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Case Series

A case series of maturity onset diabetes of the young: Searching for a polar bear in a snowstorm

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ABSTRACT

Monogenic diabetes occurs due to a defect in a single gene or a chromosomal locus. The various modes of inheritance occurring include autosomal recessive, autosomal dominant, and non-Mendelian traits or can occur as a spontaneous case secondary to a *de novo* mutation. Although uncommon, monogenic diabetes accounts for 2.5–6% of diabetes in the paediatric age group and usually presents under 25 years of age. Monogenic diabetes can be classified into four major groups: (1) Maturity onset diabetes of the young (MODY), (2) neonatal and early infancy diabetes, (3) monogenic insulin resistance syndromes, and (4) diabetes affiliated with extra-pancreatic features. MODY is the most prevailing form of monogenic diabetes with an autosomal dominant inheritance. There are 14 subtypes of MODY that have been recognised now, and mutations in the genes *hepatic nuclear factor 1-alpha* (*HNF1α*) (MODY-3), glucokinase (MODY-2) *HNF4α* (MODY-1) account for about 95% of all MODY cases. According to a study in the UK, 80% of the MODY cases are misdiagnosed as either Type 1 or Type 2 diabetes mellitus. In our case series, we report 4 cases of MODY and compare their various characteristics. A genetic test was performed for children and adolescents with diabetes mellitus who had a strong history of diabetes in the family and tested negative for islet cell antibodies. Although there have been cases of MODY that have been previously reported worldwide, they usually fall under the types – MODY-3, MODY-2, and MODY-1, whereas we identified one adolescent with Kruppel-like factor-11 gene mutation giving rise to MODY-7 and two adolescents with paired box gene-*4* gene mutation causing MODY-9, both of which contribute to <1% of the cases of MODY reported worldwide.

Keywords: Maturity onset diabetes of the young, Kruppel-like factor-11, Paired box gene-4

INTRODUCTION

Monogenic diabetes occurs due to a defect in a single gene or a chromosomal locus. The various modes of inheritance occurring include autosomal recessive, autosomal dominant, non-Mendelian traits or can occur as a spontaneous case secondary to a *de novo* mutation. The most commonly recognised forms of diabetes mellitus include the polygenic forms of diabetes, such as type 1 or type 2 diabetes. Although uncommon, monogenic diabetes accounts for 2.5–6% of diabetes in the paediatric age group[1] and usually presents under 25 years of age. Monogenic diabetes can be classified into four major groups: (1) Maturity onset diabetes of the young (MODY), (2) neonatal and early infancy diabetes, (3) monogenic insulin resistance syndromes, and (4) diabetes affiliated with extra-pancreatic features.[1] MODY is the most prevailing form of monogenic diabetes with an autosomal dominant inheritance. There are 14 subtypes of MODY that have been recognised now, and mutations in the genes hepatic nuclear

factor 1-alpha (*HNF1α*) (MODY-3), glucokinase (MODY-2) *HNF4α* (MODY-1) account for about 95% of all MODY cases [Table 1].[2] Through this case series, we aim to report rarer forms of MODY and present a comparison of their various characteristics in terms of their presentation and management.

CASE SERIES

Case 1

A 1.6-year-old female child with a history of polyuria, polydipsia for 2 weeks, and lethargy for 1 day presented to the paediatric emergency and was admitted with moderate diabetic ketoacidosis. She was initially diagnosed with type 1 diabetes mellitus (T1DM), started on continuous infusion with insulin, and then shifted to a basal-bolus regimen. As all islet cell antibodies were negative and did not have optimum glycaemic control, a genetic test was done, and she was diagnosed with MODY-1 due to *HNF4α* gene mutation.

Case 2

A 10.9-year-old female adolescent presented to our paediatric endocrinology outpatient department (OPD) with a history of polydipsia and polyphagia for 2 months. She was overweight, and on evaluation, glycated haemoglobin (HbA1C) was 7.9% with negative islet cell antibodies. As she had a strong family history of diabetes, genetic analysis revealed MODY-7 resulting from a Kruppel-like factor-11 (*KLF-11*) gene mutation.

Case 3

A 14.6-year-old male adolescent presented to our paediatric endocrinology OPD with a history of polyuria, polydipsia, and weight loss of 16 kg in 2 months. He was morbidly obese, had an HbA1C of 16.2%, and was initially being treated for type 2 diabetes mellitus (T2DM) with insulin and lifestyle modifications. Islet cell antibodies were negative, and genetic analysis found a paired box gene-4 (*PAX-4)* gene mutation leading to MODY-9.

