic she was sent home later that day on insulin injections.

The paediatrician at the time requested some extra tests for Holly, but in view of her age she was started on insulin. Tests performed around the time of diagnosis included the following:

- Oral glucose tolerance test: fasting result was 10.4 mmols/l. The 2 h result was never taken/recorded.
- HbA_{1c} of 9.2%.

Figure 1. Back row: John Benson (Holly's father) and Holly's paternal grandparents (Karen and Simon). Front row: Lisa Bensen (Holly's mother) and Holly.

ARTICLE POINTS

1 Maturity onset diabetes of the young (MODY) is characterised by a young age of onset, non-insulin dependence and autosomal dominant inheritance.

2 MODY is frequently misdiagnosed as type 1 or type 2 diabetes.

3 Diagnostic genetic testing can confirm MODY and define the subtype which has implications for treatment.

4 The MODY link nurse played a pivotal role in the investigation into the possibility that Holly had MODY.

5 Holly was taken off insulin injections and now successfully manages her diabetes with oral hypoglycaemic agents.

KEY WORDS

- **MODY**
- **Genetic testing**
- **HNF-4α**
- **Quality of life**
- **Genetic counselling**

Jo Dalton is a Specialist Practitioner in Paediatric Diabetes at Morecambe Bay Hospitals Trust; Maggie Shepherd is a Senior Clinical Research Fellow at Peninsula Medical School, Exeter.

Table 1. Features aiding distinction between MODY and type 1 and type 2 diabetes

Type of diabetes	MODY	Type 2 diabetes	Type 1diabetes
Non-insulin dependent	Yes	Yes	No
Number of parents affected	1	1–2	0–1
Obesity	+/-	+ + +	+/-
Acanthosis nigricans	-	+ +	-
Prevalence in racial groups	low	high	low
Ketoacidosis	+	+	+ +

+ = present; - = absent; +/- = may be present or absent

PAGE POINTS

1 A mutation in the hepatocyte nuclear factor 4α (HNF-4α) gene is a rare cause of MODY in the UK, accounting for only 3% of cases.

2 Holly's father had been diagnosed with type 2 diabetes at the age of 21 years and had always been on oral hypoglycaemic therapy.

3 The MODY link nurse encouraged me (JD) to pursue the possibility that Holly had MODY with our paediatrician.

- GAD antibodies were negative (0.8 u/ml). This suggested that her diabetes was less likely to be caused by an autoimmune type 1 diabetes process.
- C-peptides (off treatment) were normal (602 pmol/L). This indicated that Holly was producing insulin of her own. However, the presence of detectable c-peptide may be misleading within the first 5 years of diagnosis due to the possibility of a 'honeymoon' period in type 1 diabetes.

A blood sample was sent some time later for genetic testing to look for a mutation in the hepatocyte nuclear factor 1α (HNF-1α) gene. This is the most common cause of MODY in the UK, accounting for approximately 69% of cases. No mutation in the HNF-1α gene was identified in Holly. Holly continued on insulin treatment for the next 2 years. Her doses were never really altered as her home blood glucose monitoring showed little need for increases in her insulin. Holly's height and weight were checked at each clinic visit, and she was growing along the 75th centile and was generally well and asymptomatic.

MODY link nurse involvement

I (JD) discussed Holly (then aged 13 years) with the MODY link nurse in the region who asked for more information about Holly and whether any other family members were known to have diabetes (Shepherd et al, 2003a). Holly's father, John, had been diagnosed with type 2 diabetes at the age of 21 years and had always been on oral hypoglycaemic therapy. This was unusual as John was not overweight and had been diagnosed at a young age, so I would have expected him to have type 1 diabetes. John was taking repaglinide, but not at the doses his GP had prescribed. He was advised to take one dose before his breakfast, lunch and evening meal. He actually took one with breakfast and one with his evening meal, but none at lunchtime as it made him feel hypoglycaemic. John was happy with his treatment. It appeared no other family members had diabetes and John's parents were both still alive and well.

The MODY link nurse encouraged me to pursue the possibility that Holly had MODY with our paediatrician. The paediatrician had some reservations as Holly was doing well on her current treatment. My opinion was that if Holly did not have type 1 diabetes, she may be able to come off her insulin and take tablets instead. This could make a huge difference to her daily life and could influence her career choices. Holly was not adverse to taking her insulin injections, but the thought of not having to take injections was obviously appealing. I had to tread gently because if I was wrong and Holly did have type 1 diabetes, her hopes could be falsely raised.

Time for action

The MODY link nurse contacted the family and started to build a more complete picture. Holly's DNA sample in Exeter was retested for a mutation in the hepatocyte nuclear factor 4α (HNF-4α) gene as it was thought that she was likely to have one of the subtypes of MODY. MODY due to a mutation in the HNF-4α gene has similar characteristics to HNF-1α MODY but is much less common, accounting for only 3% of MODY cases in the UK.

