CASE REPORT

Primary male factor infertility due to asthenospermia in maturity-onset diabetes of the young type 5 (MODY 5): uncommon presentation of an uncommon disease

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SUMMARY

Mutations in hepatocyte nuclear factor-1 β gene result in a multisystemic syndrome where a monogenic form of diabetes (maturity-onset diabetes of young type 5; MODY 5) and renal anomalies, usually bilateral multiple cysts are the most characteristic findings. Many of them have pancreatic structural abnormalities as well. A plethora of extrapancreatic manifestations like altered liver function tests, hypomagnesaemia, hyperuricaemia with/without gout and urogenital malformations, particularly in females are also components of the syndrome. Structural malformation of male urogenital tract is rare in MODY 5, even rarer is asthenospermia. We encountered a young non-obese individual having insulin-requiring diabetes following secondary oral agent failure with primary male factor infertility secondary to asthenospermia. A suggestive family history, lack of acanthosis, negative pancreatic autoimmunity, hypomagnesaemia, bilateral renal and epididymal cysts, and absence of body and tail of pancreas pointed towards underlying MODY 5.

BACKGROUND

Maturity-onset diabetes of the young (MODY), initially recognised by Tattersall in 1974,¹ is an autosomal-dominant monogenic form of young-onset diabetes that is typically diagnosed before 25 years of age; however, diagnosis may be made in older individuals as well. MODY results from mutations in one of the at least 13 genes on different chromosomes that have been reported to date and is thought to account for about 2% of diabetes.² Most of the identified mutations in the culprit genes interfere with body's ability to secrete insulin, and MODY is broadly classified into two groups: transcription factor MODY and glucokinase MODY (MODY 2). Mutation of hepatocyte nuclear factor (HNF) -1 β is associated with MODY 5, and it accounts for about 5% of all MODY cases. The HNF-1 β is encoded by human transcription factor 2 gene and is expressed in a wide variety of tissues including kidney, pancreas, genitourinary epithelium, liver and lung during embryogenesis. As a result, this particular variety of transcription factor MODY is associated with a number of extrapancreatic features, of which renal involvement is most common. Renal cysts are the most frequently detected feature of HNF-1 β associated kidney

disease, and MODY 5 is also known as renal cysts and diabetes (RCAD) syndrome. The other extra-pancreatic manifestations include abnormal liver function tests, hypomagnesaemia, hyperuricaemia with/without early-onset gout and neurological features like autism spectrum disorders and cognitive impairment. Genital tract malformations have also been described in HNF-1 β -associated disease. Females are commonly affected with various forms of uterine structural malformations secondary to abnormal development of the Müllerian ducts resulting in bicornuate uterus, uterus didelphys, rudimentary uterus or double vagina or even Mayer-Rokitansky-Küster-Hauser syndrome which includes congenital aplasia of the uterus, cervix and the upper vagina. On the other hand, genital tract malformations have rarely been reported in males, including cryptorchidism, agenesis of the vas deferens, hypospadias/phimosis, epididymal cysts and asthenospermia.³⁻⁵ HNF-1 β -associated disease is, therefore, considered to be a multisystem disorder, and all these features can be present without a family history, as half of the mutations in HNF-1 β occur de novo.³

CASE PRESENTATION

A 34-year-old man, married for 3 years and suffering from male factor primary infertility was referred for glycaemic control. He had been diagnosed with diabetes at 27 years of age and had been on insulin for the preceding 5 years for secondary oral anti-diabetic agent failure. He had a family history of diabetes in both first-degree and second-degree relatives (figure 1). Clinical examination revealed a normotensive thin-built individual having a body mass index (BMI) of 18.9 Kg/m² without clinical features of insulin resistance. Systemic examination including funduscopy was unremarkable with a testicular volume of 25 mL and bilaterally palpable vas deferens.

INVESTIGATIONS

Seminal fluid analysis done in the past has been summarised in table 1.

Recent investigations are as follows:

- ▶ Complete blood count: normal.
- ▶ Fasting plasma glucose (FPG): 189 mg/dL.
- ▶ Postmeal plasma glucose (PPPG): 168 mg/dL.

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Figure 1 Family tree of the patient. Arrow denotes the index case. Red colour denotes individuals with diabetes.

