The coexistence of autoimmune diabetes and maturity-onset diabetes of the young (MODY): a case series

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Summary

The coexistence of autoimmune diabetes and maturity-onset diabetes (MODY) is rare. The absence of pancreatic autoantibodies is a key factor prompting MODY genetic testing. In this study, we report three cases of young-onset diabetes with progressive beta-cell dysfunction, strongly positive glutamic acid decarboxylase (GAD) antibodies, and genetic confirmation of pathogenic gene variants of HNF-1A, HNF-4A, and ABCC8-MODY. The first case is a woman diagnosed with HNF-1A-MODY diabetes more than 30 years after her diagnosis of adult-onset diabetes at 25 years. She required insulin after her fourth pregnancy. She became ketotic on oral hypoglycaemic agents (OHAs) and subsequently, her GAD antibodies tested positive. The second case is a woman diagnosed with diabetes at 17 years who was subsequently diagnosed with HNF-4A-MODY after many hypoglycaemic episodes on low-dose insulin. GAD antibodies were strongly positive. The last case is a man diagnosed with diabetes at 26 years who was well controlled on OHAs and required insulin years later due to sudden deterioration in glycaemic control. His ABCC8-MODY was diagnosed upon realisation of strong family history and his GAD antibodies tested positive. All subjects are now treated with insulin. Less than 1% of subjects with MODY have positive autoantibodies. These cases highlight individuals who may have two different types of diabetes simultaneously or consecutively. Deterioration of glycaemic control in subjects with MODY diabetes should highlight the need to look for the emergence of autoantibodies. At each clinic visit, one should update the family history as MODY was diagnosed in each case after the development of diabetes in their offspring.

Learning points:

• These cases highlight the rare coexistence of autoimmune diabetes and MODY.
• Deterioration of glycaemic control in subjects with MODY diabetes should highlight the emergence of autoantibodies.
• One should revise and update the family history as the diagnosis of MODY was made after the development of diabetes in offspring.
• Understanding the spectrum of diabetes allows for precision medicine.

Background

Maturity-onset diabetes of the young (MODY) is an autosomal dominant rare form of diabetes (1–5% of all diabetes mellitus cases) characterized by age of onset before 25 years old and lack of beta-cell autoimmunity. Traditionally, it has been known that <1% of subjects with MODY have positive autoantibodies glutamate decarboxylase (GAD) and islet antigen-2 (IA-2), the same proportion as is found in the healthy background.
population (1). The occurrence of overt autoimmune diabetes and MODY is exceedingly rare. The absence of pancreatic antibodies, especially when measured at the diagnosis of diabetes, is a key factor when considering MODY diabetes and genetic testing (2). To the best of our knowledge, most of the cases described so far present subjects with MODY diabetes, and it is the unexpected deterioration in glycaemic control which leads to the diagnosis of autoimmune diabetes. In this study, we report three cases of young-onset diabetes with progressive beta-cell dysfunction over time with coexisting strongly positive GAD antibodies and genetic confirmation of a pathogenic gene variant of HNF1-A, HNF4-A, and ABCC8-MODY.

**Case presentation**

**Case presentation 1**

A 25-year-old woman presented in 1976 with pruritus vulvae and fatigue. She had glucosuria with ketones and random blood glucose of 11.1 mmol/L. Her BMI was 23.8 kg/m². She was started on 12 units of retard insulin as she was planning pregnancy. She had five children (largest 4.6 kg at 37 weeks gestation) and she remained on multiple-dose insulin (MDI) post-partum. Her medical history included Graves’ disease treated with neomercazole. She had no retinopathy or abnormal physical findings on examination. In 2006, her daughter aged 18 years with a BMI of 25.8 kg/m² presented with a 6-month history of polyuria, polydipsia, and weight loss. She was subsequently diagnosed with autoimmune diabetes. In view of the family history, MODY was suspected. Pedigree is shown in Fig. 1. Treatment details for all cases are shown in Table 1.

**Investigations**

Her HbA1c was 7.6% in 1987, 9.7% in 1988, and 9.1% in 1990. Insulin doses were increased to 36 units daily reducing HbA1c to 7.5%. In 2000, her HbA1c was 8.9% and she was controlled on 40 units of insulin daily. Genetic testing was positive for a pathogenic *HNF1A*-MODY (NM_000545.8:c.872dup., gene mutation in exon 4.) for her and her daughter. Her oral glucose tolerance test (OGTT) in 2007 showed a fasting blood glucose of 7.8 mmol/L and 2 h glucose of 23.7 mmol/L. Fasting C-peptide was 297.9 mmol/L. Her BMI had then increased to 33.2 kg/m².

**Treatment**

After confirming HNF1A-MODY, she was trialed on gliclazide MR of 120 mg PO OD and metformin of 500 mg PO OD and became hyperglycaemic with positive blood ketones of 1.5 mmol/L. She was immediately restarted on insulin. GAD antibodies were positive by 72 μ/mL (0–1 μ/mL) and IA-2 antibodies were negative.

