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CASE REPORT

A Case of 17q12 Microdeletion Syndrome in a MODY5 Type Diabetes with HNF-1β Gene Mutation Accompanied

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Abstract: Maturity Onset Diabetes of the Young (MODY) is an autosomal dominant inherited disorder prevalent among adolescents. Typically, it manifests with hyperglycemia before the age of 25. MODY5 is attributed to a mutation in the Hepatocyte Nuclear Factor-1β (HNF-1β) gene. A complete absence of HNF-1β is observed in 50% of those with MODY5. The 17q12 microdeletion syndrome closely linked with MODY5. Its incidence in the general population is around 1 in 14,500 and is linked with facial deformities, diabetes, polycystic kidneys, pancreatic hypertrophy, liver anomalies, and neuropsychological impairments. The most primary clinical signs are predominantly associated with the HNF-1β gene deletion. We chronicle the case of a male of 19 years of age diagnosed with diabetes, who, alongside persistent liver damage and polycystic kidneys, was referred from a community hospital to the Xuzhou Central Hospital. His clinical presentation included diabetes, liver dysfunction, polycystic kidneys, lipid irregularities, insulin resistance, and fatty atrophy. Subsequent genetic screening unveiled a 17q12 chromosomal deletion and an absence of the Hepatocyte Nuclear Factor-1β (HNF-1β) gene. Hence, for adolescent patients lacking a familial diabetes history but exhibiting symptoms like polycystic kidneys, liver damage, lipid irregularities, and fatty atrophy, a thorough assessment for the 17q12 microdeletion syndrome becomes imperative.

Keywords: 17q12 microdeletion syndrome, HNF-1β gene, special-type diabetes, MODY5, polycystic kidneys, liver damage

Introduction

Special types of diabetes arise from the distinct or combined effects of genetic and environmental factors on individuals. These factors ultimately lead to elevated blood sugar levels due to impaired insulin secretion from pancreatic β-cells or reduced sensitivity to insulin in peripheral tissues, known as insulin resistance. These conditions possess well-defined etiological underpinnings.[1] With continued advancements in understanding these unique forms of diabetes, new pathways emerge for both the prevention of β-cell dysfunction and the discovery of novel treatments targeting insulin resistance.

Maturity Onset Diabetes of the Young (MODY) is an autosomal dominant inherited disorder prevalent among adolescents. Typically, it manifests with hyperglycemia before the age of 25, although diagnosis can sometimes be made later in life. The disorder is characterized by an inherent defect in pancreatic β-cell function, but these cells often retain some of their functionality.[2] Though the onset usually occurs before 25, the disease progresses slowly. Its symptoms closely resemble those of standard diabetes, leading to frequent misdiagnoses as either Type 1 or Type 2 diabetes.[3] Modern molecular genetics have identified at least 14 gene mutations related to MODY, of which MODY5 is attributed to a mutation in the Hepatocyte Nuclear Factor-1β (HNF-1β) gene.[4–7] Specifically, MODY5 is triggered by a mutation in the HNF-1β gene, and a complete absence of HNF-1β is observed in 50% of those with MODY5.[8,9] Comprehensive epidemiological studies focused on the Asian demographic, especially within China, remain limited.

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The 17q12 microdeletion syndrome (OMIM: 614527), closely linked with MODY5, is characterized by polycystic kidneys, diabetes, and Müllerian duct abnormalities. This condition can either be an inherited autosomal dominant trait or result from a spontaneous deletion. Its incidence in the general population is around 1 in 14,500 and is linked with facial deformities, MODY5 diabetes, polycystic kidneys, pancreatic hypertrophy, liver anomalies, and neuropsychological impairments. The deletion covers approximately 1.4 Mb and includes 15 genes, such as HNF-1β and LHX1. The severity of clinical symptoms often aligns with the extent of gene deletions.[8,10] While the 17q12 microdeletion syndrome entails the loss of 15 genes, recent studies indicate that most primary clinical signs are predominantly associated with the HNF-1β gene deletion.[11] HNF-1β gene deletion was initially thought to be associated with renal malformations, but current studies have found an expanding phenotype of HNF-1β gene deletion that includes lower urinary tract malformations and renal magnesium wasting.[12]

Research on the 17q12 microdeletion syndrome, which includes the HNF-1β gene deletion, and its association with adolescent diabetes accompanied by polycystic kidneys, liver impairment, lipid anomalies, and fatty atrophy is sparse. In this case report, we describe the clinical manifestations and therapeutic approach for a patient with MODY5 diabetes exhibiting liver impairment and polycystic kidneys due to the 17q12 microdeletion syndrome. This contributes to broadening our understanding of the clinical presentations and variability inherent to specific diabetes subtypes, furnishing clinicians with valuable insights for evaluating and diagnosing these special types of diabetes.

