Co-existence of monogenic diabetes and autoimmune diabetes: A case study

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Article points

1. Co-existence of maturity onset diabetes of the young (MODY) due to a glucokinase gene (GCK) mutation and type 1 diabetes is rarely diagnosed.
2. This case study discusses a child with a dual diagnosis of type 1 diabetes and GCK-MODY.
3. It is important to recognise the co-existence of these conditions, as symptoms of hypoglycaemia at blood glucose levels usually considered "within target" poses management challenges.

Key words

- GCK-MODY
- Glucokinase gene mutation
- Maturity onset diabetes of the young
- Monogenic diabetes
- Type 1 diabetes

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Co-existence of maturity onset diabetes of the young (MODY), due to a glucokinase gene (GCK) mutation and type 1 diabetes is rarely diagnosed. The threshold for activation of counter regulatory hormones in people with GCK mutation is higher. Fluctuations in blood glucose (BG) levels and significant hypoglycaemia on attempts at normalising BG levels complicate management in people with a dual diagnosis. This article highlights the challenges faced in the management of a dual diagnosis. Resetting the threshold for hypoglycaemia and target BG, combined with insulin pump therapy, enabled us to significantly reduce hypoglycaemia and improve quality of life. It is important to recognise the co-existence of type 1 diabetes and GCK-MODY, as symptoms of hypoglycaemia at BG levels usually considered "within target" poses management challenges.

Maturity onset diabetes of the young (MODY) is a form of monogenic diabetes that is inherited in an autosomal dominant fashion. Mutations within the glucokinase (GCK) gene account for around 20% of UK MODY and are characterised by mild, stable hyperglycaemia. Type 1 diabetes, in contrast, is an autoimmune condition caused by auto-antibodies against pancreatic islet cells, leading to beta-cell destruction. A combination of the two conditions is very rarely diagnosed despite the population prevalence of 1.1 in 1000 for GCK-MODY (Chaker et al, 2014).

In this article, we share the challenges faced in the management of a child with a dual diagnosis of type 1 diabetes and GCK-MODY. We discuss the details of diagnosis and management of GCK-MODY; counter regulatory hormone mechanisms in GCK-MODY; and people with dual diagnosis. We also highlight some key considerations in the management of children with a dual diagnosis.

Case description

A 14-month-old Caucasian boy presented with polyuria and polydipsia at his local hospital. His blood glucose (BG) was 23 mmol/L, he was ketotic and his HbA_{1c} was 119 mmol/mol (13%). He was suspected to have type 1 diabetes and was commenced on insulin therapy. Islet cell and glutamic acid decarboxylase (GAD) antibodies were positive. Three months later, his older sibling presented with similar symptoms, aged 3 years, and type 1 diabetes was suspected. His hyperglycaemia (BG was 8.6 mmol/L) and ketonuria resolved promptly with insulin therapy. Islet cell and GAD antibodies were negative. His HbA_{1c} was 49 mmol/mol (6.6%). Negative antibodies and minimal insulin requirements prompted consideration of monogenic diabetes. On oral glucose tolerance test, fasting BG was 6.5 mmol/L and 2-hour post glucose load BG was 6.6 mmol/L. His insulin was stopped.

Concomitantly, his younger sibling aged 2 months was also found to have fasting hyperglycaemia (8 mmol/L) during investigation for failure to thrive. Further family history revealed an accidental discovery of raised BG level in the paternal grandfather at 41 years of age. He was thought to have type 2 diabetes and was diet controlled. This

prompted a BG check on the father, who had fasting hyperglycaemia (8.6 mmol/L).

Hyperglycaemia in three generations of the family prompted genetic investigation for monogenic diabetes. All family members with hyperglycaemia tested positive for a heterozygous deletion on exons 5 and 6 of the GCK gene on chromosome 7, confirming the co-existence of type 1 diabetes and GCK-MODY in the index case (*Figure 1*).

Management and progress

The index case was initially managed with multiple daily injections at his local hospital. This proved to be very challenging, however, as attempts to normalise BG levels resulted in recurrent episodes of disabling hypoglycaemia, with episodes of fitting. He was referred to our centre for tertiary care and consideration of continuous subcutaneous insulin infusion (CSII), with a view to improving glycaemic control and reducing the frequency of hypoglycaemic episodes.

