CASE REPORT

Diabetic ketoacidosis in the setting of HNF1A-maturity onset diabetes of the young

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SUMMARY

A female patient was treated for type 1 diabetes following presentation at 12 years of age with hyperglycaemia, polydipsia and weight loss. Eleven years later, while screening relatives attending a genetic diabetes clinic, she was identified as potentially harbouring a mutation in the *hepatocyte nuclear factor 1A* (*HNF1A*) gene. Biochemical testing supported the diagnosis of HNF1A-maturity onset diabetes of the young (MODY) and genetic screening was positive for a heterozygous mutation in the *HNF1A* gene. The patient transitioned from insulin to sulfonylurea therapy. Three years later, in the setting of poor metabolic control, the patient presented to the emergency department with a history of nausea, vomiting and palpitations. A diagnosis of diabetic ketoacidosis (DKA) was confirmed and successfully treated. Although a diagnosis of HNF1A-MODY is rarely considered in a patient with a history of DKA, we demonstrate that DKA is possible in the setting of non-compliance with sulfonylurea therapy.

BACKGROUND

Maturity onset diabetes of the young (MODY) is a heterogeneous group of monogenic causes of β -cell dysfunction¹ and can account for 1–5% of all diabetes cases diagnosed before the age of 45 years.² Hepatocyte nuclear factor 1A MODY (HNF1A-MODY) is the most common form of MODY in adults, accounting for about 50% cases in the UK.¹ Individuals are normoglycaemic in childhood and diabetes typically presents in the second to fourth decade of life.¹ HNF1A-MODY is caused by heterozygous mutations in the *HNF1A* gene and is associated with progressive β -cell failure and increasing hyperglycaemia due to reduced insulin secretion.³

Many patients with subsequently genetically proven MODY are often presumed to have type 1 or type 2 diabetes at initial presentation. However, it is important to correctly classify these patients in order to define prognosis, facilitate family counselling and allow optimal therapeutic management.^{4,5} In an attempt to improve diagnosis rates, recent research efforts have focused on the discovery of non-genetic biomarkers, such as high-sensitivity C reactive protein (CRP) for prioritising individuals for genetic testing.⁶

The treatment for HNF1A-MODY differs from type 1 diabetes mellitus, as patients are sensitive to the hypoglycaemic action of sulfonylureas. Furthermore, as absolute insulin deficiency is not typical for this condition, patients with HNF1A-MODY classically do not develop diabetic ketoacidosis (DKA). Indeed, there exists just one

previous report in the literature describing two cases of DKA in the setting of HNF1A-MODY.⁷ We describe one further case with the rare co-occurrence of DKA and HNF1A-MODY. Along with the two prior cases, it serves to challenge current attitudes on selecting patients for screening for MODY and has implications for future guidelines on screening, along with patient and clinician education.

CASE PRESENTATION

We present the case of a 25-year-old female patient who was treated as type 1 diabetes mellitus at the age of 12 years on the basis of a random glucose level of 16 mmol/L, and symptoms of polydipsia and weight loss. At the time of presentation, she did not have ketonuria, and antglutamic acid decarboxylase (anti-GAD) and pancreatic islet cell antibodies were not tested.

Following diagnosis, the patient had extremely poor glycaemic control secondary to non-compliance with insulin and her glycated haemoglobin (HbA1c) ranged between 80 (9.5%) and 120 mmol/mol (13.1%). On two occasions, she presented to the emergency department and was diagnosed with DKA requiring a 48 h hospital admission on each occasion. On the first occasion, the patient was 20 years of age and prescribed a total daily dose of insulin of 18 units at the time of presentation. This was in the form of a multiple daily injection regimen of insulin glargine 8 units at night and insulin aspart three times a day—2 units with breakfast, 3 units with lunch and 5 units with the evening meal. Her HbA1c was 120 mmol/mol (13.1%) at this time. On the second occasion, the patient was 22 years of age and her HbA1c remained very elevated at 118 mmol/mol (12.9%). Her total daily dose of insulin had been titrated to 40 units and comprised of insulin glargine 20 units at night, and insulin aspart 4 units with breakfast and 8 units with lunch and the evening meal. Insulin omission was identified as the precipitating factor on each occasion in the setting of severe gastroenteritis-type symptoms. The patient's poor glycaemic control persisted despite extensive multidisciplinary team input, including medical, diabetes nurse specialist, dietician and psychologist reviews. The patient did not attend multiple scheduled visits for retinal screening but at 21 years of age retinal examination revealed bilateral changes consistent with non-proliferative diabetic retinopathy. Urine testing revealed evidence of microalbuminuria with the albumin/creatinine ratio measuring 58 and 39.5 mg/mol on two occasions when the patient

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was 22 years old (normal range ≤ 3.5 mg/mol). Therapy with an ACE inhibitor was recommended at multiple clinical encounters but the patient declined this therapy. Blood pressure was consistently below the target of 130/80 mm Hg.

