

Genetics and rare forms of Diabetes

Patient Scenario

Sam is 3 years and 8 months old and was diagnosed with Type 1 diabetes when he was 14 months. His brother, Tom, also showed signs of impaired glucose tolerance when he was 3 years and 10 months old. Tom was not started on insulin until a month after diagnosis. At around this time, Michael was born and was tested positive for glucokinase (GCK) deficiency. Further testing of the family revealed that all 3 children (Sam, Tom, Michael) as well as their father had an uncommon form of diabetes called Maturity-Onset Diabetes of the Young (MODY).

Key points for dietitians

- Maturity-Onset Diabetes of the Young (MODY) affects 1-2% of people with diabetes and can often go unrecognised or is mistaken for Type 1 or Type 2 diabetes. The main features of MODY are that it develops before the age of 25 years, it runs in families, and is often due to a change in a single gene that is passed from a parent carrier to their child. MODY is usually treated with lifestyle changes such as diet and increased physical activity, although some forms of MODY may require treatment with tablets or insulin.
- MODY is confirmed by a diagnostic genetic test. Blood samples are sent to a molecular genetics laboratory for analysis. Information can be found at www.diabetesgene.org
- There are other rare forms of diabetes caused by single gene mutations. These include two types of neonatal diabetes mellitus (NDM), diabetes due to mutations in mitochondrial DNA (MIDD) and mutations that cause insulin resistance. These are likely to be diagnosed before referral to a dietitian. However, dietitians should be aware of their Regional Genetics Centre which can be found at www.bshg.org.uk. Referral should only be where a single-gene disorder is suspected.
- Asking about family history is a routine part of dietetic assessment for conditions such as diabetes and obesity. For advice about taking a family history visit www.geneticseducation.nhs.uk.
- It is important to correctly diagnose monogenic diabetes as it can predict the clinical course for the patient, explain other clinical features and guide the most appropriate treatment. Diagnosis will have implications for other family members, often correcting the treatment for other diabetic relatives as well as allowing appropriate genetic counselling.

Genetics concepts underpinning diabetes

Genetic factors in Maturity-Onset Diabetes of the Young (MODY)

MODY is characterised by slow onset of symptoms, the absence of obesity, and with no evidence of ketosis or beta cell autoimmunity. It is most often managed without insulin injections. MODY displays an autosomal (non-sex linked) dominant pattern inheritance, generally spanning 3 generations. All children of an affected parent have a 50% chance of inheriting the affected gene and developing MODY. There are at least 6 forms of MODY, each of which is caused by a mutation in a different gene that is directly involved in beta cell function. Because MODY phenotypes vary depending on which gene is involved, genetic testing may also assist in the treatment of the disease.

Genetic factors in Neonatal Diabetes Mellitus (NDM)

Neonatal Diabetes Mellitus presents as an insulin-sensitive hyperglycaemia diagnosed in the first months of life. Infants with NDM have low birth weight due to intrauterine growth retardation and may present with lethargy, poor eating, seizures, dehydration and failure-to-thrive. It occurs at a frequency of about 1 in 400,000 people and can be either transient or permanent. Permanent NDM has been linked to mutations in several genes, including KCNJ11, GCK, and IPF1. Permanent NDM related to KCNJ11 accounts for approximately 50% of all cases and appears to be responsive to sulfonylurea therapy. However, permanent NDM related to GCK and IPF1 require insulin replacement. Permanent NDM related to KCNJ11 develops within weeks (rather than days) and persists into the second and third years of life. Only genetic testing can differentiate between Permanent NDM and Transient NDM in newborns.

Genetic factors in Maternally Inherited Diabetes with Deafness (MIDD)

Maternal Diabetes with Deafness is a rare, monogenic form of the disease caused by mutations in the mitochondrial genome, most frequently the A3243G tRNA^{Leu} substitution. Impaired pancreatic beta cell insulin secretion is its major pathophysiological mechanism. In terms of its clinical presentation, it has similar symptoms to Type 1 diabetes and Type 2 diabetes. It is usually diagnosed in early adulthood, but age range of onset is wide (Malecki, et al., 2006).

Genetic factors causing severe insulin resistance

Although obesity is the most common cause of insulin resistance, genetic defects that disrupt the action of insulin can cause insulin resistance. One symptom of severe insulin resistance is a skin disorder called acanthosis nigricans, causing areas of skin to have hyperpigmentation and hyperkeratosis.

Patient Scenario

Following the diagnosis of glucokinase deficiency, Tom was taken off insulin, but toddler Sam has a dual diagnosis and is currently on an insulin pump. The dietitian working with the family has taught the parents carbohydrate counting to help manage Sam's Type 1 diabetes.

The dietitian's knowledge of the role of glucokinase, which acts as a "glucose sensor" for the pancreas, has helped the dietitian to explain the implications of MODY2 to the family. The condition is characterised by fasting blood glucose between 5.5-8.5 mmol/L, which is stable throughout life. Complications are extremely rare. However, individuals with MODY2 have the same risk of developing Type 2 diabetes as other members of the general population. The dietitian encourages the family to adopt healthy eating patterns, maintain healthy body weights and keep physically active.

Role of genetics in the treatment and prevention of diabetes

For individuals with MODY, knowledge of the underlying defect (MODY1, MODY2 etc) is likely to lead to better management and improved prognosis. Given the autosomal dominant inheritance of all forms of MODY, individuals with a diabetic parent may also wish to have genetic testing, as early diagnosis and correct treatment may help reduce long-term complications.

For example, some individuals with MODY3, responsible for 70% of all cases of MODY, have previously been classified as having Type 1 diabetes. People with MODY3 are extremely sensitive to the hypoglycaemic effects of sulfonylureas, which is the treatment of choice. Good control of blood glucose and cholesterol levels are important in this type of MODY, as vascular complications are common. Getting the right treatment is associated with a positive impact on lifestyle and self image. It is therefore essential that dietitians understand the genetics of these rare forms of diabetes as it may be useful in guiding clinical management.

Further information and references

Malecki MT et al.(2006) Rev Diabet Stud, 3(4):205-207.

www.bda.uk.com British Dietetic Association

www.dmeg.org.uk Diabetes Management and Education Group of the BDA

www.diabetes.org.uk Diabetes UK

www.diabetesgenes.org Diabetes Research Department and Centre for Molecular Genetics at Peninsula Medical School

www.ncbi.nlm.nih.gov National Institute of Biotechnology Information (NCBI) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): The Genetic Landscape of Diabetes