Keeping diabetes in the family: lessons from a family with HNF-1α MODY

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Summary

Establishing a precise diagnosis of the aetiology of diabetes can impact on treatment and prognosis and provides information for other family members about their risk of developing diabetes. Maturity-onset diabetes of the young (MODY), part of the differential diagnosis of diabetes presenting in children and young adults, is most commonly caused by mutations in the hepatocyte nuclear factor 1 alpha (HNF-1α) gene. Although many families display the classic diagnostic criteria of autosomal-dominant family history and age of onset before 25 years, frequently diagnostic confusion arises with both type 1 and type 2 diabetes and this can lead to considerable delay in arriving at the correct diagnosis.

This family case study is based on a proband found to have MODY due to an HNF-1α mutation after doubts were raised about the aetiology of her diabetes 23 years after the original diagnosis. It illustrates many features of the presentation, investigation and potential problems associated with the diagnosis and management of HNF-1α. It also demonstrates the challenges involved in detecting rare forms of diabetes and the far-reaching effects that making such a diagnosis has on the family as a whole. The difficulties encountered in detecting the proband's true aetiology in this case suggest that more systematic pathways should be in place at or close to diagnosis for identifying monogenic forms of diabetes.

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Key Words

HNF-1α; MODY; genetics of diabetes; C-peptide; predictive testing; case study

Introduction

Being able to give a precise diagnosis of their type of diabetes to an individual can impact on treatment and prognosis, and provides information for other family members about their risk of developing diabetes. This is of particular relevance when considering monogenic forms of diabetes such as maturity-onset diabetes of the young (MODY) caused by mutations in the hepatocyte nuclear factor 1 alpha (HNF-1α) gene.

MODY is one of the differential diagnoses of diabetes presenting in children and young adults,[1] and is estimated to account for 2% of all cases of non-insulin-dependent diabetes in Europe.[2] Mutations in six genes, all dominantly inherited, cause MODY,[1] with mutations in the transcription factor HNF-1α accounting for 70% of MODY cases in the UK. Families frequently (although not always) fit the classic clinical picture of two or more consecutive generations of a family affected, with one or more individuals diagnosed with non-insulin-requiring diabetes before 25 years of age.[3]

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Clinical features of MODY due to HNF-1α mutation

Patients with HNF-1α mutations are normoglycaemic in childhood, but develop a progressive β-cell defect, resulting in diabetes in the second to fifth decades of life.[4] In a UK series, formal diagnosis of diabetes occurred in 65% by age 25 and 95% by age 45,[2] and overall there is a >98% lifetime risk of developing diabetes. Treatment requirements are also progressive and complications occur if good control is not maintained. As the pathophysiology involves β-cell dysfunction, the insulin resistance characteristic of type 2 diabetes is not generally seen.[5] Other clinical features include a low renal threshold for glucose, which is seen in mutation carriers before the development of diabetes[6] and can be a useful screening tool.

One of the most striking features of HNF-1α mutations is the sensitivity seen to the sulphonylurea class of oral hypoglycaemic agents (SUs). This was observed in anecdotal reports and confirmed in a randomised controlled trial.[7] Those with HNF-1α mutations had a four-fold greater fall in fasting plasma glucose on treatment with gliclazide compared to type 2 diabetes controls, whereas the response to metformin was similar in both groups.

The effect is similar with the insulin secretagogue nateglinide.[8] HNF-1α subjects frequently report hypoglycaemia when commenced on standard doses of SUs. Thus low-dose SUs (starting dose gliclazide 40 mg once daily) should be the first-line pharmacological treatment in HNF-1α MODY. Those with HNF-1α MODY treated with insulin since diagnosis can often be transferred to SUs with no deterioration in control when the genetic diagnosis is made.[9] This is one feature of HNF-1α MODY that has a huge potential clinical and personal impact.

An HNF-1α mutation should be suspected in a young adult presenting with non-insulin-requiring diabetes, no evidence of β-cell autoimmunity indicated by antibody screening, and no evidence of the metabolic syndrome. However, because of the young age of onset, in many cases individuals are assumed to have an early presentation of type 1 diabetes and are treated with insulin from diagnosis. Equally, those presenting as slightly older adults may be assumed to have lean type 2 diabetes. These diagnostic labels are very seldom challenged, and it often takes a chance clinical finding, such as evidence of continued endogenous insulin secretion in someone assumed to have type 1 diabetes or the development of non-insulin-requiring diabetes in a younger family member, before the diagnosis of MODY is considered. Data from the National UK MODY testing laboratory suggest there is an average delay of 13 years following onset of diabetes before a genetic diagnosis is made (S Ellard, personal communication), and presumably there is a proportion of families who are never identified.

