Asymptomatic fasting hyperglycaemia, a case of Glucokinase maturity onset diabetes of the young with a novel mutation

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SUMMARY

Maturity onset diabetes of the young (MODY) is not commonly encountered in clinical practice. It is rare and can be difficult to differentiate from type 1 and type 2 diabetes. To confirm the diagnosis, genetic testing must be done which is not readily available and is expensive. This patient presented with asymptomatic fasting hyperglycaemia and was previously diagnosed to have type 2 diabetes. Further investigations showed that she had normal β−cell function and normal insulin resistance. Diabetic autoantibodies were all negative. Confirmatory genetic testing was done and she was found to have a genetic variant at the glucokinase gene at Exon 7, c.830T>G (p.Val277Gly). Screening of the patient's father also revealed the same genetic variant, showing an autosomal dominant pattern of inheritance. This clinical case illustrates a patient that was misdiagnosed to have type 2 diabetes and confirmed with genetic testing to have glucokinase MODY. This changes the clinical management of the patient as no further treatment and investigation is required as there are no lifelong consequences of developing complications of diabetes.

INTRODUCTION

Maturity onset diabetes of the young (MODY) is a rather rare form of diabetes which is a separate entity from type 1 and type 2 diabetes. It is inherited in an autosomal dominant fashion and typically presents before the age of 25.[1] Genetic mutations result in diabetes due to their effects on β–cell dysfunction.[2]

To date there have been at least 13 genes identified that cause MODY and additional genes exist that are yet to be identified.[3] Mutations in the glucokinase (GCK), hepatocyte nuclear factor 1 alpha (HNF1A), hepatocyte nuclear factor 4 alpha (HNF4A) and hepatocyte nuclear factor 1 beta (HNF1B) genes are the most common causes of MODY, and they account for 32%, 52%, 10%, and 6%, respectively, of cases in the United Kingdom (UK).[3] The prevalence of these causes varies in different countries. In countries where glucose testing is done more frequently to screen for diabetes, GCK mutations predominates in these countries, such as France, Germany, Italy and Spain.[2]

Patients with GCK MODY mutation also known as MODY 2, usually present with asymptomatic fasting hyperglycaemia, which is present from birth and remains stable throughout life. One of the challenges in diagnosing MODY is distinguishing it from type 1 and type 2 diabetes as clinical features are similar and features may overlap.[2] Presentation of patients with GCK MODY are usually incidental as the mild hyperglycaemia does not lead to any overt symptoms and findings of a raised fasting glucose are usually incidental during a health check-up.[5]

This clinical case illustrates a young patient who was misdiagnosed as type 2 diabetes mellitus and was confirmed to have GCK MODY.

CASE REPORT

A 31-years-old lady was referred to the general medical clinic for further management of young type 2 diabetes. She was previously diagnosed to have type 2 diabetes and started on Metformin 500 mg twice daily by a private health clinic. Further questioning revealed that she had known to have abnormal fasting glucose since the age of 20 when she went for a general health screening. Over the past 10 years, she has monitored her fasting glucose and reported it to range from 6.8 to 7.1 mmol/L. However, as she felt well with no symptoms she did not think to investigate further. She has a strong family history of diabetes, with both her parents diagnosed to have type 2 diabetes on treatment. All her maternal relatives were also diagnosed to have type 2 diabetes. Her paternal family history was not known as her father was adopted.

Physical examination showed that she was a slim lady with a BMI of 17. Her waist circumference measured was 64 cm. Other systemic examinations were unremarkable.

Blood investigations were ordered as summarised in Table I. Elevated fasting glucose at 7.4 mmol/L with a HbA1c reading of 6.4% were diagnostic of type 2 diabetes. Diabetic autoantibodies were not detected. As she did not fit the clinical phenotype of a patient with type 2 diabetes, further testing was done.

A glucagon stimulation test (GST) was done to assess the pancreatic β–cell function. Glucagon 1 mg was given, and glucose, C-peptide and insulin levels were taken at 0 min and 6 min after administration. The results of the C-peptide and insulin are as summarised in Table II. The GST showed that she had normal β–cell function.