Following referral to our centre, he was commenced on CSII. We undertook diagnostic continuous glucose monitoring (CGM) on both the father and our patient to determine BG targets. The father's lowest BG was 5.5 mmol/L. As our patient was under 5 years of age at the time, we set the lower limit of his blood glucose at 6.5 mmol/L, which was 1 mmol/L higher than the father's lower limit. Any BG <6.5 mmol/L was treated as hypoglycaemia. The family received intensive education and CSII was optimised by adjusting hourly basal rates based on BG readings and use of dual wave (square wave) bolus to prevent late post-prandial BG rise. The frequency of hypoglycaemia and hypoglycaemic seizures reduced significantly following this and his parents reported improved quality of life. He showed a gradual improvement in HbA_{1c} during the 4-year follow up period (*Figure 2*, overleaf). His total daily insulin requirement remained stable at 0.75–0.85 units per kg per day. Despite good adherence to treatment, it was not possible to achieve the usual type 1 diabetes target HbA_{1c} of <58 mmol/mol (<7.5%) as a consequence of coexisting GCK-MODY.

"Hyperglycaemia in three generations of the family prompted genetic investigation for monogenic diabetes."

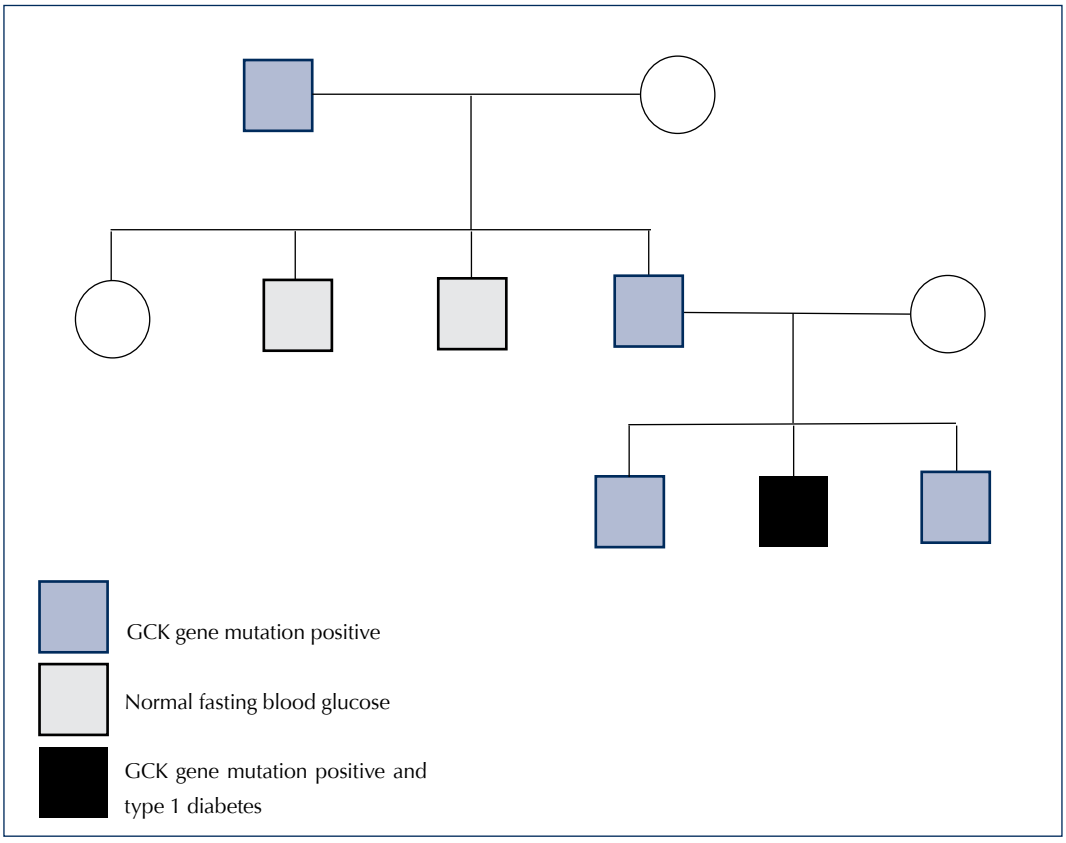

Figure 1. Family tree demonstrates members with positive glucokinase gene mutation in three generations and our patient with GCK-MODY and type 1 diabetes.