Eleven years postdiagnosis, the patient's paternal aunt and two children were reviewed in the genetic diabetes clinic and were found to have HNF1A-MODY. On review of the family tree, our patient was identified as potentially harbouring a mutation in the *HNF1A* gene. Further testing supported the potential diagnosis of HNF1A-MODY in our patient with:

1. A low renal threshold for glucose with glycosuria in the setting of a serum glucose of 5.1 mmol/L
2. Detectable C peptide of 500 pmol/L with a serum glucose of 10 mmol/L
3. Negative anti-GAD and pancreatic islet cell antibodies

The patient underwent genetic testing and this was positive for the same heterozygous mutation in the *HNF1A* gene (*Exon 2; c.391C>T, p.Arg131Trp*) (Exeter, UK) as that of her relatives with HNF1A-MODY. Subsequently, additional family members were diagnosed with HNF1A-MODY and the pedigree is demonstrated in figure 1.

Under close supervision which involved daily attendance at the diabetes clinic for the first week, the patient underwent a trial of discontinuation of insulin therapy. She was started on gliclazide 80 mg twice daily and had a good clinical response with all glucose readings measuring <7.0 mmol/L. For the next 6 months, the patient continued to maintain regular telephone and email contact with the diabetes service and reported good glycaemic control. Unfortunately, she did not attend for repeat blood testing to assess HbA1c or other metabolic parameters. After this time, her adherence to the treatment regimen deteriorated once again and she did not maintain follow-up with the endocrinology service.

Three years after the start of sulfonylurea therapy, the patient presented to the emergency department reporting a 3-day history of nausea, vomiting and palpitations. She reported total non-compliance with the gliclazide therapy in the preceding weeks. Positive findings on clinical examination included tachycardia (heart rate 120 bpm) and dry mucous membranes.

INVESTIGATIONS

Capillary blood glucose on presentation was 23 mmol/L and capillary blood ketones measured 4.5 mmol/L. A venous blood gas revealed metabolic acidosis (pH 7.19; $p\text{CO}_2$ 4.28; $p\text{O}_2$ 3.44; bicarbonate 12.0, anion gap 22.6, lactate 0.5). Serum sodium was 142, potassium 4.7, glucose 20, urea 12 and

creatinine 90 mmol/L. CRP was <5 mg/L, white cell count $11.2 \times 10^9/\text{L}$, haemoglobin 13.8 g/dL and platelets $431 \times 10^9/\text{L}$. Toxicology screen including alcohol, paracetamol and salicylate levels were negative. HbA1c was 115 mmol/mol (12.7%). Chest X-ray was normal and urine dipstick was 4+ for ketones.

DIFFERENTIAL DIAGNOSIS

The diagnosis in this case is DKA. The differential diagnosis includes other causes of a high anion gap metabolic acidosis including lactic acidosis, renal failure and toxins such as alcohol and salicylates. These diagnoses are all unlikely based on the history, examination and biochemical findings.

TREATMENT

The patient responded well to treatment with intravenous insulin and potassium-containing fluids. Prior to discharge from hospital, she received re-education regarding her diagnosis and the potential to develop further episodes of DKA. Repeat C peptide levels along with anti-GAD and pancreatic islet cell antibodies tests were completed and once daily long-acting insulin therapy was added to her diabetes regimen until these results became available.

OUTCOME AND FOLLOW-UP

Outpatient review was arranged at the time of discharge. Review of results revealed persistently negative anti-GAD and pancreatic islet cell antibodies. Bloods taken while gliclazide was temporarily discontinued demonstrate that the patient continues to have a detectable C peptide level of 718 pmol/L with a serum glucose of 14 mmol/L. From a safety perspective, the patient has continued on once daily long-acting insulin therapy in addition to sulfonylurea therapy. She now has regular contact with the multidisciplinary team with the aim of improving compliance with therapy.