**Outcome and follow-up**

Her current HbA1c is 7.3% on 36 units of insulin. She has diabetic retinopathy R1. Her medications include aspirin, lipitor, and eltroxin. Her daughters’ GAD and IA-2 antibodies tested negative, and she is well controlled on gliclazide MR of 60 mg daily with HbA1c of 6.4% 14 years post-diagnosis of diabetes.

**Case presentation 2**

A 17-year-old girl presented in 1960 with polydipsia, polyuria, and weight loss. She was diagnosed with type

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**Figure 1**

Pedigree number 1 (p.Gly292fs) of this family showing inheritance of *HNF1A* mutation. The arrow indicates the proband. Squares represent males and circles represent females. Filled symbols represent people with diabetes. N/T denotes not genetically tested.

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1 diabetes and started on insulin. She had four children (largest 4.1 kg at 38 weeks gestation). Her daughter was subsequently diagnosed in 2009 with gestational diabetes (GDM) age 36, and due to low insulin requirement postpartum and a family history of diabetes, MODY was suspected. In 2019, she was on MDI insulin 32 units daily with a HbA1c of 6.9%. However, she had multiple episodes of hypoglycaemia. Her BMI was 27.4 kg/m². Pedigree is shown in Fig. 2.

**Investigations**

A 75 g OGTT omitting insulin showed fasting blood glucose of 4.9 mmol/L and 2-h blood glucose of 21.5 mmol/L. Fasting C-peptide was 136 mmol/L. Genetic testing identified a novel mutation c.-179T>C in the P2 promotor of the HNF-4A gene in both her and her daughter.

**Treatment**

She was trialed on gliclazide MR of 120 mg PO OD with inadequate glycaemic control and was restarted on MDI insulin 26 units daily. Subsequently, her GAD antibodies were positive >2000 IU/mL (nl < 9) and IA-2 antibodies were negative.

**Outcome and follow-up**

Her most recent HbA1c was 8.6% on 26 units of MDI insulin. She had R3A active proliferative retinopathy in her left eye (2015) and in her right eye (2017), treated with laser photocoagulation. Her daughter’s GAD and IA-2 antibodies tested negative, and she was well controlled on gliclazide of 80 mg PO OD with an HbA1c of 6.7%.

**Case presentation 3**

A 26-year-old male presented with blurred vision and hyperglycaemia. He was initially diagnosed with type 1 diabetes and started on MDI. After 2 years, he stopped his insulin and found he had more energy. He was started on gliclazide of 160 mg PO OD and his HbA1c was 5.4% 16 years after diagnosis. His OHA requirement changed over the years with gliclazide MR 30 mg PO OD, janumet 50/1000 mg PO BD, and pioglitazone 10 mg PO OD and his HbA1c increased to 9.2%. He was commenced on Lantus 12 units daily. He was of average weight. In view of a strong family history of diabetes, MODY was suspected.

**Investigations**

Genetic testing detected a pathogenic-activating mutation p.Arg1138Trp (NM_001287174.3:c.3547C>T, exon 28) in the ABCC8 gene. His HbA1c in 2017 was 87 mmol/mol (10.1%). He had an episode of hyperglycaemia with positive blood
ketones of 2 mmol/L after omitting his overnight insulin accidentally.

**Treatment**
His OHAs were discontinued, and he was started on MDI. Subsequently, his GAD antibodies were >2000 IU (nl < 9) and IA-2 antibodies tested positive.

**Outcome and follow-up**
Four years later, his HbA1c was 7.8% on Tresiba 28 units and short-acting insulin 14 units pre meals. He has no evidence of diabetic retinopathy. His thyroid peroxidase (TPO) antibodies were positive at 251.7 IU/mL; however, he remains euthyroid.

**Discussion**
This case series describes the very rare association between MODY and autoimmune diabetes. A study including the most common forms of MODY diabetes concluded that GAD antibodies were present in only 5/508 individuals (<1%), and none had islet-cell antibodies. Although their study selected only patients who were already diagnosed with MODY diabetes, a sub-analysis showed that 64% of probands with no previous antibody testing prior to the genetic test showed a positive rate of 0.6% (1). A prospective national study done in a paediatric Swedish cohort (2) did not find any subjects with MODY diabetes in the autoantibodies positive group of 3471 individuals, confirming a prevalence of <0.1%. This is the same as the proportion of pancreatic islet autoantibodies found in the healthy background population. In marked contrast, 25% of 28 Czech MODY subjects were positive for GAD or IA-2 antibodies (3). Schober et al. reported a positive autoimmunity prevalence of 17% in a German and Austrian cohort with MODY diabetes, but 20% of patients did not have genetic confirmation of MODY diabetes (4). To date, the absence of pancreatic autoantibodies and the presence of pancreatic residual function seem to be the most helpful criteria in the selection of candidates for genetic testing. Genetic screening is not recommended if autoantibodies are strongly positive suggesting autoimmune diabetes, unless the pedigree is suggestive of MODY and other members are diabetic and autoantibody-negative.