Case Report

A man of 19 years of age was referred to Xuzhou City Central Hospital on July 8, 2020, presenting with symptoms of dry mouth, excessive thirst, frequent urination, fatigue, and a one-month history of weight loss. Two weeks prior, he had consulted with the local county hospital. His postprandial 2-hour blood glucose was recorded at 40 mmol/L, with an HbA1c of 17.3% and ALT of 122U/L. Urine tests showed a sugar level of 4+ and no ketone bodies. He was prescribed a regimen of 20U Regular insulin to be administered subcutaneously before meals and 30U of Detemir insulin subcutaneously at bedtime. Six days later, reevaluation revealed fasting blood glucose levels of 18.6 mmol/L and postprandial 2-hour levels of 23.97 mmol/L, with an elevated ALT at 433U/L. The patient reported no family history of diabetes, hypertension, mental illnesses, or any significant medication history. He was a full-term baby delivered via caesarean section, with a birth weight of 3.3 kg and no infectious disease history. There was no consanguinity in his family; his parents were unrelated and in good health, with no known genetic disorders, congenital anomalies, diabetes, or psychiatric conditions in their family history.

Physical Examination: Height: 180 cm, Weight: 45 kg, BMI: 13.89 kg/m2 (For context, the standard height and weight for a 17-year-old Chinese male are 172.3 cm and 60.68 kg, respectively), Abdominal circumference: 68 cm, Body temperature: 36.5°C, Heart rate: 75 bpm, Blood pressure: 115/70 mmHg. The patient displayed a noticeably slender physique with a pronounced thinness and marked subcutaneous fat atrophy. There was no observed ectopic fat deposition. Cardio-pulmonary auscultation revealed no abnormal findings. His abdomen appeared concave without palpable hepatic or splenic enlargement. He exhibited no signs of abdominal tenderness. Hair distribution in the pubic and axillary regions appeared normal, and the external genitalia did not show any evident abnormalities. Both lower extremities were devoid of edema.

Extended Medical History: From childhood, he had always been thin despite maintaining a regular diet. His height increased steadily, and he began to manifest secondary sexual characteristics around the age of 15. Growth and pubertal development occurred concurrently, but his growth had plateaued in the past half year. Historically, he had been a reserved individual, tending to avoid social interactions and speaking minimally even with family. Academically, he performed moderately and did not engage in physical activities. During the ward rounds, interactions with him were smooth, indicating reasonable communication skills.

Additional Examinations: Electromyography (EMG): No significant abnormalities detected; Ophthalmic Examination (Fundoscopy): Normal; Electrocardiogram (ECG): Presence of accelerated atrial ectopic rhythm; Abdominal Ultrasound: Liver, gallbladder, pancreas, and spleen appear normal. The right kidney shows multiple cystic formations, while the left kidney displays polycystic changes; Cardiac Ultrasound: Within normal limits; Ultrasound of the Neck and Lower Limb Vasculature: No discernible abnormalities; Chest CT Scan: Clear.

Biochemical Analysis: before treatment: Fasting blood glucose: 18.6 mmol/L; 2-hour postprandial blood glucose: 23.97 mmol/L; Routine urinalysis: glucose 4+, ketones absent; A detailed analysis of β-cell functional markers revealed: Fasting insulin: 2.55μU/mL; Fasting C-peptide: 1.31 ng/mL; 1-hour post-meal insulin: 9.97μU/mL; 1-hour C-peptide: 2.78 ng/mL; 2-hour post-meal insulin: 9.38μU/mL; 2-hour C-peptide: 3.21ng/mL. These findings suggest a compromised insulin secretion. An initial treatment with a continuous subcutaneous Regular insulin infusion was administered. Once stabilized, the regimen was modified to pre-meal Regular insulin (14U before breakfast, 18U before lunch, 18U before dinner) combined with Glargine insulin (36U, before sleep). Despite the patient's slender limbs and physique, noticeable all-over subcutaneous fat atrophy, and abnormal lipid profiles (TC: 6.58 mmol/L, TG: 1.96 mmol/L, LDL: 3.48 mmol/L, HDL: 2.15 mmol/L, Lpa: 517 mg/L, apoA1: 2.02 g/L), there was no evidence of ectopic fat accumulation. Although congenital generalized lipodystrophy was a consideration, genetic testing revealed no known mutations related to fat atrophy. Thus, treatment with Thiazolidinedione drugs (TZDs) was initiated on a tentative basis. (Table 1 displays the laboratory result and reference range).