Once the diagnosis of HNF-1α has been established, genetic testing can be performed in other family members. This will confirm that others with diabetes have the same aetiology and will identify unaffected mutation carriers at risk of developing diabetes later in life. The latter is referred to as a predictive test and, as in other areas of genetics, the decision whether to proceed with such a test depends on individual and family attitudes.[10–12]

Case history

The following case study of an extended family with MODY due to HNF-1α mutation illustrates many features of the presentation, investigation and potential problems of diagnosis and management seen in MODY.

Alison, aged 49, was investigated after doubts were raised about the classification of her diabetes. Initially she presented with hyperglycaemia, aged 25 at the time of the premature delivery at 33 weeks' gestation of a 4 kg baby; this was attributed to gestational diabetes. During her second pregnancy a year later she commenced insulin, which she subsequently remained on and was assumed to have type 1 diabetes. She had a strong family history of diabetes in her mother, maternal grandmother, two maternal uncles, and later two of her sisters and a maternal first cousin (see Figure 1A).

Control was suboptimal over the years and she developed severe microvascular complications, including laser-treated retinopathy, peripheral neuropathy leading to a partial foot amputation, and chronic renal impairment. Renal function worsened in 2005 when she had pyelonephritis requiring left nephrectomy. As her renal function deteriorated, her insulin requirement reduced until she stopped insulin treatment in 2006. The diagnosis of type 1 diabetes was revisited and the presence of endogenous insulin secretion was confirmed when a random C-peptide level was shown to be measurable at 0.57 nmol/l (normal fasting range 0.2–0.5 nmol/l). C-peptide is co-secreted from the β-cells with insulin, but is not found in pharmaceutical preparations of insulin. It is thus a marker solely for endogenous insulin and is usually undetectable within 3 years of the diagnosis of type 1 diabetes. This suggested that Alison had a different form of diabetes. Initially an HNF-1β mutation was considered due to the combination of renal disease and diabetes;[1] however, the histology of the resected kidney did not support this,[13] showing a combination of diabetic nephropathy and chronic pyelonephritis. Subsequently HNF-1α mutation was thought to be the most likely cause of her diabetes, which was confirmed in 2007 with sequencing of the HNF-1α gene.

Following Alison's diagnosis, her first-degree relatives were investigated for possible MODY.

Her second sister Eileen, aged 52, had also presented with gestational diabetes during her third pregnancy aged 31. She was normoglycaemic afterwards, but also developed gestational diabetes in later pregnancies and a formal diagnosis of diabetes was made at age 37. At review she was taking only metformin 850 mg twice daily and was assumed to have type 2 diabetes. She did not have any diabetic complications. On examination she had body mass index (BMI) 26.2 kg/m^2 and blood pressure (BP) 125/78. HbA_{1c} was 7.2% with fasting glucose of 9.4 mmol/l. Mutation testing confirmed that Eileen carried the same HNF-1α mutation as her sister. Eileen's clinical team was informed of the finding and advised that the most effective treatment for HNF-1α MODY is low-dose SU. A change to this treatment was advised should HbA_{1c} persistently remain above 7%.

Alison's eldest sister Karen, aged 56, had developed gestational diabetes in both pregnancies. Subsequently she had been diagnosed

