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M Alvarez and others | Maturity-onset diabetes of the young type 3

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Maturity-onset diabetes of the young type 3 and premature ovarian insufficiency: chance or causality: a case report and literature review

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Summary

We present the case of a 23-year-old patient with maturity-onset diabetes of the young type 3 (MODY 3) and premature ovarian insufficiency (POI). There is no known correlation between MODY 3 and POI, although POI can impair glucose metabolism, and MODY can cause microvascular complications such as POI. We did not find literature describing a correlation between these two pathologies nor did we find similar cases described in the literature.

Learning points:

- Maturity-onset diabetes of the young type 3 (MODY 3) is an infrequent cause of diabetes that should be considered in young patients with atypical presentation of type 1 or type 2 diabetes.
- MODY 3 can be associated with microvascular complications of diabetes, which is why it is important to diagnose as early as possible.
- Impairment of glucose metabolism has been demonstrated in patients with premature ovarian insufficiency and menopause.

Background

We present the case of a 23-year-old patient with premature ovarian insufficiency (POI 1–6) and maturity-onset diabetes of the young type 3 (MODY 3). The first suspicion was the possibility of an autoimmune aetiology given the known correlation between type 1 diabetes mellitus and premature ovarian failure. However, it remained important to consider alternate diagnoses, such as MODY 3, due to its potential connection with premature ovarian failure.

No literature was found documenting genetic correlation between these two pathologies nor did were similar cases found described in the literature.

Case presentation

A 23-year-old female patient was evaluated for hyperglycaemia in a primary care studies clinic. She had a history of POI beginning at the age of 15 and had been prescribed oestrogens and medroxyprogesterone. Studies indicated persistent hyperglycaemia in the diabetic range over the previous 2 years so she was diagnosed with type 1 diabetes and prescribed insulin glargine six units a day, thus achieving target range glucose and HbA1c levels. The physical examination showed that she was not overweight and there were no signs of insulin resistance. She had no personal or family history of diabetes, MODY, or psychiatric disorders and POI.

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Investigation

Studies were performed after stopping oestrogens, resulting in the following findings: oestradiol, less than 5 pg/mL; follicle-stimulating hormone (FSH), 90 mIU/mL; luteinizing hormone, 29 mIU/mL, Karyotype was normal, 46XX, and anti 21 hydroxylase antibodies at less than 0.3 negative; thyroid-stimulating hormone (TSH), 1.3 mUI/L; prolactin, 13 ng/mL; basal cortisol, 10 µg/dL; and adrenocorticotropic hormone, 29 pg/mL. During the last 3 years, she had altered glucose levels (Table 1).

C peptide and antibodies for type 1 diabetes mellitus were measured. Peptide C level was normal at 1.8 ng/mL. Negative anti-pancreatic islets, negative anti-insulin, negative anti-zinc channels, and negative anti-glutamic acid decarboxylase antibodies were found. Microalbuminuria was 3.8 mg/L, normal. Evaluation for retinopathy was normal. Total cholesterol level was 179 mg/dL, LDL 106 mg/dL, HDL 43 mg/dL, and triglycerides 149 mg/dL. Transvaginal pelvic ultrasound was normal, and ovaries were of normal size and appearance.

Due to the patient's history, low insulin requirements, normal C peptide, and patient record, the possibility of MODY was considered. Using a Gencell Pharma comparative genomic hybridization technique, whole-exome sequencing found HNF1A (NM 000545): c.511C T; p.ARrg171*; heterozygosis. This mutation (OMIM no. 600696/AD) is associated with autosomal dominant MODY type 3.

Treatment

Due to the diagnosis of MODY 3, insulin treatment was suspended, and treatment with glimepiride, 2 mg per day, was started to maintain adequate control of glucose and HbA1C levels (Table 1).

Outcome and follow-up

Due to the diagnosis of MODY 3, insulin treatment was suspended and treatment with glimepiride 2 mg per day was started with adequate control in glucose and HbA1C.

Discussion

This is a case of a young female patient with diabetes and POI. The possibility of an autoimmune-related cause was the first suspicion given the known correlation between type 1 diabetes mellitus and POI. However, it is important to consider alternate diagnoses such as MODY, due to its possible connection with POI.

Maturity-onset diabetes of the young

MODY is a monogenic form of diabetes mellitus. It generally presents as an early onset of diabetes without insulin resistance and in the absence of autoimmunity. The prevalence is approximately 1.1 per 10 000 people (7, 8) and represents less than 1–2% of patients with diabetes (7, 8, 9).

Multiple types of monogenic diabetes have been described. The most common subtypes (10–60%) are the hepatocyte nuclear factor 1 alpha (HNF1A-MODY3) mutations, 4 alpha (HNF4A-MODY 1) mutations, and the glucokinase mutations (MODY2) (7).

MODY is characterized by an autosomal dominant inheritance (9, 10), and patients often have a strong family history of diabetes. Patients are characterized with insulin independence, absence of antibodies against beta cells of the pancreas, and evidence of the production of endogenous insulin. These are all characteristics that are atypical in type 1 diabetes, as well as in patients with type 2 diabetes. The absence of signs of insulin resistance could be a sign of monogenic forms of diabetes (11).

HNF1A-MODY 3 develops as a result of a mutation in the gene hepatocyte nuclear factor 1 alpha, which is found on chromosome 12, in the 12q24 region (3). It is expressed in pancreatic B cells, in the liver, and in the intestines. HNF1A is a fundamental transcription factor for proteins involved in glucose transport and metabolism, an example of which is the glucose transporter GLUT 2. It has an autosomal dominant inheritance with high heterogeneity and variability. This appears to be related to the location of the mutation and manifests as diabetes in early adulthood, due to a progressive dysfunction at the level of the B cells in the pancreas. It has a high penetrance, developing diabetes in 63% of people aged up to 25 years and in 96% of those aged up to 55 years (12, 13).

