CASE REPORT

An Adolescent with Unexplained Diabetes Mellitus and Associated Congenital Genitourinary Anomalies: A Case Report

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ABSTRACT

Maturity-onset diabetes of the young (MODY) is a rare form of diabetes in Malaysia and globally. At least 14 recognised types are linked to different genetic mutations. Mutations in the glucokinase (GCK) gene and the hepatocyte nuclear factor 1 alpha and 4 alpha (HNF1A/HNF4A) genes account for nearly 80% of MODY cases, highlighting the importance of these genetic factors. We present a young female patient with a single right kidney, a bicornuate uterus, and diabetes mellitus. Her strong family history of diabetes and renal issues underscores the importance of recognising this diagnosis. Genetic testing is the gold standard for diagnosing MODY, but access and affordability can be challenging for patients in Malaysia.
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INTRODUCTION

Maturity-onset diabetes of the young (MODY) is a rare form of diabetes in Malaysia, as it is globally. A study indicated that among 2,429 young adults with phenotypic Type 2 diabetes, only 18 individuals (approximately 0.74%) were found to carry a pathogenic or likely pathogenic MODY variant[1]. This suggests that MODY is underdiagnosed and may be misclassified as Type 2 diabetes due to its rarity and the overlap in clinical features between the two conditions. Meanwhile, T1DM and T2DM are polygenic; MODY is caused by mutations in a single gene, making it a monogenic form of diabetes. If a parent has a gene mutation associated with MODY, there is a 50% chance that their child will inherit it [2]. It typically develops in adolescence or early adulthood, usually before age 25 [3]. Genetic testing is the gold standard for MODY diagnosis; however, it may only be readily available or affordable for some patients in Malaysia. A family history of diabetes across generations is a strong indicator.

There are at least 14 recognised types of MODY, each linked to a different genetic mutation of MODY; of these genes, mutations in the glucokinase (GCK) and hepatocyte nuclear factor 1 alpha /4 alpha (HNF1A/HNF4A) genes are responsible for nearly 80% of all cases of MODY[3].

Maturity-Onset Diabetes of Young Type 5 (MODY 5) is a rare type of monogenic diabetes caused by mutations in the HNF1β gene, which encodes the hepatocyte nuclear factor 1 beta. This condition is characterised by diabetes and various extra-pancreatic features, such as abnormalities in the kidneys and urogenital system[2].
We aim to present a case involving a young female patient who has a history of a single right kidney and a bicornuate uterus, along with a diagnosis of diabetes mellitus. A strong family history of diabetes and renal abnormalities occurring at a young age should prompt clinicians to consider this diagnosis.

CASE REPORTS

We report a case of a 17-year-old lady, referred to the[MOU3.1] Paediatric Endocrine Clinic, Hospital Universiti Sains Malaysia, with diabetes mellitus but also had associated congenital renal anomalies (right single

kidney) and Mullerian anomalies. She first presented to us at the age of 13 years old, primarily with diabetes mellitus on account of polydipsia and polyuria with loss of weight over the past one-year period. Her blood sugar level during the first review was 25 mmol/L with serum ketone 0.2 mmol/L. There was no preceding history of diabetes ketoacidosis. She was initially treated with Oral Metformin up to 1 gram twice a day, given ketone negative, and was otherwise well. Her Hba1c indicated suboptimal glycemic control with a level of 14.5%. Later, basal multiple-dose insulin therapy was introduced: SC Glargine 25 units at night and SC Apidra 10/15/15 units three times daily (1 unit/kg/day) to optimise her glycemic control. [MOU4.1]In addition, her diabetic autoantibodies were negative: Islet cell autoantibodies (ICA), Glutamic acid decarboxylase (GAD), and insulin autoantibodies with an average level of C-peptide 0.858 mmol/L (Range: 0.37-1.47 mmol/L).

At the age of 16 years old, she began having cyclical dysmenorrhea lasting three days, which led to school absenteeism. She presented to the gynaecology department on account of frequent intolerable dysmenorrhea the following year. She first attained her menarche at 12 years, and her menstrual history was unremarkable. Physical examination revealed a young lady with a BMI of 31.5 kg/m^2 above 95th centile (obese). She was in puberty with Tanner stage 4 in both breast and pubic hair, and there was no acanthosis nigricans. The first ultrasonography showed a left ovarian cyst measuring 13x10cm and a unilateral kidney cyst. A computed tomography abdominal/ pelvic scan revealed a large pelvic complex cystic mass (10.2cm x 10.2cm x 10.1 cm x 14.3 cm), likely ovarian in origin, with surrounding mass effect, and a single right kidney with the simple renal cyst—tumour markers sent for CA-125 97 U/mL and CEA 1.1 ng/mL (Figure 1 and Figure 2). Renal function tests showed normal urea and creatinine levels.

