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Reminder of important clinical lesson

Diabetes in the young but not needing insulin – what type is it?

Umesh Dashora,[1] Rachael Golton,[2] Amanda Combes,[1] Sathis Kumar[1]

[1]Endocrinology and Diabetes Department, Conquest Hospital, St Leonards on Sea, UK;
[2]Diabetes Department, Conquest Hospital, St Leonards on Sea, UK

Correspondence to Dr Umesh Dashora, umesh.dashora@esht.nhs.uk

Summary

A 57-year-old female who was diagnosed with diabetes at the age of 22 is presented. She was initially controlled with diet alone and then was prescribed oral glucose lowering treatment over the next 35 years. She was referred to the diabetes clinic for insulin start because of poor control of diabetes. In view of her presentation at such a young age and strong family history, a possibility of maturity onset diabetes in young was considered and the genetic test confirmed hepatocyte nuclear factor-1 α mutation on chromosome 12. Further oral treatment and attention to lifestyle modification improved control avoiding insulin therapy.

BACKGROUND

- Diabetes in young people usually results from β cell destruction and insulin is needed for survival.
- Increasingly however we are finding young people with diabetes (2–5% of people with apparent diagnosis of type 2 diabetes) due to genetic defects. This type was formerly called maturity onset diabetes of the young (MODY),[1] but is now known to be a group of increasingly recognised heterogeneous disorders resulting from independent genetic defects.[2 3] This form of diabetes is mild, can be treated with oral therapy and does not usually require insulin.
- It is important to recognise this type of diabetes to avoid unnecessary use of insulin.

CASE PRESENTATION

A 57-year-old female was referred to the diabetes clinic to start insulin for poor control of diabetes (HbA_{1c} 9.5%). She was diagnosed with diabetes at the age of 22. She was controlled initially on diet for 3 years. Later, metformin and glimepiride were added, a combination that she received for over 17 years. Later she was prescribed rosiglitazone. This was stopped following the adverse 'media coverage' linking it to poor cardiovascular outcomes.

Interestingly she never had ketonuria and was free from complications despite 35 years of diabetes. She also had a strong family history. Her father, brother and two sisters were all diagnosed with diabetes before, or in their early 20's. They were also managed on oral glucose lowering drugs. On examination, the height was 1.69 m, weight 81.0 kg, abdominal circumference 91.4 cm and body mass index (BMI) 28.4.

INVESTIGATIONS

Hepatocyte nuclear factor (HNF)-1 α mutation was picked up on genetic testing.

DIFFERENTIAL DIAGNOSIS

- Diabetes in a young person is usually type 1 diabetes. This type of diabetes results from β cell destruction which is usually immune mediated but can occasionally be non-immune. Testing for antibodies to islet cell, glutamic acid decarboxylase, insulin and tyrosine pyrophosphatase is helpful in making the diagnosis in some cases.[4] People with type 1 diabetes need insulin for survival.
- Some adults with apparent type 2 diabetes (about 10 per cent) have antibodies and need insulin earlier than expected. These are sometimes referred to as latent autoimmune diabetes of adults or type 1.5 diabetes.[5–7] Most patients however, would need insulin within 3 to 5 years of diagnosis.
- Increasingly typical type 2 diabetes can present at an early age due to the increasing prevalence of obesity in the young, giving rise to insulin resistance. Our patient was not particularly obese at diagnosis with height 1.69 m, weight 60 kg and BMI 21 which would be against this diagnosis.
- Finally, it is also possible for people with type 1 diabetes to develop type 2 diabetes by way of increasing weight and insulin resistance.[8] Our patient however, has maintained her BMI over the years.

TREATMENT

The patient's glucose control improved with an increase in the dose of glimeperide (from 4 mg to 6 mg daily), addition of sitagliptin 100 mg daily and further attention to lifestyle modification.

OUTCOME AND FOLLOW-UP

HbA_{1c} improved from 9.5% to 7.4% in 15 months with the above measures and the lady still does not have any major complications of diabetes even after 36 years of diagnosis. It is possible that with increase in weight and the attendant insulin resistance, if her HbA_{1c} deteriorates, she might need insulin in future.

DISCUSSION

Monogenetic β cell diabetes is well described and was called MODY with a number of subtypes referring to

specific genes containing mutation which lead to defective insulin production signalling.[2 3] Importantly approximately 15–20% of families which appear to have MODY do not have mutations in the commonly tested genes raising the possibility of further genetic defects that are yet to be discovered.[9] It is therefore important to keep this possibility in mind in patients who have strong family history of diabetes over two or three generations and develop diabetes at young age but do not appear to need insulin.

Some of the known types of independent genetic defects are summarised below;

1. HNF-4-α (formerly called MODY 1) – A mutation in this gene on chromosome 20 can lead to reduced insulin secretion.
2. Glucokinase gene (formerly called MODY 2) – A mutation in this gene on chromosome 7 leads to defective phosphorylation of glucose and reduced insulin secretion. This type of diabetes in more commonly reported in American Blacks and does not lead to vascular complications.
3. HNF-1-α (formerly MODY 3) – the mutations in this gene on chromosome 12 is seen in European patients and can affect insulin secretion. These patients have glycosuria and marked sensitivity to sulphonylurea compared to metformin.
4. Insulin promoter factor 1 (formerly MODY 4) – Mutations in this gene can lead to reduced binding of protein to the insulin gene promoter and reduced insulin secretion.
5. HNF-1-β (MODY 5) – Mutations in this gene lead to early onset diabetes along with other somatic abnormalities (renal, genital and hepatic).
6. Neurogenic differentiation factor-1 – This genetic mutation was formerly called MODY 6 and works as a switch for endocrine pancreatic development.

Learning points

- Diabetes in young people is usually type 1 and needs insulin to prevent ketoacidosis but if there is a strong family history, monogenic diabetes or MODY should be suspected.
- Diagnosis of MODY is confirmed by genetic testing of blood.
- This type of diabetes responds well to sulphonylureas and does not need insulin.
- Some forms of MODY (HNF 1 and HNF 4) have additional abnormalities like renal cysts, genital abnormalities, high uric acid and lipid abnormalities.
- Some forms (glucokinase or MODY 2) have stable mild hyperglycaemia and require no treatment.

Competing interests None.

Patient consent Obtained.

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