Co-existence of type 1 diabetes and monogenic diabetes in one family: getting the diagnosis right

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Introduction

Despite having been recognised since the 1970s, monogenic diabetes is still frequently misdiagnosed as either type 1 (T1) or type 2 (T2) diabetes mellitus (DM).[1,2] It is estimated that 2% of diabetes diagnosed before the age of 20 years is monogenic diabetes,[3] and that 3.6% of patients under 30 are likely to have monogenic diabetes.[4] Despite this, as many as half of the patients with monogenic diabetes in general diabetes clinics remain undiagnosed.

Accurate diagnosis of diabetes subtype ensures appropriate treatment, reducing the risk of complications and also reducing the treatment burden on the patient. Identifying other family members through genetic testing can ensure they too are appropriately diagnosed and treated.

It is possible for monogenic diabetes to be present in families who also have T1DM and T2DM. Here we present a family with both HNF1A (MODY3) monogenic diabetes with a negative HNF1A mutation and T1DM.

Case history

Our patient was diagnosed with diabetes when nine years old in 1964 following symptoms of thirst and weight loss. Her mother had been diagnosed with diabetes the previous year after having a baby with significant macrosomia (over 4.5 kg). Our patient was started on insulin. However, between January and September 1964 the insulin dose was gradually reduced and she was started on tolbutamide 500 mg once daily, which was increased to three times daily by the time she was aged 10 in 1965. At clinic appointments the success of tolbutamide was measured by the absence of glycosuria and ketonuria. It had not previously been thought possible to stop insulin in children with diabetes and the success of her being on tolbutamide generated interest in the medical literature in the early 1960s. In clinic in the late 2000s she admitted that for much of her childhood she had not taken the tolbutamide and had felt very well at the time.

By 1968 she began to have evening glycosuria and was started on insulin lente 12 units. She noted that the requirement for insulin occurred after she had gone through puberty. She felt that she was shorter than the rest of her family although she had UK shoe-size 7 feet. Over the following years the insulin dose was titrated as per the level of glycosuria but ketonuria was never present. She was also taking tolbutamide. She continued on this treatment until the 1980s, when she was on Actrapid and Insulatard and managed as having T1DM.

During the late 1970s and early 1980s she had necrobiosis lipoidica. The dermatology clinic prescribed aspirin and dipyridamole, without benefit. She had also developed right eye exudates and left eye microaneurysms. The first evidence of diabetes-related eye disease was noted in 1978 and by 1989 there was extensive background retinopathy in both eyes, with microaneurysms but no neovascularisation. This was a surprise to the clinical team as there had been minimal glycosuria and HbA_{1c} testing when introduced in the 1980s was often in the range 42 mmol/mol to 53 mmol/mol for this patient.

By 1987 her HbA_{1c} went up to 101 mmol/mol when she decided to reduce her insulin dose in an attempt to lose weight. At this point she developed thyrotoxicosis and was prescribed carbimazole. Throughout the 1990s it was noted that her HbA_{1c} was typically between 53 mmol/mol and 64 mmol/mol and she was unusual among most people with T1DM as she "tends to fly on automatic pilot" with very few blood tests and no hypos. Her weight at the time was 70.8 kg. The only hypoglycaemic episode noted was after a session in the gym.

In 1994 both her children were diagnosed with diabetes. Her son, aged 17 years, presented with thirst and osmotic symptoms and was started on insulin. Her daughter, aged 15 years, was noted to have glycosuria after using her brother's test strips. She was started on insulin. Both children were managed as T1DM.

Our patient developed ischaemic heart disease in the early 2000s, aged 48. This was unexpected as she was a white Caucasian non-smoker, her HbA_{1c} had been in target for much of the time it could be measured, and her body mass index was only mildly raised at 25-27 kg/m^2. In 2006 she developed

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Table 1. Summary of all individuals in the family with a diabetes diagnosis

Relative	Age at diagnosis	Initial treatment	Genetic testing	Current treatment	Final diabetes classification
Grandmother	?	Insulin	Not done	RIP at age 73 (Insulin only)	Unknown
Mother	33 years	Insulin	Not done	RIP at age 83 (Insulin only)	Unknown
Patient	9 years	Insulin	**HNF1A**	Gliclazide (stopped) Fiasp (1 unit for every 15 grams of carbohydrate) Tresiba (8 units once daily) TDD: 20-22 Units	MODY3
Son	17 years	Insulin	Negative	Insulin pump	T1DM
Daughter	15 years	Insulin	**HNF1A**	Metformin (500mg twice daily)	MODY3

coeliac disease. She was getting more frequent hypoglycaemia. She was on low doses of insulin - Actrapid 3 units twice daily and Insulatard 14 units twice daily. She was using hearing aids at this point.