Our first case illustrates a young lean woman diagnosed with type 1 diabetes. Genetic testing was prompted 31 years later after her daughter was diagnosed with diabetes and revealed HNF1A-MODY. However, after initial insulin therapy, her BMI increased to 33.2 kg/m² and her fasting C-peptide was reduced to 297.9 pmol/L. She then failed sulphonylurea therapy and developed ketones. Her GAD antibodies were positive suggesting the coexistence of latent autoimmune diabetes in adults. The presence of a pathogenic HNF1A gene variant and strongly positive GAD antibodies would increase the rate of beta-cell loss and result in a more severe phenotype. Her longstanding diabetes and BMI may also contribute to her need for treatment.

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**Figure 2**
Pedigree number 2 (c.-179T>C) of this family showing inheritance of HNF4-A P2 promotor novel mutation. The arrow indicates the proband. Squares represent males and circles represent females. Filled symbols represent people with diabetes. N/T denotes not genetically tested.

**Table 1**
<table>
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<th>HNF4-A P2 Promotor</th>
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insulin. Most subjects with HNF1A-MODY are successfully maintained on sulphonylurea therapy (5, 6) with 20% requiring the addition of insulin. Her daughter remained well controlled on sulphonylurea after 14 years of diabetes.

The coexistence of autoimmune diabetes and HNF1A-MODY is extremely rare but has been described previously. Three of five subjects from McDonald et al. cohort had HNF1A-MODY and one individual did not require insulin treatment (1). Bowden et al. reported an accidental diagnosis of HNF1A-MODY, type 1 diabetes, and type 2 diabetes in a 17-year-old female with positive GAD and islet cell antibodies (7). Maltoni et al. described a child with negative autoimmunity at HNF1A-MODY diagnosis; however, a few months later with deterioration of glycaemic control, antibody testing was positive (8).

Our second case describes a lean woman presenting with diabetes in the 1940s treated with insulin. Genetic testing was prompted when her daughter was diagnosed with gestational diabetes with low insulin requirements post-partum. Her fasting C-peptide was 136 pmol/L and she had a suboptimal response to gliclazide MR of 120 mg PO OD and required insulin. Her GAD antibodies were >2000. Her daughter was GAD antibody-negative and well controlled on low-dose gliclazide. HNF-4A is a relatively rare type of MODY which usually responds to a low-dose sulphonylurea. The c.-179T>C mutation in the HNF4A P2 promoter is novel and occurs within the HNF1A/HNF1B transcription factor-binding site and is predicted to affect the transcription of the HNF4A gene. It co-segregates with diabetes in this family and is associated with a gradual decrease in endogenous insulin secretion. Shepherd et al. found in a large systematic study a dual diagnosis of HNF4A-MODY and type 1 diabetes with GAD antibodies in one subject (6). Recently, a 12-year-old girl diagnosed with HNF4A-MODY had deterioration of glycaemic control after 3 years and tested positive for IA-2 antibodies (9).

Our third case describes a lean male presenting with diabetes initially and was insulin-treated. He was then managed with OHAs alone for 29 years. Subsequently, he became insulin-dependent with positive autoantibodies. Genetic testing revealed an activating pathogenic mutation p.Arg138Trp (c.3547C>T, exon 28) in the ABCC8 gene. He is currently treated with insulin for coexisting type 1 diabetes. Subjects with activating mutations in the ABCC8 gene develop diabetes which is usually controlled with low-dose sulphonylurea (10). We are not aware of other case reports with coexistence of type 1 diabetes and ABCC8-MODY. However, associations of ABCC8 and KCNJ11 gene variants with type 1 diabetic children have been shown in south Indians.

These cases highlight the coexistence of two forms of diabetes in one individual. The presence of a pathogenic gene variant plus significantly positive GAD antibodies would increase the rate of beta-cell loss and reduce the response to sulphonylurea. All three cases demonstrated a high GAD antibody titre which would be deemed clinically significant. Two of the subjects developed positive blood ketones when their insulin was discontinued suggesting that the positive titre was clinically significant. A single, low GAD antibody titre or a positive islet-cell antibody may not be significant; however, this was not the case in the three subjects described here. The response to sulphonylurea will however depend on the duration of diabetes and BMI (6). Earlier genetic diagnosis and sulphonylurea treatment may have more favourable outcomes. At each clinic visit, one should revise and update the family history as the diagnosis of MODY diabetes was made after the development of diabetes in their offspring or other family members. Unexpected deterioration of glycaemic control in subjects with MODY diabetes should highlight the need to look for the emergence of autoantibodies as the diagnosis of MODY does not exclude the risk of developing type 1 diabetes.

Patient’s perspective
We welcome comments from your patient; their own description of their experience may help other patients or clinicians who are dealing with a similar problem. If your patient would like to contribute, please ensure they include only relevant personal details. Patients may describe their symptoms, how any tests and treatments affected them, and how the problem is now.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been obtained from the three patients prior to publication of the article and accompanying images.

Author contribution statement
Dr Eimear O Donovan and Dr Begona Sanchez-Lechuga performed the literature review and constructed the manuscript. Emma Prehn contributed to the data collection and images. Dr Maria Byrne is the patients diabetologist and she reviewed and edited the manuscript.
References


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