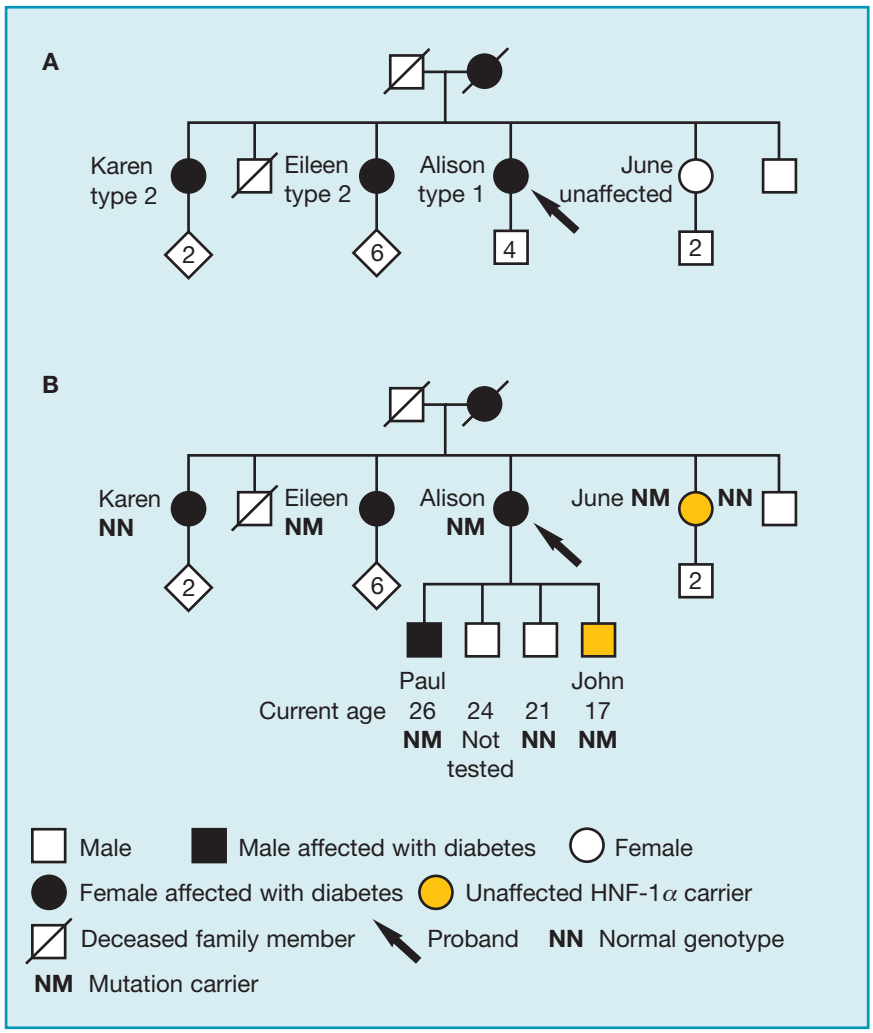

Figure 1. The family pedigree (A) before investigation of diabetes aetiology (Alison, the proband, is arrowed) and (B) after correct assignment of HNF-1α mutation status in Alison's first-degree family

with type 2 diabetes at 52 years and was moderately controlled on maximal doses of metformin and gliclazide (HbA_{1c} 8.5%). She had a BMI of 30.2 kg/m^2 and was also being treated for hypertension and dyslipidaemia. There was no acanthosis nigricans. Genetic screening in Karen showed that she did not carry the mutation in HNF-1α and did in fact have type 2 diabetes. This is known as a 'phenocopy', i.e. she displays the phenotype (diabetes) but not the genetic change. This illustrates the possibility of co-existence of other forms of diabetes, particularly in large families. Importantly for Karen, this meant that her children were not at risk of inheriting the HNF-1α mutation. However, they have around a 30% increased risk of developing type 2 diabetes later in life.

Alison's younger sister June, aged 46, was not known to have diabetes. She went on to have a normal 75 g oral glucose tolerance test (OGTT); fasting glucose 5.4, 2 hour 6.8 mmol/l with glycosuria +++ at 2 hours. She elected to have a predictive genetic test and was found to be a carrier of the HNF-1α mutation. The glycosuria was consistent with the low renal threshold associated with HNF-1α. The expectation is that June will develop diabetes over the next few years; follow-up with annual OGTT was recommended, as it has been shown that the post-challenge value is frequently diagnostic of diabetes before fasting values.[14]

Alison's brother, aged 39, and three of Alison's four sons, aged 17–26, also attended for screening with OGTT and predictive testing. None of these individuals were known to have diabetes, but her 26-year-old son, Paul, was found to have diabetes on OGTT (fasting glucose 8.0, 2 hour 13.0 mmol/l). He was asymptomatic with HbA_{1c} 6.4%. Genetic testing confirmed that he carried the same HNF-1α mutation as his mother. No treatment was required at this stage, but 6-monthly HbA_{1c} was recommended, with low-dose gliclazide to be commenced if HbA_{1c} rises. The main advantages of early diagnosis for Paul are, firstly, that screening for diabetic complications can be commenced; secondly, appropriate treatment can be instigated without any prior period of poor control; and, thirdly, he can be supported to be proactive in his self-care and adopt lifestyle changes. Importantly, as the cause of his diabetes is known, he will no longer be at risk of being misdiagnosed with type 1 diabetes or commenced on insulin unnecessarily.

Alison's youngest son John had a normal OGTT (fasting glucose 4.9, 2 hour 6.8 mmol/l with no glycosuria), but predictive genetic testing showed he was also a mutation carrier. He was advised to have annual diabetes testing with OGTT.