The first suspicion of monogenic diabetes was raised in 2006, noting the strong family history of diabetes and the lack of diabetic ketoacidosis on insulin cessation. Her anti-GAD was negative (other antibodies were not checked at the time). Her daughter, now in her 20s, had omitted insulin for a prolonged period of time with no adverse features. Our patient was referred to clinical genetics and had positive genetic testing in 2010 for HNF1A. Her urinary C-peptide was 3.47 nmol/L with a urinary C-peptide: creatinine ratio of 0.68, suggesting significant endogenous insulin production (below 0.20 absolute insulin deficiency, above 0.60 significant insulin production). She was started on gliclazide 40 mg daily. By the end of 2010 she was off insulin and on gliclazide 80 mg three times a day.

At this point further genetic testing on her family was undertaken. Her mother remained on insulin until her death in 2014 and did not undergo any genetic testing. Her daughter was also found to be positive for HNF1A. She stopped insulin and was started on metformin, with good diabetes control. Her son also underwent genetic testing but no HNF1A mutation was identified. He has continued insulin pump therapy.

Our patient had a cerebellar stroke in 2017, with lacunar infarction and small vessel disease. By 2021 she had stopped gliclazide as it was no longer effective. Currently (2023) she is on Tresiba 8 units once daily and Fiasp 1 unit for every 15 grams of carbohydrate and is using the Freestyle Libre monitoring system with 85% time in range.

Discussion

This case report demonstrates T1DM and monogenic diabetes co-existing in the same family. A summary of all family members affected with diabetes can be seen in Table 1. Changes in the HNF1A gene cause reduction in the amount of insulin produced by the pancreas, with relatively normal insulin production as a child but a gradual decrease during progression into adulthood,[5] in contrast with the more rapid loss of insulin production in T1DM.[6]

The case report also highlights how a single genetic test may not provide complete information for the entire family. Had our patient's son been the first to have the genetic test it might have been inferred that the rest of the family were also negative. Therefore, a single negative genetic test in a family should not prevent further genetic testing being carried out.

A distractor here was the presence of other conditions also associated with T1DM. Our patient had necrobiosis lipoidica, which has been more commonly associated with T1DM but has also been described in monogenic diabetes.[7] Family members of people with T1DM are more likely to have other autoimmune conditions even if they do not have T1DM.[8] Up to 7.5% of patients with T1DM have hyperthyroidism,[9] and 15% have coeliac disease.[8] HNF1A mutations are not associated with any increased risk of autoimmune conditions.[10] The presence of co-existing but unrelated autoimmunity could potentially be a distractor from suspecting monogenic diabetes.

There is considerable variation amongst families in the expression of MODY3 and the degree of hyperglycaemia.[11] More than 200 different HNF1A mutations have been described, and the type and location of the mutation may affect clinical phenotype. Maternal hyperglycaemia may also play a role since offspring with MODY were typically diagnosed 10-15 years earlier when their mothers had been diagnosed with MODY before rather than after pregnancy.[11]

There were features early on in our patient's clinical course to suggest that this might not be T1DM, particularly the omission of insulin in both the patient and her daughter for long periods without development of significant hyperglycaemia or diabetic ketoacidosis. It is unclear how quickly the speed of progression to insulin would have been affected if she had taken tolbutamide regularly as a child. It was believed that the tolbutamide had been effective initially but, in reality, often it had not been taken. The widespread testing of all patients with a T1DM diagnosis can help identify those with retained C-peptide production and therefore indicate where an alternative diagnosis should be considered prior to carrying out genetic testing.[6]

Key messages

- Type 1 Diabetes and monogenic diabetes may exist within the same family
- Genetic testing should be done on all family members to ensure accurate diagnosis
- Co-existing but unrelated autoimmune conditions may be a distractor from suspecting monogenic diabetes

Conclusions

Whilst making the diagnosis of monogenic diabetes may help in the diagnosis of other family members, the high prevalence of T1DM and T2DM means that there may be many families with more than one diabetes subtype present, so genetic testing should not be limited to single family members. Other co-existing autoimmune conditions more prevalent in people with T1DM may not adequately differentiate between monogenic diabetes and T1DM. Therefore, affected individuals need to undergo genetic testing and other causes of diabetes should be considered if genetic testing is negative.

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