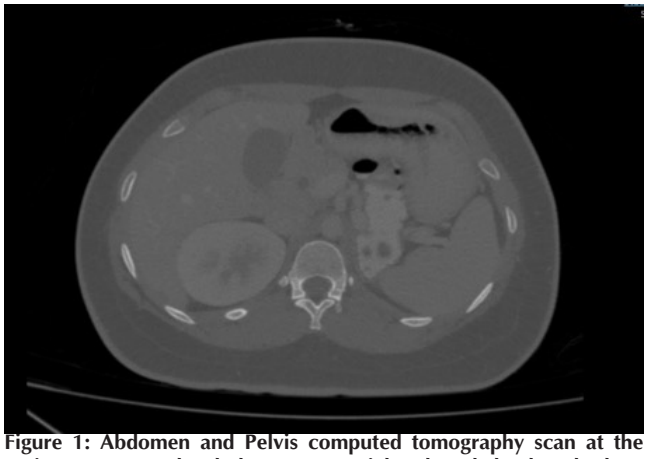

Figure 1: Abdomen and Pelvis computed tomography scan at the patient's pancreas level; the pancreas, right adrenal gland, and spleen are unremarkable. Absent left kidney and left adrenal gland. Regular enhancement of the right kidney with the extrarenal pelvis. The right renal cyst noted at the lower pole measures 1.4cm x 2.0cm. There are no complex features within. No calculus or hydronephrosis.

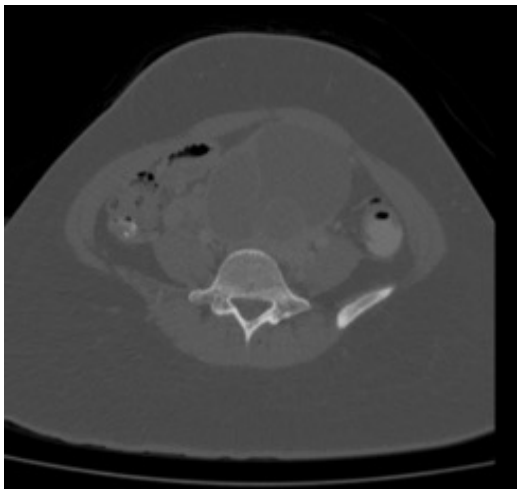

Figure 2: Abdomen and Pelvis computed tomography scan; There is large multiseptated cystic mass arising from the pelvic region. This cystic mass measures 10.2cm x 10.1cm x 14.3 cm (APxWxCC). It has thick enhancing wall measuring 0.8cm of maximum thickness (at inferior part). The septate also thickened and enhanced measuring approximately 2.4mm. There is no enhancing solid component within. No fatty components or calcifications. No solid papillary projection.

Thereafter, an exploratory laparotomy, hemi-hysterectomy, with left salpingo-oophorectomy, omentectomy, and examination under anaesthesia with diagnostic hysteroscopy, was performed, and the right ovary was spared. Intraoperative findings revealed a left endometrioma 10x10 cm, multiloculated, containing a chocolate cyst. However, they could not identify the left fallopian tube. Furthermore, the intraoperative findings showed a bicornuate uterus with a functioning uterus on the right side and a non-communicating uterus on the left side. Nonetheless, the vagina and cervix were seen. Post-operatively, it was uneventful, with good sugar levels, and she could be discharged home three days after the procedure. Additionally, histopathology findings reported left ovarian endometrioma and an endometriotic cyst of the left ovary with normal uterus morphology.

She was born full-term with a birth weight of 2 kg and an uneventful antenatal history. Her father has early onset diabetes mellitus, diagnosed at 18 years old, and was managed on short-acting insulin administered thrice daily. Her paternal uncle was diagnosed with DM in his mid-thirties and was managed with an oral hypoglycemic agent (OHA). A diagnosis of monogenic form of diabetes was suspected since she had an onset of diabetes at the age of 13 years old, absent acanthosis nigricans, positive family history with onset less than 30 years old, and renal/Mullerian duct abnormalities (Figure 3). A targeted gene panel, a whole-exome sequencing panel, was performed to test for Maturity Onset Diabetes of Young (MODY). The panel indicated a positive result for the HNF1B gene mutation c.766C>T (p.Pro256Ser), resulting in an amino acid change at codon 256 from proline to serine (p.Pro256Ser).