Alison's other son and her brother did not have diabetes on testing and did not carry the HNF-1α mutation. Thus they could be advised that their risks of developing diabetes were not greater than that of the general population.

Figure 1B shows the revised family tree after investigation of Alison's

first-degree relatives and assigning the correct genetic diagnosis.

Between them Eileen and June have several children, some of whom are <18 years of age. They were advised their children had a 50% risk of inheriting the abnormal gene and thus developing diabetes later in life.

Investigation of relatives

Diabetes screening for adults is straightforward with OGTT, as described above, but for younger children testing may need to be arranged in collaboration with paediatric services. It is relatively uncommon for HNF-1α diabetes to present in the first decade, but clearly young children should have formal testing if symptomatic. The advantage of knowing that a parent has HNF-1α is that children would not be automatically assumed to have type 1 diabetes and, in the absence of an acute presentation, they would not need to be started on insulin (although in any case of doubt it is advised to start insulin and await genetic testing and assessment of progress before making further management decisions).

Older children have an increasing risk of developing diabetes (about 50% by age 20),[2] but may not tolerate or wish for formal glucose testing. In these cases the presence of post-prandial glycosuria is a useful home screening test, with positive values triggering more formal testing.

Predictive genetic testing in under-18s is not straightforward. Although parents on occasion request this for young children,[12] it is generally recommended that this is delayed until the individual child can make an informed decision. A survey of a large group of HNF-1α families from Finland[10] showed that both parents and their (so far unaffected) adolescents aged 12–18 thought that predictive testing should be offered before the age of 18. However, despite receiving genetic counselling, 25% of adolescents having a predictive test were subsequently dissatisfied with their decision to go ahead. Experienced genetic counsellors should be involved in such cases.

For predictive testing in adulthood, the issues become a little clearer, although individuals' views are still important and should be explored. It is certainly advantageous to know whether annual diabetes screening is required or not. The unaffected family members in this case received counselling from a clinical genetics consultant. This provided an explanation of the mode of inheritance of HNF-1α mutations, the implication of a positive test (>98% lifetime risk of developing diabetes), the need for annual screening, and some discussion of the psychological implications of being found to be a carrier. Diabetes departments may have little experience of such issues, in which case the use of local clinical genetics expertise or a Genetic Diabetes Nurse trained at the Peninsula Medical School (see www.diabetesgenes.org for details) is recommended and can offer ongoing support to family members whatever their mutation status.

It should be emphasised that for family members already known (or found) to have diabetes, there should be no delay in performing genetic testing to assign the correct diagnosis and thus advise on management and further family screening.

Comments

This extended family demonstrates the wide range of presentations associated with HNF-1α MODY that diabetes healthcare professionals should be aware of.

Alison (the proband) had been assumed to have type 1 diabetes for 23 years. She was only detected when her insulin dose requirements fell to zero secondary to end-stage renal failure. Measurement of C-peptide confirmed residual endogenous insulin secretion. We find this a useful clinical tool in those with apparent type 1 diabetes post the honeymoon period, when endogenous insulin production is expected to be absent. Like type 2 diabetes, those with HNF-1α mutations maintain detectable insulin secretion for many years.

Eileen had been assumed to have type 2 diabetes, but she also displayed atypical features, being lean and normotensive. Thus the simple absence of insulin resistance in apparent young-onset type 2 diabetes can be used to differentiate from HNF-1α MODY.[5]

Given the family history, we expected Karen to also be affected. However, she had a much later age of onset of diabetes than the rest of the family and had symptoms more typical of type 2 diabetes with the presence of metabolic syndrome. This illustrates that other kinds of diabetes are seen in MODY families and confirmatory genetic screening should always be performed.

Paul was asymptomatic, but diagnosed with diabetes on testing, emphasising that high-risk individuals should be advised to have diabetes screening.

Several adult family members opted for predictive testing after clinical genetics counselling and two family members were found to be unaffected mutation carriers. These individuals have a >98% lifetime risk of developing diabetes and require annual diabetes screening, preferably with OGTT.

This family case study demonstrates how challenging detecting rare forms of diabetes can be and that making such a diagnosis does have far-reaching effects on the family as a whole. The difficulties

encountered in detecting the proband's true aetiology in this case suggest that more systematic pathways should be in place at or close to diagnosis for identifying monogenic forms of diabetes. Assessing whether insulin resistance is a feature, and routine use of tools such as β-cell antibodies and C-peptide levels, can help select those to refer for genetic testing.

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Conflict of interest statement
None

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