- ▶ Glycated haemoglobin (HbA1c): 8.9% [National Glycohaemoglobin Standardization Program (NGSP)]; 74 mmol/mol [International Federation of Clinical Chemistry (IFCC)].
- ▶ Pancreatic autoantibodies: negative.
- ▶ Postmeal c-peptide: 0.9 ng/mL (reference: >1.8 ng/mL).
- ▶ Creatinine: 1.3 mg/dL.
- ▶ Urine microscopy: urine protein positive.
- ▶ Magnesium: 1.4 mg/dL (reference: 1.6–2.5).
- ▶ Uric acid: 7.1 mg/dL (reference: 3.5–7.2).
- ▶ Triglyceride: 178 mg/dL; high-density lipoprotein cholesterol (HDL-c): 41 mg/dL.
- ▶ Alanine aminotransferase: 34 U/L (reference 9–43); aspartate aminotransferase: 38 U/L (reference: 0–40)
- ▶ Ultrasonography (USG) abdomen: non-visualisation of body and tail of pancreas. Multiple cysts were seen in both renal cortices. On the right side, the largest cyst was 9×11 mm, and on the left side, the largest cyst had a diameter of 12×12 mm (figure 2).
- ▶ USG of scrotum: multiple cysts were seen in head, body and tail regions of both epididymides, largest one having a diameter of 8×21 mm (figure 2).
- ▶ CT and MRI scans of abdomen: multiple renal cysts and absence of body and tail of pancreas (figure 3).
- ▶ Testosterone, prolactin, follicle stimulating hormone (FSH), luteinising hormone (LH): normal.

TREATMENT, OUTCOME AND FOLLOW-UP

At presentation, the patient was on twice daily premixed insulin. Insulin was continued at the same dosage, and metformin was added which was gradually increased to 2 g/day. Magnesium supplementation was given. After 3 months of presentation, his glycaemic parameters fell within target range (FPG: 110 mg/dL, PPPG: 156 mg/dL; HbA1c: 6.8%).

DISCUSSION

Patients with MODY are often misdiagnosed as type 2 diabetes, particularly if hyperglycaemia is first detected in adulthood. A number of reasons like increasing prevalence of diabetes among youths, positive family history of diabetes, lack of characteristic clinical features and therapeutic response to insulin secretagogues add to this confusion. Similarly, if they present in their early teens, the default diagnosis is usually type 1 diabetes, and they are put on insulin, sometimes with multiple daily injections a day. Given the absence of a typical phenotype and the cost of genetic analysis, it is indeed a challenge to distinguish MODY from the large number of people with young-onset type 2 and type 1 diabetes. In the absence of genetic studies, certain biochemical and radiological parameters are however helpful to the clinicians working in resource-restricted settings to suspect MODY and its types. These include low renal glucose threshold, low C-reactive

Table 1 Summary of seminal fluid analysis

	28/08/2015	07/01/2016	10/02/2016
pH	8.2	8.5	8.5
Sperm concentration	20 million/mL	15 million/mL	17 million/mL
Motility	100% non-motile	90% non-motile	100% non-motile
Morphology	10% normal	15% normal	8% normal
Fructose (Qualitative)	Present	Present	Present

Figure 2 Ultrasonography showing cysts (white solid arrows) in right (A) and left (C) epididymides. Cysts are also seen in right (B) and left (D) kidneys.

protein levels on high-sensitivity assay and high HDL-c in MODY 3; macrosomia, transient neonatal hyperinsulinaemic hypoglycaemia, low HDL-c, low lipoprotein A1 and A2 with raised low-density lipoprotein (LDL) cholesterol in MODY 1; renal cysts and renal developmental disorders along with a number of extrapancreatic features in MODY 5.⁶ Pancreatic ultrasound is another simple tool that can play an important role at times. MODY 5 is associated with pancreatic hypoplasia, agenesis of the dorsal or caudal pancreas, and MODY 8 is associated with pancreatic atrophy and increased fat content, sometimes massive, known as pancreatic lipomatosis. Though pancreatic atrophy is perhaps the most common structural pancreatic abnormality in patients with HNF-1 β mutations, complete lack of pancreatic body and tail or a slightly atrophic head along with lack of visualisation of the main pancreatic duct is characteristic. These morphological abnormalities indicate agenesis of the dorsal pancreas, the embryonic structure that gives rise to the pancreatic body,

tail and a small part of the head. Agenesis of only the pancreatic tail with preserved body and head, calcifications in the pancreatic head, however has also been reported.⁷ Moreover, presence of bilateral multiple renal cysts on USG also serves as a surrogate marker of MODY 5. In addition to MODY 5, the differential diagnoses of bilateral multiple renal cysts include early-onset autosomal-dominant polycystic kidney disease (ADPKD), autosomal-recessive polycystic kidney disease, nephronophthisis, medullary sponge kidney, idiopathic cystic dysplasia, tuberous sclerosis and von Hippel-Lindau syndrome.³ Interestingly, most patients with MODY 5 are often wrongly diagnosed to have ADPKD.