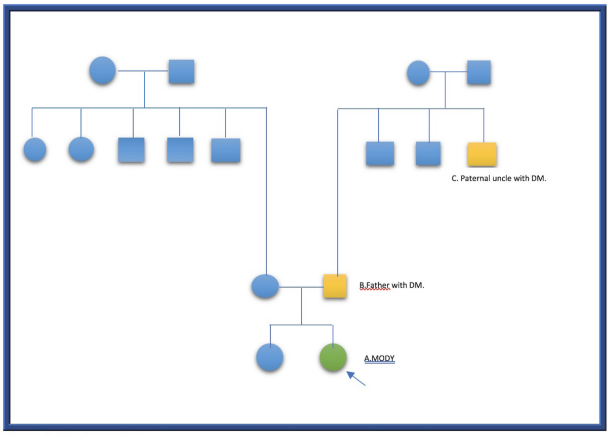

Figure 3[MOU9.1]: Family pedigree
A. Patient with MODY-5.
B. Father with DM diagnosed at 18 years old, on insulin.
C. Paternal uncle with DM diagnosed at 30 years old, on oral hypoglycemic agent.

DISCUSSION

The International Society for Paediatric and Adolescent Diabetes (ISPAD) provides comprehensive recommendations on diagnosing MODY [2]. MODY can be diagnosed if there is a family history of diabetes in parents and first-degree relatives of the affected parent in persons with diabetes who do not fit the characteristics of T1D and T2D. The disease may be inherited within families as a dominant, recessive, or non-Mendelian trait or may present as a spontaneous case due to a de novo mutation. Monogenic diabetes has been categorised as neonatal or early diabetes, MODY, diabetes associated with extra-pancreatic features, and monogenic insulin resistance syndromes.

Tattersall and Fajans proposed clinical criteria for diagnosing MODY in a diabetic patient in 1975. The requirements are as follows: i) Early onset of diabetes (diagnosed before the age of 25); ii) Early onset diabetes in at least 2, ideally 3, family members; iii) Autosomal dominant mode of inheritance; iv) Non-insulin dependence (not requiring insulin even after 5 years of diagnosis). As described by Bellanne et al., renal cyst and diabetes syndrome, or HNF1B-MODY 5, is a rare form of monogenic diabetes caused by mutations in the hepatocyte nuclear factor-1 beta (HNF-1β) gene, which accounts for about 1% of all MODY cases[4]. The HNF1B transcription factor is vital during early embryonic development in the pancreas, kidneys, liver, and genital tract.

Individuals with HNF1 B mutations rarely present with isolated diabetes despite initially being described as a rare subtype of familial diabetes. These renal issues are the primary manifestation in children, even in the absence of diabetes [2]. Some may also have genital tract abnormalities, including vaginal aplasia and a bicornuate or double vagina. Female individuals with HNF1 B face reproductive system abnormalities that can complicate pregnancy. It is crucial to implement effective management strategies, including surgical correction of structural issues, such as uterine septum resection, and thorough monitoring during pregnancy[4] [5]. While there is no universal treatment for infertility in MODY-5 patients, a proactive approach that integrates diabetes management, surgical interventions, and assisted reproductive technology (ART) is essential[5].

This case, as described above, is notable because there is a lack of typical characteristics of type 1 diabetes (no pancreatic autoantibodies, low insulin requirement for five years after diagnosis and absence of ketoacidosis) or type 2 diabetes (no signs of insulin resistance-acanthosis nigricans) in the presence of a strong family history [4]. The clue to the diagnosis of MODY 5 includes the atypical presentation of DM, but it is also associated with genital and renal anomalies. Additionally, babies born with HNF1B often have low birth weight due to decreased insulin secretion in utero, which explains her low birth weight, as noted above.

Treatment for MODY varies depending on the specific genetic mutation. Some individuals may manage their diabetes with lifestyle changes and oral medications, while others may require insulin therapy. Unlike type 2 diabetes, individuals with MODY do not necessarily produce excess insulin but may have reduced insulin production [1]. She maintained excellent glycaemic control on basal multiple dose insulin therapy with SC[MOU1.1] Glargine 25 units at night and SC Apidra 10/15/15 units three times daily (1u/kg/day), [MOU2.1] achieving an Hba1c of 6.8%, with no reported dysmenorrhea during outpatient reviews. Apart from a simple right renal cyst, there were no signs of renal impairment. The aetiology of the disease determines appropriate treatment, as effective management is essential to prevent complications and ensure optimal health for individuals with MODY.

CONCLUSION

This case highlights the significance of MODY and underscores the importance of recognising the potential overlap between diabetes, renal disorders and Mullerian anomalies, particularly in young patients, especially when there is a family history suggestive of a monogenic form of diabetes[MOU7.1]. A high index of suspicion and appropriate diagnostic testing, including genetic analysis, can lead to an accurate diagnosis of MODY 5 and guide management.

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