A 35-year-old woman with type 1 diabetes attended the antenatal diabetes clinic at the John Radcliffe Hospital, Oxford, early in the pregnancy of her second child. She had had type 1 diabetes since the age of 13 on the background of a strong family history of type 1 diabetes in her mother, uncle and cousin. She had a normal range BMI pre-pregnancy. Her first pregnancy had been successful with the birth of a son at 37 weeks gestation, weighing 3.5kg.

It was noted in the current pregnancy that she had very tight glycaemic control and that her HbA1c had fallen from 5.9% to 5.3%, using relatively small total daily doses of insulin (Lantus 2 units per day, Novorapid 2–4 units tds), with a tendency towards hypoglycaemia.

Given her clinical picture and family history, a query was raised as to her underlying diabetes type. Her GAD and ICA pancreatic auto-antibodies were checked and found to be negative, and her C-peptide level was very low at 277pmol/L, with a concurrent glucose level of 5.0mmol/L. Monogenic diabetest had already been considered and tested for back in 1999 by the paediatric team. Results from the Department of Molecular Genetics at the Royal Devon & Exeter Hospital stated that she was negative for an HNF1A gene mutation. However, other MODY subtypes had not been tested for and so targeted next-generation sequencing of the known MODY genes on the family’s saved samples was requested.

No known pathogenic mutation was identified, but a novel heterozygous missense variant (p.Thr211Asn, NM_175914:4.c.632C>A) in the HNF4A gene was found. The patient’s mother, who was diagnosed with presumed type 1 diabetes at the age of 15, was also heterozygous for the variant. The patient was certainly atypical for type 1 diabetes and the presence of the mutation in the mother would suggest that the mutation is likely to be pathogenic (although there was a 50% chance of the mother having the variant regardless).

Despite good glycaemic control, the baby’s abdominal circumference was greater than the 97th centile for growth on the 28-week scan. Subsequent growth is demonstrated in Figure 1. At 34 weeks, the patient developed an antepartum haemorrhage, was admitted for IV steroids (to aid fetal lung maturation), and underwent delivery by caesarean section shortly afterwards. The baby’s weight was 3.8kg, which is greater than the 99th centile for this gestational age.

Ultimately, it would seem likely that this genetic variant had implications in this pregnancy. HNF4A plays a key role in determining fetal birthweight and mutations result in an increase in birthweight by an average of 800g.1 Ten percent of HNF4A MODY patients also have transient neonatal hypoglycaemia, although this was not found in this case. Fetal growth increasing above the 75th centile, in spite of good glycaemic control in the mother, is also indicative of good evidence for pathogenicity.

As with all forms of diabetes, in a variety of settings, it is important to be increasingly aware of the many different types of monogenic diabetes and their associated complications.2–4

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