Holly's case was discussed with the MODY team in Exeter who came up to Cumbria to take clinical details and blood samples from other willing family members. Both of Holly's parents and her paternal grandparents were tested. Details about MODY, its treatment and inheritance were clarified with the family and the implications of genetic testing were discussed. Holly has younger twin sisters who were not tested at this time as they had shown no signs of having diabetes. However, predictive testing is available following appropriate genetic counselling should they decide that they would like this in the future. This would identify whether or not they had inherited the affected gene (Shepherd, 2001b).

Results

The process of genetic testing can take time, but the result for this family was significant and had major implications for Holly's treatment. Holly and her father were both found to have a novel mutation in the HNF-4α gene. Neither of her paternal grandparents or paternal uncle were affected. This indicated that the mutation in the HNF-4α gene had occurred spontaneously in John. We were all excited by this information and the family were pleased to have the cause of their diabetes identified.

The new diagnosis meant that Holly could come off her insulin injections and try sulphonylurea tablets. After seeking advice from Exeter, we arranged to stop the insulin in the morning and start a quarter of a gliclazide tablet (20 mg). This seemed a tiny dose, but experience with other families indicated it was a sensible starting point (Shepherd, 2003b). There were also some salient safety points to discuss with Holly:

- She had to be warned about hypoglycaemia and how to treat it.
- Her diet should be healthy.
- Holly was asked to initially perform at least pre-meal and pre-bedtime blood glucose testing.
- She needed the skills, knowledge and equipment to test for ketones if necessary.

I (JD) kept in daily contact with Holly for the first few weeks as recommended and spoke to her year head at school to explain hypoglycaemia and why she may be doing extra blood glucose monitoring in school.

Practical issues

I (JD) had thought that Holly's father would be happy for her to come off her insulin, but he was unsure how she would manage. He felt that while she was well on insulin she should stay on it. The paediatrician had similar views, but both were persuaded to give her a trial with gliclazide for 3 months.

In November, 2002, Holly was keen to try the new regimen, but realised that her diet would need to be improved. With Christmas approaching it was decided that half a tablet (40 mg) might be more practical to allow small amounts of festive foods to be consumed. At the beginning of 2003, the gliclazide dose was reduced to 20 mg and has remained so for the last year. Holly's most recent HbA_{1c} was 6.6%, which is better than all of her previous results on insulin. This finding is similar to many HNF-1α patients who have been able to transfer from insulin to sulphonylureas (Shepherd, 2003c). All of Holly's blood glucose readings are now within the 4–8 mmol range and her diet is healthy.

Holly's long-term follow-up will be the same as that given to adolescents with type 1 diabetes. Annual screening for complications continues as people with HNF-1α and HNF-4α MODY are at risk of diabetes complications, but the change in Holly's quality of life has been profound. In the future Holly is likely to need to increase her gliclazide doses, and eventually may need to return to insulin, but at the moment this feels like a long way off. Many people with HNF-1α and HNF-4α MODY have good glycaemic control on small doses of sulphonylureas for many years.

Implications for practice

This case has lessons for other healthcare professionals working in the field of diabetes. There are probably other DSNs who have uncertainties about the diagnosis given to some of their patients with diabetes and we know that many people with MODY are misdiagnosed as having type 1 or type 2 diabetes. Holly's re-classification of diabetes started from a gut feeling which led to further investigation with a positive outcome for the family and improvement in Holly's quality of life. If you have any patients you think could have MODY and would like to find out more information visit the website www.diabetesgenes.org. ■

Shepherd M (2001a) Recognising maturity onset diabetes of the young. *Journal of Diabetes Nursing* **5**(6): 168–72

Shepherd M, Ellis I, Ahmad AM et al (2001b) Predictive genetic testing in maturity onset diabetes of the young (MODY). *Diabetic Medicine* **18**: 417–21

Shepherd M, Stride A, Ellard S, Hattersley AT (2003a) Integrating genetics into diabetes care: a new role for DSNs. *Journal of Diabetes Nursing* **7**(8): 289–92

Shepherd M (2003b) 'I'm amazed I've been able to come off injections': patients' perceptions of genetic testing in diabetes. *Practical Diabetes International* **20** (9): 338–43

Shepherd M, Pearson ER, Houghton J et al (2003c) No deterioration in glycaemic control in HNF-1α maturity onset diabetes of the young following transfer from long term insulin to sulphonylureas. *Diabetes Care* **26**(11): 3191–92

PAGE POINTS

1 The genetic testing result was significant for this family and had major implications for Holly's treatment.

2 The new diagnosis of HNF-4α MODY meant that Holly could come off her insulin injections and try sulphonylurea tablets.

3 I (JD) kept in daily contact with Holly for the first few weeks as recommended and spoke to her year head at school to explain hypoglycaemia and why she may be doing extra blood glucose monitoring in school.

4 Holly's most recent HbA_{1c} was 6.6%, which is better than all of her previous results on insulin.

5 Holly's long-term follow-up will be the same as that given to adolescents with type 1 diabetes due to the risk of developing diabetes complications.

Pseudonyms have been used throughout the article to protect the identity of the family involved.

Acknowledgements

Many thanks to Jane Houghton, (MODY Link Nurse – North West) for her involvement in investigating this case.