Diabetes mellitus and male factor infertility are both common disorders, and they may often coexist. Interestingly, diabetes itself can affect spermatogenesis at different steps leading to infertility, and a role of reactive oxygen species has been postulated. Sperm count, sperm concentration, total motility and progressive motility have been found

Figure 3 CT (left panel) MRI (T2 weighted) (right panel) scans denoting absent body and tail of pancreas (white solid arrow). Multiple renal cysts are also seen bilaterally.

to be significantly less in patients with diabetes compared with age and BMI-matched controls, and the abnormal seminogram has been termed as 'diabetic seminopathy'.⁸ Moreover, metformin has been shown to improve oligo-terato-asthenozoospermia in men with metabolic syndrome suggesting a possible pathogenic role of insulin resistance as well.⁹ However, presence of diabetes and infertility in young males should alert the physicians to consider certain disorders, cystic fibrosis and myotonic dystrophy in particular. Cystic fibrosis-related diabetes is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40%–50% of adults. Many of them have bilateral congenital absence of the vas deferens and/or seminal vesicles rendering them infertile. Non-palpable vas deferens, low semen volume, alkaline seminal fluid (pH >7.2) with absent/ or low fructose level should ask for genetic testing for cystic fibrosis. Patients of myotonic dystrophy may develop diabetes mellitus secondary to insulin resistance and primary hypogonadism (oligozoospermia or azoospermia with or without androgen deficiency) occurs in approximately 80% of them. Typical facies, myotonia, muscle weakness, testicular atrophy, low testosterone (in approximately 20%–40% of men) with disproportionately elevated FSH compared with LH levels are suggestive of myotonic dystrophy in patients with diabetes. Certain clinical conditions like Cushing syndrome, hereditary haemochromatosis and complex genetic disorders like Klinefelter syndrome, Down syndrome, Prader-Labhart-Willi syndrome, Laurence-Moon-Bardet-Biedl syndrome and Alström syndrome are also associated with diabetes and infertility but these patients have distinct morphology and can be diagnosed easily. Last but not the least, patients with type 1 diabetes rarely manifest primary hypogonadism as a part of autoimmune polyglandular syndrome type 2 and about 30%–50% of men with type 2 diabetes have low serum free testosterone and low or low-normal gonadotropin levels, consistent with secondary hypogonadism.¹⁰

Though a number of extrapancreatic features in addition to renal cysts have often been described in MODY 5, male urogenital structural abnormalities and asthenospermia are rare. Asthenospermia, azoospermia secondary to bilateral atresia of vas deferens and bilateral epididymal cysts were found in patients with HNF-1 β mutation.¹¹ In a study involving 27 adult individuals from 20 families with HNF-1 β nephropathy, infertility was reported in 2 of 14 males of the cohort. Congenital absence of bilateral vas deferens with cryptorchidism was found in one of them. Only one of those 14 males had bilateral epididymal and vas deferens cysts.¹² In a recently published large series of HNF1 β syndrome involving 201 adult patients (mutations (n=101) or deletion (n=100)), abnormalities have been found in 16 of 20 males investigated specifically for genital tract anomalies. Seminal abnormalities have been detected in seven, epididymal cysts in four, cryptorchidism in three, varicocele in three, enlarged seminal vesicles in two and absent vas deferens in one of these individuals.¹³ The exact mechanism of asthenospermia in patients of MODY 5 is still unknown. HNF-1 β is expressed in the male internal genital organs like epididymis, vas deferens and seminal vesicles which are derived from the Wolffian duct and also in the external genital organs like prostate and testes; so HNF-1 β supposedly play a role in sperm maturation and mutation HNF-1 β perhaps result in male factor infertility.^{14 15}

Though most of the patients of transcription factor MODY are usually responsive to sulfonylureas at least initially,

patients with MODY 5 are usually managed with insulin often initiated within the first 3 years from the diagnosis.⁵ In addition to a primary defect in insulin secretion characteristic of MODY, a component of hepatic insulin resistance is typical of MODY 5. In contrast, peripheral insulin sensitivity is preserved, suggesting an important role of metformin in managing such patients.¹⁶

Though we could not perform genetic analysis to confirm MODY 5 in this man, features like family history, lack of obesity and acanthosis, hypomagnesaemia and USG appearance of the pancreas and kidneys all point towards underlying HNF-1 β mutation.

Learning points

- Individuals with young-onset diabetes and a strongly positive family history either on paternal or maternal side without obesity, acanthosis nigricans or insulin dependence should be evaluated for maturity-onset diabetes of the young (MODY). Low normal c-peptide levels and negative pancreatic autoantibodies in insulin-treated young individuals and absence of typical diabetic dyslipidaemia (high triglycerides and low high-density lipoprotein cholesterol) in young diabetics treated with oral agents should also alert the treating physicians about possible MODY.
- Pancreatic imaging findings can guide genetic analysis and therapy for patients with suspected monogenic diabetes mellitus and should, therefore, be part of the diagnostic process for young individuals presenting with diabetes.
- Bilateral multiple renal cysts with or without atrophy of body and tail of pancreas and epididymal cysts on ultrasonography particularly if associated with hypomagnesaemia and hyperuricaemia in a young individual with diabetes is highly suggestive of MODY 5.
- A correct diagnosis of MODY and its type will allow appropriate treatment to be selected for both diabetes and extrapancreatic manifestations and result in better glycaemia control and less complications in the long run.
- Though diabetes mellitus and male infertility often coexist, physicians should be aware of clinical entities like cystic fibrosis, MODY 5 and myotonic dystrophy, particularly in a young male presenting with diabetes and infertility.

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