Page points

1. We expected the HbA_{1c} in our patient to be consistently high due to the dual diagnosis; however, the overall trend in HbA_{1c} gradually improved.
2. His threshold for treatment of hypoglycaemia has now been reset to 5.5 mmol/L as he has grown older and hypoglycaemia episodes are now extremely rare.
3. Use of CGM in conjunction with a low-glucose suspend feature-enabled insulin pump has been encouraged, especially overnight.

The patient's father and sibling had HbA_{1c} values of 48–54 mmol/mol (6.5–7.1%), which is consistent with the HbA_{1c} reported in people with GCK mutations. We expected the HbA_{1c} in our patient to be consistently high due to the dual diagnosis; however, the overall trend in HbA_{1c} gradually improved.

His threshold for treatment of hypoglycaemia has now been reset to 5.5 mmol/L, as he has grown older and hypoglycaemia episodes are now extremely rare. Use of CGM in conjunction with a low-glucose suspend feature-enabled insulin pump has been encouraged, especially overnight.

Discussion

GCK-MODY

Genetics

Glucokinase is a key regulatory enzyme in the pancreatic beta-cell. It plays a crucial role in the regulation of insulin secretion. Mutation in the genes encoding GCK can cause both hypoglycaemia and hyperglycaemia (Osbak et al, 2009). Homozygous inactivating mutation in GCK causes a more severe form and presents as permanent neonatal diabetes (Osbak et al, 2009), whereas a heterozygous inactivating mutation causes GCK-MODY, characterised by mild, stable fasting hyperglycaemia.

Prevalence

The prevalence of GCK-MODY in the general population is said to be 1.1 in a 1000 (Chaker et al, 2014). The first survey on the prevalence of type 2 diabetes and MODY in UK children reported a crude minimum prevalence of all forms of MODY of 0.17/100 000 (Ehtisham et al, 2004) and 50% of these were due to GCK mutation. All cases of MODY were confirmed to be antibody negative in this survey.

Diagnosis

People with GCK-MODY usually have a mild fasting hyperglycaemia present from birth and only mild glycaemic deterioration with ageing (McDonald and Ellard, 2013). Although present from birth, hyperglycaemia is only incidentally discovered in adulthood (Osbak et al, 2009). Post-prandial glucose excursions in these individuals are modest, with a 75 g oral glucose tolerance test increment less than 3 mmol/L in 70% of people and 4.6 mmol/L in 95% (McDonald and Ellard, 2013). A large proportion (up to 43%) of all incidental persistent mild hyperglycaemia seen in non-obese young adults has been shown to be attributable to GCK-MODY (Feigerlová et al, 2006). HbA_{1c} in subjects <40 years