Elevated liver enzymes were identified prior to the patient's admission. Although treatments to protect the liver and reduce enzymes were employed, the liver enzyme levels remained consistently high. Comprehensive screenings, including tests for hepatitis A, B, C, and E, thyroid function, autoantibodies, a spectrum of liver antigens, a full spectrum of antinuclear antibodies, ANCA, an exhaustive immunology panel, and a series of tumor markers all returned negative results. This excluded primary biliary cholangitis, autoimmune and viral hepatitis, suggesting persistent liver impairment. Moreover, testing for pancreatic autoantibodies (GADA, IA-2, ICA, and IAA) also came back negative, effectively ruling out T1DM.

Given the patient's distinct symptoms —diabetes, liver damage, polycystic kidneys, abnormal lipid levels, insulin resistance, fat atrophy, and the lack of developmental and behavioral abnormalities — in-depth genetic testing was deemed necessary. After securing informed consent from the patient, we extracted genomic DNA from peripheral blood leukocytes and conducted whole exome sequencing. The findings identified a copy number deletion of 1262.331Kbp in the 17q12 region, leading to a loss of the HNF-1β gene. This deletion corresponds with the 17q12 microdeletion

Table 1 Laboratory Result and Reference Range

Parameter	Result	Reference Range
PBG#	23.97mmol/L	4.0–7.8mmolL
FBG#	18.6mmol/L	3.9–6.1mmol/L
INS*	2.55μU/mL	2.6–24.9μU/mL
C-P	1.31ng/mL	1.1–4.4ng/mL
1-Hour post-mealinsulin*	9.97μU/mL	5–10 times INS
1-Hour C-peptide*	2.78ng/mL	5–6 times C-P
2-Hour post-meal insulin*	9.38μU/mL	5–10 times INS
2-hour C-peptide*	3.21ng/mL	5–6 times C-P
HbA1c#	17.3%	4–6%
GLU#	(+ + + +)	(-)
KET	(-)	(-)
ALT#	122U/L	9.0–50.0U/L
TC#	6.58 mmol/L	≤5.2mmol/L
TG#	1.96 mmol/L	≤1.7mmol/
LDL#	3.48 mmol/L	≤3.12mmol/L
HDL#	2.15 mmol/L	1.04–1.74mmol/L
Lpa#	517 mg/L	1.0–300.0 mg/L
APOA1#	2.02 g/L	1.2–1.8g/L

Notes: #Indicates a high value; *Indicates a low value.
Abbreviations: PBG, 2-hour postprandial blood glucose; FBG, Fasting blood glucose; INS, Fasting insulin; C-P, FastingC-peptide; HbA1c, glycosylated hemoglobin; GLU, Glucose; KET, Urinary Ketone body; ALT, glutamic-pyruvic transaminase; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; Lpa, lipoprotein (a); APOA1, apolipoprotein A1.

syndrome, closely matching the patient's clinical presentation, which includes MODY5 type diabetes, liver impairment, and polycystic kidneys. Subsequent CNVseq sequencing of the patient's parents showed the absence of variations in the father's chromosome 17, but a deletion in the same region of the mother's chromosome. This confirms that the mutation was maternally inherited. Given the region contains the HNF-1β gene, which is sensitive to haploinsufficiency, it was classified as a pathogenic variation.(Gene Testing Company: Shanghai Weihansi Biomedical Technology Co., Ltd; report number: 2020WES44566)

Discussion

The 17q12 microdeletion syndrome is a rare genetic disorder. Current research robustly establishes the interconnections between the HNF-1β gene mutation and this syndrome.[13] Our case report confirmed this mutation within the HNF-1β gene. The patient, diagnosed at the age of 17, exhibited diabetes accompanied by polycystic kidneys and liver damage. This aligns with the clinical indicators of young-onset diabetes. Two distinct gene tests confirmed the diagnosis as MODY5 type diabetes resulting from an HNF-1β gene deletion.

