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Case report

Family history in the diagnosis of monogenic diabetes "leads and misleads"

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ABSTRACT

Always granting that *de novo* mutations are possible, family history and biological characteristics are nonetheless crucial for the diagnosis of monogenic diabetes. We report here the case of two patients with monogenic diabetes in which the initial family history misled the diagnostic work-up and did not support the diagnosis. Family history details changed substantially after the molecular diagnosis was established.

Key words: Family history; Glucokinase; Hepatic nuclear factor-1ß; Monogenic diabetes

INTRODUCTION

Any medical history should include family history given that in many diseases there is a genetic component and in some cases inheritance is crucial. In diabetes mellitus (DM), a family history with many affected members usually points to the diagnosis of Type 2 DM (T2DM). The concordance of T2DM in monozygotic twins is 60-90%, and in first-degree relatives of patients with T2DM, the risk of impaired glucose tolerance increases more than 5-fold.[1] In type 1 diabetes (T1DM) the risk of inheritance is lower, with a concordance of 30% in monozygotic twins and a disease risk in first-degree relatives of 5-10%.[2-4] However, when the inheritance pattern is autosomal dominant and the patient has neither have autoimmunity against the beta-cell or a metabolic syndrome phenotype, it is compelling to consider the possibility of monogenic DM due to defects in the beta cell. Monogenic DM represents 1-2% of DM in Europe.[5,6] In the diagnosis of monogenic DM, the family tree is important since the characteristics of other family members can help to identify the affected gene and reduce the cost of diagnosis.[7] Thus, it is important that

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family history is correct. We report on two patients with monogenic DM in whom where initial history was misleading because it was incorrect, despite being taken from well-educated subjects enjoying good family relationships.

PATIENT 1

A 33-year old man diagnosed with DM when he was 14 after detection of simple hyperglycaemia. He came to the outpatient consultation, having been referred by his partner (health professional). His family history is summarized in Figure 1.

The patient had normal weight (BMI 21 kg/m^2) and reported fasting plasma glucose figures between 6.7-7.2 mmol/l in the absence of drug treatment. Additional work-up: glycated haemoglobin (HbA1c) 6.6% (49 mmol/mol) (reference values 4.6 - 5.8%; 27-40 mmol/mol), negative antiGAD antibodies, C peptide in the low normal range (348 pmol/l, reference values 298-1324 pmol/l) coinciding with fasting plasma glucose in the diabetic range (7.3 mmol/l).

The family history was consistent with monogenic DM (autosomal dominant inheritance pattern and diagnosis before 25 years in two members).[7] Mild

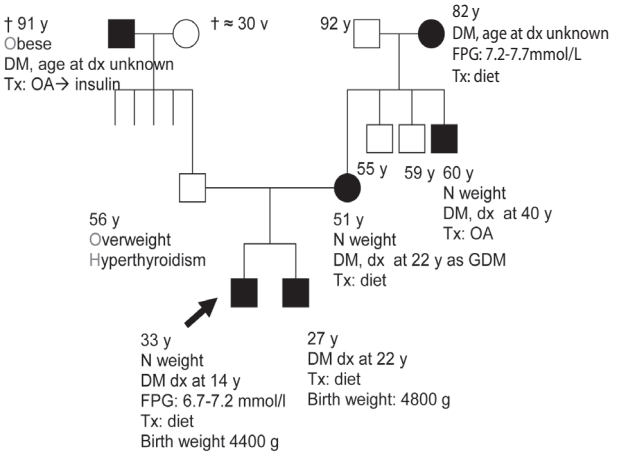

Figure 1. Family history of diabetes mellitus in patient 1 at consultation. Filled forms indicate family members with diabetes. y: years; DM: diabetes mellitus; Tx: treatment; OA: oral agents; Dx: diagnosis; FPG: fasting plasma glucoses; N: Normal; GDM: gestational diabetes mellitus: GCK: glucokinase. After diagnosis of the index case, GCK mutation was confirmed in all affected individuals and birth weight figures were modified to 3650 and 4259 g respectively.

hyperglycaemia in all affected members and absence of complications after long duration of DM suggested glucokinase (*GCK*) deficiency. However, the remarkably high birth weight of the index case and his brother was not typical of *GCK* deficiency where a normal or low birth weight of affected subjects (depending on the presence or absence of maternal DM) is characteristic.[8] In the genetic work-up (guided by the frank macrosomia in the two brothers) the first studied gene was *HNF4A*.[9] Subsequently, *HNF1A* and *GCK* genes were analyzed and a heterozygous mutation was detected in the latter (c.1183G>T; p.Glu395X) in exon 9. The mutation is an already described stop-codon mutation in a highly conserved region. On our obtaining the results of the genetic study, the patient was questioned again about his birth weight and that of his brother. After asking his mother, he reported that birth weights were 3650 g and 4259 g respectively. All the family members with diabetes were found to have the mutation.

PATIENT 2

A 32-year old woman (healthcare professional) who consulted for pregnancy planning. She had been diagnosed with T1DM at 19 years of age (simple hyperglycaemia, HbA1c 19.5% (194 mmol/l), negative antiGAD antibodies). She was receiving insulin treatment with a bolus-basal schema resulting in acceptable glycaemic control. She did not have diabetic complications, either late or acute. She had also been diagnosed of a hypoplastic kidney and mild renal failure. During follow-up the patient became pregnant three times while sustaining in acceptable glycaemic control (first HbA1c in pregnancy ranging from 5.3% (34 mmol/mol) to 6.1% (43 mmol/mol) and she had three spontaneous miscarriages. The infertility study detected a bicornuate uterus.