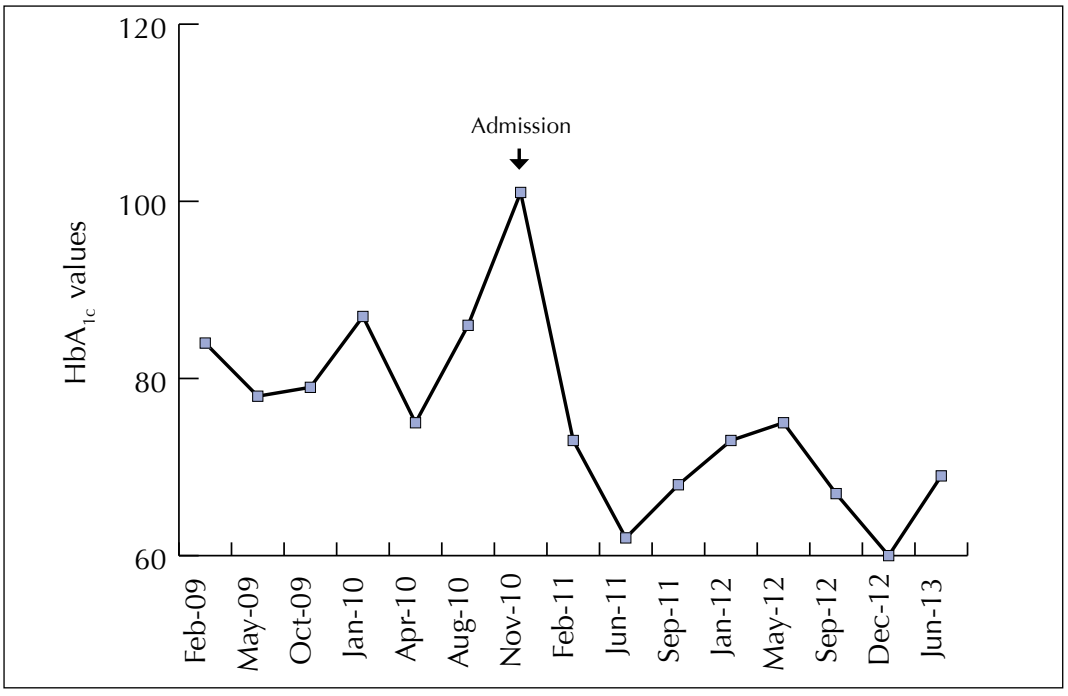

Figure 2. Trend in HbA_{1c} and improvement following admission for commencing insulin pump therapy, education of family, continuous glucose monitoring and resetting threshold for treatment of hypoglycaemia.

Table 1. Recognition of GCK-MODY based on laboratory test results and key clinical features (McDonald and Ellard, 2013).

Persistent fasting hyperglycaemia	5.5–8.5 mmol/L.
Oral glucose tolerance test glucose increment	120-minute glucose, minus 0-min glucose of <3.0 mmol/L.
Pancreatic auto-antibodies	The prevalence of pancreatic autoantibodies in MODY is the same as in controls.
HbA_{1c}	Near normal. Values >55 mmol/mol (7.2%) would be suggestive of an alternative diagnosis.
Persistent fasting C-peptide production	Stimulated serum C-peptide >200 pmol/L.
Family history	A parent will usually have mild fasting hyperglycaemia (5.5–8.5 mmol/L).

Page points

1. People with GCK-MODY have a minimal risk of long-term micro and macrovascular complications and for this reason they are not offered treatment, although diet and exercise advice may be necessary.
2. It is important that HbA_{1c} levels and hyperglycaemia continued to be monitored.

old with GCK mutation is usually 38–56 mmol/mol (5.6–7.3%; Steele et al, 2013). With the increasing use of HbA_{1c} in the diagnosis of diabetes (Farmer, 2012), the number of people with GCK mutation misdiagnosed with other forms of diabetes may increase leading to unnecessary treatment and screening for complications (Steele et al, 2013). Use of HbA_{1c} to diagnose diabetes classifies all individuals with GCK-MODY having an HbA_{1c} >48 mmol/mol as having some form of diabetes. This can be minimised to some extent by the use of age-related HbA_{1c} reference ranges for GCK-MODY (Steele et al, 2013). The diagnosis of GCK-MODY based on clinical and laboratory features are listed in *Table 1*.

Management

People with GCK-MODY have mild, stable hyperglycaemia with minimal risk of long-term micro and macrovascular complications and for this reason they are not offered treatment, although diet and exercise advice may be necessary. It is important, however, that HbA_{1c} levels and hyperglycaemia continue to be monitored.

Outcome

One study demonstrated that, despite a median duration of 48.6 years of hyperglycaemia, people with a GCK mutation had low prevalence of microvascular and macrovascular complications, in comparison to control subjects and those with young onset of type 2 diabetes (Steele et al, 2014).