Patients with HNF1A mutations have an adequate response to the hypoglycaemic effects of sulfonylureas. Sulfonylureas are the treatment of choice for patients with MODY 1 and 3 and may allow for the withdrawal of insulin in patients misdiagnosed with type 1 diabetes mellitus without the risk of ketoacidosis (11). Patients with MODY 3 regularly maintain beta cell function for at least 2 to 4 years after diagnosis. The long-term treatment with sulfonylureas is associated with weight gain and impaired endogenous insulin production, and over time, this can lead to insulin dependence in patients with type 2 diabetes mellitus (14).

Although we do not have information specific to the present case, MODY 3 is also associated with transient

Table 1 The patient's laboratory test results.

Date	HbA1C	Fasting glucose	After load glucose	Oestradiol	FSH
04/12/2018		125 mg/dL 6.94 mmol/L			
05/16/2019	7.0%	118 mg/dL 6.55 mmol/L	218 mg/dL 12.1 mmol/L	Less than 5 pg/mL	47 mIU/mL
04/05/2020	6.8%				
12/15/2020	6.8%	78 mg/dL 4.33 mmol/L			
24/09/2021	6.0% (on sulfonylurea)				
08/09/2021	6.1% (on sulfonylurea)				
10/16/2021	6.1% (on sulfonylurea)			Less than 5 pg/mL	90 mIU/mL

and persistent hyperinsulinemic hypoglycaemia and macrosomia (15, 16).

Patients with MODY 3 can also present microvascular and macrovascular complications with a similar prevalence to that observed in patients with type 1 and type 2 diabetes. These complications are directly related to poor disease control. Therefore, it is very important to achieve adequate glycaemic control (17).

As in this case, MODY 3 can result from *de novo* mutations in patients without a family history of diabetes in 7% of cases (18).

POI

Normal ovarian function requires the presence of multiple well-functioning genes working in a coordinated fashion. It is believed that 1% of women under 40 years old and 0.1% of those under 30 years old develop POI (19).

The prevalence of ovarian failure is influenced by regional and environmental factors and more frequently occurs in African-American and Hispanic women and to a lesser extent in Asian women. A family history of ovarian failure has been reported in approximately 14% of women and has been associated with chromosomal abnormalities and some genetic mutations (20). Women with POI are at increased risk of cardiovascular disorders, osteoporosis, some degree of cognitive impairment, and earlier mortality (20, 21). Its aetiology is variable where genetic, autoimmune, iatrogenic, and idiopathic causes are documented, with up to 50% of women diagnosed before the age of 20 having a genetic cause, 25% having FMR mutations, 70% having X chromosome abnormalities, and 5% having other diverse mutations (22). More than 50 genes (NR5A1, NOBOX, FIGLAF, and FOXL2) are related to the aetiology of premature ovarian failure, playing an important role in folliculogenesis (23).

The clinical presentation of POI is characterized by oligo/amenorrhea for at least 4 months, menopause symptoms, infertility, and elevated FSH levels >25 mIU/mL on two occasions taken more than 4 weeks apart (24).

The diagnostic tests should include a pregnancy test, thyroid hormones, prolactin, cortisol am, androgen levels, karyotype, fragile X mental retardation 1 genotype (particularly if there is a family history of POI or if the woman is under 30 years old), vitamin B 12 and folic acid levels, and adrenocortical antibodies and 21-hydroxylase antibodies as a marker with the highest diagnostic sensitivity for autoimmune aetiology (25).

POI occurs in approximately 10% of cases in the context of an autoimmune polyglandular syndrome, where it is related to thyroid disease, type 1 diabetes mellitus, and Addison's disease. No relationship has been found in the presence of menopause in women with diabetes, compared to women without diabetes (26). Diabetic patients with complications due to poor glycaemic control present alterations in their menstrual cycle that could be related to oestrogen deficiency causing vascular aging, which is a determining factor in the pathogenesis of ovarian aging. Clinical studies have reported that strict glycaemic control was associated with an improvement in menstrual irregularity and fertility (27). Impairment of glucose metabolism has also been demonstrated in patients with POI, which could be a factor that facilitated the diagnosis of MODY 3 in this patient (28).

Women should start hormone therapy as soon as the diagnosis is made because this will improve vasomotor and urogenital symptoms, as well as provide favourable effects on bone and cardiovascular health. These patients should be monitored by a health professional due to the possible side effects that can develop with hormone therapy. Counselling should also be provided to patients seeking fertility, as there are currently several options. These include oocyte donation, seen as the most reasonable option. However, it is important to clarify that success rates are relatively low, so constant emotional support and accompaniment are required during treatment (5).

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Conclusions

MODY 3 is a rare form of diabetes associated with risks of micro- and macrovascular complications. We present a case of a patient with MODY 3 and POI. We did not find a genetic plausibility connecting these pathologies; however, there is a well-known association between type 1 and type 2 diabetes and POI. In addition, a known impairment of glucose metabolism has also been demonstrated in patients with POI and menopause, which could be a factor that facilitated the diagnosis of MODY 3 in this patient. Taking into account that no microvascular disease was documented in the patient, it is unlikely that this form of monogenic, autosomal dominant diabetes is responsible for microvascular complications leading to POI in this woman. It is important to bear in mind the differential diagnosis of MODY in young patients with diabetes because it has key implications in treatment and prognosis.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/relative of the patient.

Author contribution statement
Mauricio Alvarez: Assessment of the patient and preparation of the manuscript. Alejandra Alvarado: Assessment of the patient and preparation of the manuscrip. Oswaldo Rincón: Preparation of the manuscript. Francisco Puentes: Preparation of the manuscript.

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