The extrapancreatic manifestations of the patient suggested a monogenic DM due to a mutation in *HNF1B* despite the absence of a suggestive family history (Figure 2).[10-12]

The genetic study demonstrated a whole *HNF1B* gene deletion. During the consultation, after being informed of the diagnosis, the patient expanded on the family history details (Figure 3), now including DM with an autosomal dominant inheritance pattern and kidney disease in an uncle.

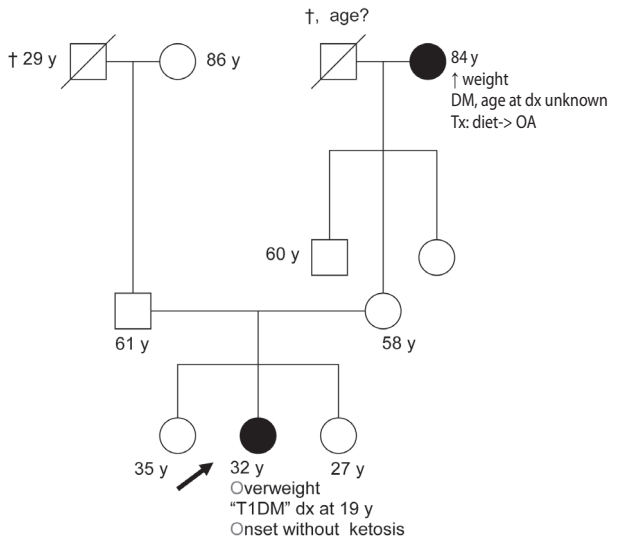

Figure 2. Family history of diabetes mellitus in patient 2 before genetic diagnosis. Filled forms indicate family members with diabetes. y: years, DM: diabetes mellitus; Tx: treatment; OA: oral agents, dx: diagnosis, T1DM: diabetes mellitus type 1.

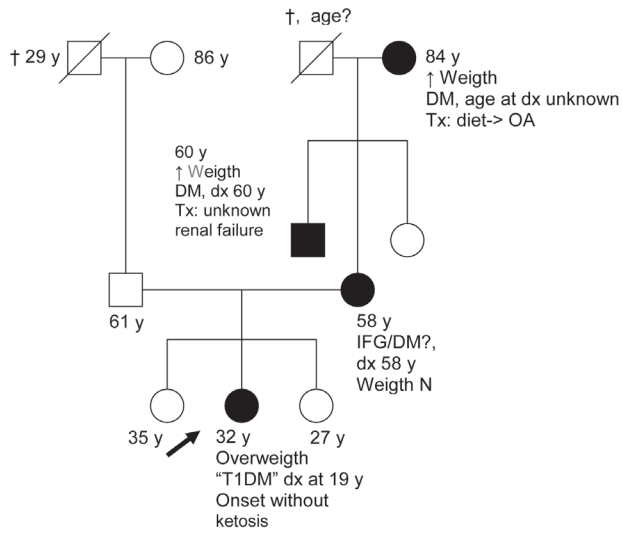

Figure 3. Family history of diabetes mellitus in patient 2 after diagnosis of *HNF1B* deletion. Filled forms indicate family members with diabetes.y: years, DM: diabetes mellitus; Tx: treatment; OA: oral agents, dx: diagnosis, IFG: impaired fasting glucose, T1DM: diabetes mellitus type 1; *HNF1B*: hepatic nuclear factor 1ß.

Molecular diagnosis was not performed in family members after diagnosis of index case.

DISCUSSION

Usual indications for the diagnosis of monogenic DM are the presence of a consistent family history, absent features of metabolic syndrome, one or more members diagnosed before 25 years of age, lack of autoimmunity against the beta cell and relative preservation of beta cell function.[7] Additional features (birth weight, extra pancreatic manifestations) provide guidance on the specific gene defect. However, family history is not a prerequisite since mutations can be novel ones.[13]

In the first patient, family history was consistent with monogenic DM and mild hyperglycaemia pointed to a *GCK* deficiency. However, frank macrosomia in the two affected brothers suggested a mutation in *HNF4A*.[9] Knowledge of the genetic diagnosis prompted a recheck of birth weights, which were in fact lower than initially reported but nevertheless included a macrosomic newborn. Fetal macrosomia is rare (but possible) in subjects with *GCK* deficiency. In affected infants born to affected mothers, the rate of macrosomia has been reported to be 8,9%[14] and according to published information on birth weight mean and standard deviation,[15-17] the upper limit of birth weight in this group would range between 4163 and 4802 g.

In the second patient, extrapancreatic manifestations clearly indicated a *HNF1B* defect even though when a family history of diabetes with an autosomal dominant inheritance pattern was lacking. Once the genetic diagnosis was known, the revised family history was also suggestive of a *HNF1B* mutation.

Recently, a clinical prediction model has been developed to predict an individual's probability of having MODY among young adults with diabetes.[18] The calculator is available at http://www.diabetesgenes.org/content/mody-probability-calculator with an indication that it requires further validation. With the information available at the first consultation, it would give a MODY positive predictive value of >75% in the first patient and <5% in the second. This would not, however, have been a significant help in our patients since there was no problem in considering a MODY diagnosis in the first patient but only in assigning the required importance to the mild hyperglycaemia vs increased birth weight when seeking to identify a specific type. In the second patient, the problem was the

incomplete family information that also contributed to the low positive predictive value of the calculator.

Family history is included within monogenic diabetes criteria,[7] but these case reports illustrate that it can have its limitations even when information comes from apparently reliable sources. Clinical and biological features are also crucial for diagnosis.

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