DISCUSSION

This case describes the unusual association of DKA and HNF1A-MODY. The patient in question was initially treated as type 1 diabetes and there was a delay of 11 years before the correct diagnosis was made. This was despite the fact that she manifested a number of clinical characteristics of patients with HNF1A mutations. These characteristics include:

1. Young-onset diabetes that shows characteristics of not being insulin-dependent, for example, detectable C peptide when glucose >8 mmol/L outside a normally expected honeymoon period (3 years)⁸
2. Family history of diabetes with a parent affected^{6 8}
3. A very large glucose increment (>5 mmol/L) at oral glucose tolerance test⁸
4. Glycosuria at relatively normal blood glucose levels due to a low renal threshold^{6 8}
5. Marked sensitivity to sulfonylureas^{1 8}

Following clinical evaluation, genetic testing confirmed the diagnosis. The mutation in this case was previously described in a North American family with HNF1A-MODY in 1997.⁹

It is important to identify patients with HNF1A-MODY as successful transition from insulin to oral therapy has been demonstrated in patients even after prolonged use of insulin.^{10 11} Under close supervision, insulin was discontinued in this case and sulfonylurea therapy established. It was hoped that this therapeutic intervention would lead to improved glycaemic control given the previous poor compliance with insulin. However, despite an initial response, poor metabolic control persisted. Support from the multidisciplinary team including a

Figure 1 Family pedigree: males and females with diabetes mellitus (■ and ●) and unaffected males and females (□ and ○). Heterozygous hepatocyte nuclear factor 1A (HNF1A) mutation carriers are denoted + and non-carriers – under each individual when known. Our patient is indicated by the black arrow.

clinical psychologist did not result in any improvements. Qualitative research has revealed that transferring from insulin to sulfonylurea therapy tends to have a positive impact on well-being in patients with HNF1A-MODY but support is needed for patients to adjust, with many having grown up with the belief that they would require lifelong insulin therapy.¹² Further research is needed in the area of adherence to treatment in HNF1A-MODY and exploring ways to address non-compliance as highlighted in this case.

The development of DKA in a patient with HNF1A-MODY is rare and just two previous cases are described.⁷ DKA occurs in the setting of insulin deficiency and increased counter-regulatory hormones resulting in the release of free fatty acids into the circulation from adipose tissue and unrestrained hepatic fatty acid oxidation to ketone bodies. Ketonaemia and metabolic acidosis ensues. DKA was previously synonymous with autoimmune type 1 diabetes and was considered a rare occurrence in other forms of diabetes. However, it has been described in patients with type 2 diabetes, especially during times of catabolic stress such as trauma, surgery or infections.¹³ While DKA is unlikely to be a presenting feature of the condition, the potential exists for DKA to develop in HNF1A-MODY as progressive β -cell failure occurs with worsening of hyperglycaemia over time. In this case, we believe that DKA developed in the setting of long duration of diabetes and was triggered by poor compliance and dehydration. Both of the previously described patients also had poor metabolic control and severe DKA followed a course of recurrent vomiting and dehydration.⁷ We do not believe that the patient has an additional diagnosis of type 1 diabetes mellitus due to her negative antibody status, good response to gliclazide while under supervision and a persistently detectable C peptide (consistent with endogenous insulin production).

Although a diagnosis of HNF1A-MODY is rarely considered in a patient with a prior history of DKA,⁸ this case highlights this potential for patients with HNF1A-MODY to develop DKA—in this scenario in the presence of long duration of diabetes, poor compliance and dehydration. It is important that

healthcare providers and patients are aware of this potential to allow for prompt diagnosis and treatment of a potentially life-threatening condition. As improved access to genetic testing allows for increasing numbers of patients to be diagnosed with monogenic diabetes, it is likely that clinical guidelines will expand to incorporate the varying manifestations of this condition.

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Contributors AME drafted the manuscript initially, coordinated the draft reviews and completed the submission process. AC and BJ-M reviewed and modified the draft manuscripts significantly. FPD supervised the project, was involved in the initial draft, and reviewed and modified the final draft.

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Learning points

- Although an uncommon occurrence, diabetic ketoacidosis (DKA) may occur in the setting of hepatocyte nuclear factor 1A-maturity onset diabetes of the young (HNF1A-MODY).
- The risk of DKA increases with longer duration of HNF1A-MODY as progressive β -cell failure occurs with time.
- Failure to comply with treatment and intercurrent illness are associated with DKA in patients with HNF1A-MODY.

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