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Table I: Summary of investigations

Investigations	Results
Fasting glucose	7.4 mmol/L
HbA1c	6.4%
Anti-islet cells	0.34 IU/ml (Negative)
Anti-glutamic acid decarboxylase (GAD)	0.99 IU/ml (Negative)
Anti-insulinoma-associated antigen 2(IA2)	0.94 IU/ml (Negative)

Table II: Glucagon stimulation test results

	0 min	6 min
Glucose	7.0 mmol/L	8.4
C-peptide	331 pmol/L	1252 pmol/L
Insulin	22.4 pmol/L	

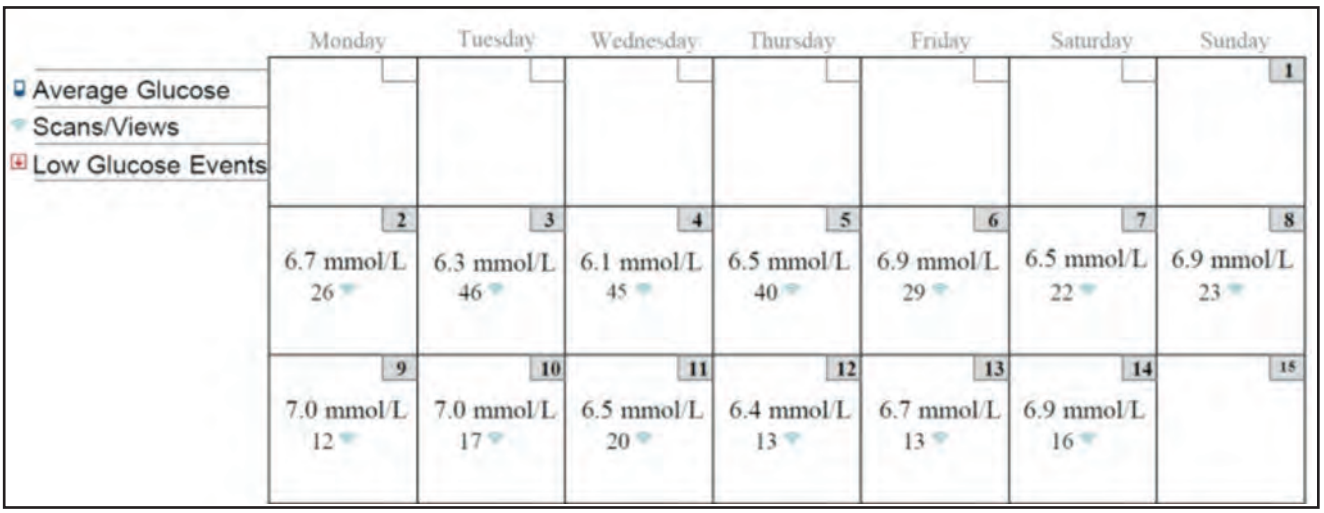

Fig. 1: Average blood glucose over 2 weeks duration

Assessment for insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR). By using the values of her fasting insulin and glucose, her calculated index was 0.9 which shows normal insulin resistance.

Medications were withheld and she was offered continuous glucose monitoring for 2 weeks to monitor her glucose trend (Figure 1). Average glucose trends ranged from 6.1 to 7.0 mmol/L.

She was informed on genetic testing for MODY as her clinical presentation did not fit type 1 or type 2 diabetes. Genetic testing would be done at a private lab in the United States and would have to be self-funded by the patient. She agreed for genetic testing to assess for MODY.

Results from the genetic testing showed that the patient was found to have a heterozygous mutation of the GCK gene at Exon 7, c.830T>G (p.Val277Gly). Further genetic screening of both her parents revealed that her father carried the same genetic variant. This genetic variant has not been reported in literature in individuals affected with GCK MODY and is not present in population databases such as the gnomAD database.

She was then confirmed to have GCK MODY and thus did not require any treatment. She continued to be asymptomatic and was told to inform if she planned to get pregnant, as she may require treatment during pregnancy.