Case 4

A 17.2-year-old female adolescent had a history of polyphagia and easy fatiguability. With an initial HbA1C of 11.8%, she was initially diagnosed to have T2DM by an adult endocrinologist. Despite being on metformin for a year, she continued to have poor glycaemic control and presented to our OPD. Genetic analysis was sent and she tested positive for MODY-9 attributable to *PAX-4* gene mutation. She was switched to insulin, and her glycaemic control improved.

Table 1: Comparison of various parameters among the four cases of MODY.

Parameter	Case 1	Case 2	Case 3	Case 4
Age at diagnosis	1.6 years	10.9 years	14.6 years	17.2 years
Gender	Female	Female	Male	Female
Clinical presentation	Polyuria, polydipsia for 2 weeks, Lethargy for 1 day	Polydipsia, polyphagia for 2 months	Polyuria, polydipsia, weight loss (16 kg) in 2 months	Polyphagia, Easy fatiguability for 4 months
DKA at presentation	Moderate DKA	No	No	No
Associated conditions	Congenital hypothyroidism	Overweight	Morbid obesity	Nil
Family history of diabetes mellitus	Nil	Father and paternal grandparents: T2DM around 35 years age	Both parents: T2DM around 40 years age	Father: DM since 20 years age-genetic test not done Mother: T2DM at 40 years of age
BMI	Not applicable	21.3 kg/m^2	37.17 kg/m^2	19.44 kg/m^2
HbA1C at diagnosis	7.6%	7.9%	16.2%	11.8%
Initial diagnosis	T1DM	T2DM	T2DM	T2DM
Initial treatment	Insulin: Basal bolus regimen	Lifestyle modifications	Insulin: Basal bolus regimen lifestyle modifications	Metformin lifestyle modifications
Islet autoantibodies	Negative	Negative	Negative	Negative
Gene mutation	*HNF4α*	*KLF-11*	*PAX-4*	*PAX-4*
MODY type	MODY-1	MODY-7	MODY-9	MODY-9
Current treatment	Glimepiride+Insulin	Metformin lifestyle modifications	Insulin: Basal bolus regimen lifestyle modifications	Insulin

DKA: Diabetic ketoacidosis, BMI: Body mass index, HbA1C: Glycated haemoglobin, T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus, DM: Diabetes mellitus, MODY: Maturity onset diabetes of the young, *KLF-11*: Kruppel-like factor-11, HNF4α: Hepatic nuclear factor 4-alpha, *PAX-4*: Paired box gene-*4*

DISCUSSION

The acronym 'MODY' was coined by Fajans and Tattersall in 1974, who defined it as 'fasting hyperglycaemia.'[3] MODY occurs due to impaired insulin secretion due to a defect in the development of pancreatic islet cells. The genes implicated in MODY hamper insulin secretion by impairment of insulin sensing, glucose metabolism in beta-cells of the pancreas, or activation of adenosine tri-phosphate-dependent potassium channels.[4] According to a study in the UK, 80% of MODY cases are misdiagnosed as one of the polygenic forms of diabetes, either T1DM or T2DM, as they have overlapping genotypic features of both. Vaxillaire and Froguel determined the major diagnostic criteria for MODY to be hyperglycaemia before 25 years of age, autosomal dominant inheritance exhibiting transmission in at least three generations, negative beta-cell autoantibodies, and functional impairment in the pancreatic beta-cells.[5,6] In our case series, we report four cases of MODY and compare their various characteristics. A genetic test was performed for children and adolescents with diabetes mellitus who had a strong history of diabetes in the family and tested negative for islet cell antibodies. Genetic counselling was done in view of the autosomal dominant fashion of inheritance.[6] Management differs among the various types of MODY, where some respond to lifestyle modifications, and some require insulin or oral antidiabetic drugs or a combination of both.[7]

CONCLUSION

Although there have been cases of MODY that have been previously reported worldwide, they usually fall under the types – MODY-3 (30–50% cases), MODY-2 (15–25% cases), and MODY-1 (5%), whereas all the other types of MODY contribute to <1% of the cases individually. In our case series, we identified one adolescent with *KLF-11* gene mutation giving rise to MODY-7 and two adolescents with *PAX-4* gene mutation causing MODY-9, both of which contribute to <1% of the cases of MODY reported worldwide. As MODY shares features of the more commonly encountered forms of diabetes, such as T1DM and T2DM, we often miss identifying MODY. Hence, the phrase 'searching for a polar bear in a snowstorm' aptly applies to identifying MODY cases among the numerous cases of type 1 and type 2 diabetes.

Authors' contributions

Both authors have contributed to compiling the data.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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