Hypoglycaemia in GCK-MODY

The counter regulatory response to hypoglycaemia is activated at a higher plasma glucose concentration in people with GCK-MODY. This may be secondary to decreased GCK activity in hypothalamic neuronal cells, or to alterations of glucose sensing in pancreatic alpha cells and liver cells (Guenat et al, 2000). In people with GCK-MODY, there is a lack of glycaemic response to pharmacologic agents as the genetic subtype determines the treatment response (Stride et al, 2014). Use of hypoglycaemic agents in GCK-MODY suppresses endogenous insulin to maintain BG at a higher level (Stride et al. 2014). However, in people with a dual diagnosis, where there is a lack of endogenous insulin, use of high doses of insulin to lower BG levels may not have the same effect and render individuals symptomatically hypoglycaemic at BG levels considered to be within target; this complicates management. Therefore, the targets have to be set at a higher level to match that of GCK-MODY, usually between 5.5–8 mmol/L.

Co-existence of GCK-MODY and type 1 diabetes

There are very few reported cases in the literature of a combination of GCK-MODY and type 1 diabetes. In the previously reported cases, the authors have not expressed any concerns of fluctuating BG levels. However, the people in these case studies were older than our patient when they developed type 1 diabetes (Calcaterra et al, 2012; Maltoni et al, 2012).

Page points

1. It is important to recognise the co-existence of maturity onset diabetes of the young and type 1 diabetes, as symptoms of hypoglycaemia at BG levels usually considered "within target" pose management challenges.
2. Counter regulatory response to hypoglycaemia is activated at a higher plasma glucose concentration in glucokinase-MODY. The target BG for these people should, therefore, be set at a higher level than in people who have type 1 diabetes alone.

There are currently 187 children and young adults under the age of 19 years with a genetic diagnosis of GCK-MODY in the UK (established by direct communication with central testing laboratory in Royal Devon and Exeter Hospital, Exeter). This gives a point prevalence of approximately 1 in 81 000 in children and young people under the age of 19 years, as per the 2011 census (Office of National Statistics, 2014). The population prevalence of GCK-MODY is said to be 1.1 in 1000 (Chaker et al, 2014). There is no evidence to suggest that GCK-MODY either protects or pre-disposes to type 1 diabetes, hence one would expect the prevalence to be 1.1 in 1000 in individuals with type 1 diabetes as well. The 2011–2012 National Paediatric Diabetes Audit reported that there are approximately 25 000 children under the age of 19 years with diabetes in the UK and 97% of them have type 1 diabetes. Therefore, our estimations suggest that there should be approximately 26 children under the age of 19 years with a dual diagnosis. However, to the best of our knowledge, there are only two genetically-confirmed cases, including our patient, with a combined diagnosis of GCK-MODY and type 1 diabetes in the UK (established through the central genetic testing laboratory in Exeter). Individuals are often misdiagnosed as having other forms of diabetes, depending on the timing of detection of hyperglycaemia (Murphy et al, 2008). In this case, our patient's older sibling was thought to have type 1 diabetes and his grandfather was misdiagnosed as having type 2 diabetes.

Achieving the target HbA_{1c} in people with this dual diagnosis may be difficult and the effect of persistent hyperglycaemia in these people is unknown. There is no literature on the long-term effect of micro- and macrovascular complications in this group, so we suggest that this requires further investigation.

Conclusions

From the case that we have presented, we can conclude that:

1. Co-existence of type 1 diabetes and GCK-MODY is currently rarely diagnosed, despite the reported population prevalence of GCK-MODY of 1.1 in 1000. GCK mutations do not protect or predispose to type 1 diabetes, therefore one would expect to find co-existence in 1.1 in 1000 people with type 1 diabetes.
2. It is important to recognise the co-existence of these conditions, as symptoms of hypoglycaemia at BG levels usually considered "within target" pose management challenges. Counter regulatory response to hypoglycaemia is activated at a higher plasma glucose concentration in GCK-MODY. The target BG for these people should, therefore, be set at a higher level than in people who have type 1 diabetes alone.
3. Identifying relevant family history is key in recognising monogenic diabetes. Planned, long-term follow-up of families with dual diagnosis of type 1 diabetes and GCK-MODY would allow us to determine optimal management strategies and assess future risks of microvascular and macrovascular complications. ■

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