DISCUSSION

GCK was the first gene to be identified to cause MODY in French and UK populations in 1992.[6] GCK MODY is characterised by persistent mild asymptomatic fasting hyperglycaemia, absence of autoimmune antibodies for type 1 diabetes, good β–cell function and an autosomal dominant mode of inheritance.[6] Among cases in the UK, GCK MODY was the second most common form of MODY.[3] In Japan, a study showed that among paediatric onset MODY, GCK mutation was the most common form of MODY detected.8 To date, there are no studies in Malaysia that analysed the prevalence of MODY in our population.

Clinical suspicion of MODY is usually characterised by non-obesity, onset before 25 years of age and positive family history suggestive of dominant inheritance.[7] This patient was underweight, known to have mild hyperglycaemia since the age of 20 and had a strong family history of diabetes, therefore genetic testing was considered in her case. Genetic testing confirmed that she inherited the GCK variant from

her father, however further details on her paternal family were unknown as her father was adopted. Although the gene is inherited from an affected parent, there may be no positive family history of diabetes if no prior screening of the parents were done to diagnose diabetes.[5] Therefore, when suspecting MODY as a diagnosis for a patient, screening of the parents with fasting glucose or HbA1c readings would be helpful.

Patients who are diagnosed to have diabetes at a young age, strong family history of diabetes, have negative diabetic autoantibodies and do not fit a diagnosis of type 1 or type 2 diabetes should be considered for genetic testing for MODY. In China, a study in a single centre was conducted which showed that from 587 children with newly diagnosed diabetes mellitus, only 11 children fit the clinical criteria for a diagnosis of MODY and genetic testing showed GCK mutations in 9 out of the 11 children tested.[4] However, in Malaysia, genetic testing is not readily available and is expensive. Furthermore, type 2 diabetes is very common in Asian populations causing difficulty in differentiating it from MODY. Therefore, genetic testing should be considered on a case-to-case basis.

Patients with GCK MODY generally do not require treatment and the mild hyperglycaemic does not lead to long term microvascular complications.[3] The only exception is during pregnancy where treatment with insulin may be required. If the foetus does not inherit the GCK mutation, it will produce more insulin in response to the maternal hyperglycaemia which will cause excess foetal growth.[2] Patients with GCK MODY are at the same risk as the general population in developing type 1 or type 2 diabetes and if this occurs, achieving glycaemic levels below their normal hyperglycaemic levels is very difficult.[5]

Although GCK MODY is rare, the diagnosis would have important implications towards treatment modalities, prognosis and follow up of those affected by it.[3] Many clinicians in the primary health care are unfamiliar with this condition and may diagnose a patient as either type 1 or type 2 diabetes if they presented to their clinics. Making a diagnosis of GCK MODY is essential to avoid unnecessary treatment and investigations.[5]

Confirmatory testing to diagnose MODY is through genetic testing. If an individual is diagnosed to have GCK MODY, family screening is recommended in those who are diagnosed to have diabetes.[5] Family members who were previously thought to have type 1 or type 2 diabetes may be able to stop treatment if the GCK mutation is detected.

The patient was able to afford genetic testing and was found to have a mutation at the GCK gene at Exon 7, c.830T>G (p.Val277Gly). More than 600 abnormal GCK gene mutations have been documented.[4] This variant was not previously reported in literature in patients affected with GCK MODY. However, in this case, it is likely a pathogenic variant as the patient exhibits typical features of GCK MODY. Further testing of her siblings should be done to determine if they carry the same genetic variant.

CONCLUSION

In a young patient aged less than 25 who presents with hyperglycaemia, is not obese, and has a positive family history of diabetes, a clinical suspicion of Maturity onset diabetes of the young (MODY) should be considered. A detailed history especially family history should be obtained, and further investigations should be considered, such as genetic testing. The diagnosis of MODY is very important to the patient and their family as it changes their clinical course and long-term prognosis.

CONFLICT OF INTEREST

None

DECLARATION

Informed consent was taken from the patient for publication of this case report. There are no competing interests.

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