17q12 Deletion and a Family History of Diabetes

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INTRODUCTION

17q12 deletion syndrome is associated with an enlarging phenotype, the most frequent clinical findings being renal and genitourinary malformations, diabetes mellitus (β-cell developmental defect) and exocrine pancreas deficiency, variable cognitive impairment with dysmorphic features.

CASE PRESENTATION

MOTHER

At the age of 18 years - T1DM treated by insulin, with poor adherence/control (average HbA1c 11%) and renal and metabolic complications development around 24 years. Renal ultrasound is normal and she presents with intellectual disability and dysmorphic features. Her father and paternal aunt were diabetic.

By the age of 33 years – MODY5 (1.4-Mb deletion in chromosome 17q12, including the *HNF1β* gene).

PATIENT 1

An 11-year-old male child presented with polyuria.

Medical history: cognitive delay (with normal brain MRI), hepatic cytolysis (non-alcoholic steatohepatitis), and ophthalmic abnormalities (right eye convergent strabismus, astigmatism).

At admission: weight 47 kg (P90), height 141 (P25), BMI 23.73 kg/m^2, head circumference (HC) 54 cm (P75). Mild cognitive impairment, behavioral difficulties, dysmorphic features (high forehead, long face, hypertelorism, depressed nasal bridge, prominent nose, thick lips, long philtrum), and joint laxity.

Biological check-up:

Glucose metabolism:
- glycaemia 317 mg/dL, glycosuria, no ketonuria
- HbA1c 7%
- insulin 40 mIU/mL (2 - 17), C peptide 1.92 nmol/L (0.37 – 1.47)
- negative T1DM markers.

Renal function: normal, uric acid level 6.9 mg/dL (2.5 – 6.4).

Hepatic tests: ALT 103 U/L, AST 150 U/L.

Radiological check-up: no renal, cardiac, skeletal or genitourinary abnormalities.

Diagnosis: MODY 5

Treatment: metformin, with immediate good glycemic control.

15 months later

severe keto-acidosis (glycaemia 372 mg/dL, pH 7.2, ketonemia, ketonuria, HbA1c 13.7%)

Current treatment: insulin 1.07 u/kg/d, with last HbA1c 9.8% and BMI 28 kg/m^2.

PATIENT 2

A 14-year-old male child, asymptomatic.

Medical history: cognitive delay (with normal brain MRI).

At admission: weight, height, BMI of 30 kg/m^2 HC 57 cm (P95). Mild cognitive impairment, dysmorphic features (high forehead, long face, hypertelorism, depressed nasal bridge, prominent nose, thick lips, long philtrum).

Biological check-up:

Glucose metabolism:
- glycaemia 121 mg/dL, no glycosuria, no ketonuria
- HbA1c 6.8%
- insulin 14.2 mIU/mL (2 - 17), C peptide 0.823 nmol/L (0.37 – 1.47)
- negative T1DM markers.

Renal function: normal

Hepatic tests: normal.

Radiological check-up: no morphological abnormalities.

Diagnosis: MODY 5

Treatment: metformin, with immediate good glycemic control.

12 months later

HbA1c 11.6%, and he had lost 4 kg over several weeks.

Current treatment: insulin 0.32 u/kg/d, with last HbA1c 5.7% and BMI 37 kg/m^2.

CONCLUSIONS

2 brothers with dysmorphic features, neurological phenotype, MODY 5, no renal abnormalities and maternally inherited 17q12 deletion including *HNF1β*. They showed similar phenotypes, with some biochemical and insulin response differences, but distinct features have been reported between family members with the same 17q12 deletion (1).

Patient 1 presented with hyperuricemia, already described as renal *HNF1β*-associated feature (2) and liver abnormalities, also reported (3).

Could their rapid progression from preserved insulin secretion to insulin deficiency be associated with progressive obesity?
MODY 5 diabetes treatment remains challenging.

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