Between 2013 and 2024, a total of 41 cases of 17q12 microdeletion syndrome with HNF-1β gene mutation were reported on Pubmed.[14–21] All reported cases of this syndrome have shown different levels of abnormal kidney development, including renal agenesis and polycystic kidneys. Additionally, some patients also showed early liver enzyme abnormalities. In a report by Yoshiyuki Omura et al[20] the patient received a diagnosis of MODY5 at 23 years old. The patient presented with a range of symptoms affecting multiple systems, including liver enzyme abnormalities, renal agenesis, and pancreatic exocrine dysfunction. Gene testing confirmed a deletion of the HNF-1β gene, leading to a diagnosis of the 17q12 microdeletion syndrome, which is similar to the case we reported. Hümeyra et al[21] reported a case of 17q12 microdeletion syndrome diagnosed at 12 years of age. The patient has no obvious structural renal abnormalities, no obvious liver enzyme abnormalities, and no facial deformities. The case had hypomagnesemia and Pancreatic developmental abnormalities, and was diagnosed with an anxiety disorder and obsessive-compulsive disorder. That's different from what we reported.

HNF-1β gene mutation was thought to be associated with renal malformations. Polycystic kidneys is the most common renal cystic disease, which also includes glomerulocystic kidney disease, renal agenesis.[22] The presence of polycystic kidneys in our patient correlates with the clinical manifestations of the 17q12 microdeletion syndrome. In addition to being associated with renal malformations, HNF-1β gene mutation is also associated with renal magnesium wasting.[12] HNF-1β is important for the expression of FXYD2, a subunit of Na+/K+-at pase involved in Mg reabsorption in distal convoluted tubules.[23] In our case there was no serum electrolyte imbalance such as hypomagnesemia. HNF-1β gene mutation is are usually associated with pancreatic hypoplasia. Pancreatic hypoplasia causes insulin deficiency, which leads to diabetes.[24] The presence of diabetes in our patient correlates with the clinical manifestations of the 17q12 microdeletion syndrome. Therefore, it's imperative to undertake routine monitoring of blood glucose levels, renal function, electrolytes, kidney ultrasounds, and to assess potential diabetes-related complications.[11]

In contrast to patients with HNF-1β mutations, those diagnosed with the 17q12 microdeletion syndrome typically have a lesser BMI and ofttimes claim insulin therapy.[10] This could elucidate our patient's below-average BMI, lean physique, and dependence on insulin treatment.

The patient's persistent liver damage is potentially attributable to the liver disease associated with the 17q12 microdeletion syndrome. It's noteworthy that this form of liver disease is a predominant feature in approximately 65% of patients with spontaneous HNF-1β gene mutations. Elevated aspartate aminotransferase (AST) and alkaline phosphatase (AP) levels, occasionally coupled with slight hyperbilirubinemia, are distinguishing traits of this liver disease.[23] Abnormal liver imaging outcomes, as evaluated via ultrasound or CT scans, are rare and typically non-specific.[24] Consequently, we advocate for consistent monitoring of any structural and functional anomalies, with a cautious approach to potential hepatotoxic substances.

Patients with HNF-1β gene mutations have an elevated risk for neurodevelopmental disorders, especially autism spectrum disorder (ASD).[25] In patients with 17q12 microdeletion syndrome, cases of learning disorder, ASD, global developmental delay were observed.[26,27] Additionally, it has been reported that facial dysmorphism may be present in some patients with 17q12 microdeletion syndrome.[8] Significantly, our diagnosed patient with the 17q12 microdeletion

syndrome did not present other severe anomalies like short stature, speech delay, developmental disorders, facial dysmorphism, or any traits suggestive of psychopathological conditions or autism.

Conclusions

This case study sheds light on the clinical presentation and therapeutic interventions for patients with the 17q12 microdeletion syndrome, further enriching our grasp of the clinical spectrum and variability inherent to special-type diabetes, thereby offering valuable insights for its assessment and diagnosis. Especially in adolescent diabetes patients lacking a familial history and exhibiting distinct clinical markers (such as polycystic kidneys, liver impairment, lipid anomalies, and fatty atrophy), the possibility of the 17q12 microdeletion syndrome should remain on the diagnostic radar.

Data Sharing Statement

The data used is already included in the article.

Ethics Approval and Consent to Participate

The case report was reviewed and licensed by the ethics committee of the Central Hospital of Xuzhou. We obtained written consent from the patient for the publication of their details. All the personal information is anonymized.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests for this work.

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