CASE REPORT

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A Case of Diabetes Mellitus Type MODY5 as a Feature of 17q12 Deletion Syndrome

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What is already known on this topic?

The hepatocyte nuclear factor-1-beta (*HNF1B*) gene, is important in the regulation of tissue-specific gene expression so that mutations in *HNF1B* may lead to organ abnormalities. However, *HNF1B* mutations may be difficult to diagnose as there is a large phenotypic variation. The 17q12 microdeletion syndrome, also termed 17q12 deletion syndrome, is a rare chromosomal anomaly caused by the deletion of a small amount of material from a region in the long arm of chromosome 17. It is typified by deletion of more than 15 genes, including *HNF1B*, resulting in organ abnormalities and neurodevelopmental disorders.

What this study adds?

In case of clinical suspicion of *HNF1B* variants, further genetic examination using other techniques such as MLPA and CGH array may be required to detect the variant. This is because deletions and duplications may not be detected using next generation screening panel techniques.

Abstract

Maturity onset diabetes of the young (MODY) is characterized by noninsulin-dependent diabetes diagnosed before the age of 25 years with an autosomal dominant inheritance. Rare mutations in the hepatocyte nuclear factor-1-beta (*HNF1B*) gene produce a syndrome that resembles MODY. About half of patients diagnosed with MODY type 5 due to *HNF1B* variants, carry a whole gene deletion, known as 17q12 deletion syndrome. 17q12 deletion syndrome is a rare chromosomal anomaly and is typified by deletion of more than 15 genes, including *HNF1B* resulting in kidney abnormalities and renal cysts, a diabetes syndrome and neurodevelopmental or neuropsychiatric disorders. A 12-year-old girl was referred after high blood sugar was detected in the hospital where she presented with polyuria and polydipsia, which had persisted for one month. Her serum magnesium (Mg) level was low at 1.5 mg/dL (normal value 1.6-2.6) and glycated hemoglobin was 14% (normal value 3.6-5.8) concurrent with a c-peptide of 1.54 ng/mL (normal value 0.8-4). MODY5 was suspected but the NGS gene panel (*ABCC8, BLK, CEL, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEUROD1, PAX4, PDX1, RFX6, ZFP57, GLIS3, FOXP3, NEUROG3, G6PC2*) did not identify any abnormality. During follow-up, her serum Mg remained low (1.2 mg/dL) together with elevated urinary Mg excretion at 172.5 mg/day. An *HNF1B* variant was again suspected in a patient with chronic hypomagnesemia with normal basal C peptide level. Abdominal computed tomography and magnetic resonance imaging revealed a 43 mm diameter, cystic lesion in the head of the pancreas, with agenesis of the pancreatic neck, trunk and tail. Genetic testing using a microarray analysis was subsequently performed and a heterozygous deletion at 17q12, including *HNF1B*, was detected. In case of clinical suspicion of *HNF1B* variants, further genetic examination using other techniques such as MLPA and CGH array may be required to detect the variant. This is because deletions and duplications may not be detected using next generation screening panel techniques.

Keywords: MODY5, 17q12 deletion, diabetes mellitus, hypomagnesemia

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Introduction

Maturity onset diabetes of the young (MODY) is a clinically heterogeneous disorder characterized by noninsulin-dependent diabetes diagnosed at a young age (<25 years) with an autosomal dominant inheritance. MODY results from heterozygous mutations in various transcription factors acting in the development and function of pancreatic beta cells (1). Mutations in hepatocyte nuclear factor-1-alpha (*HNF1A*) and the glucokinase (*GCK*) gene are most commonly identified (2). Rare mutations in the hepatocyte nuclear factor-1-beta (*HNF1B*) gene produce a syndrome that resembles MODY and has been termed MODY5 (3).

HNF1B has an important role in the regulation of tissue-specific gene expression and mutations in *HNF1B* may lead to organ abnormality in both pancreas and kidney. Affected patients can develop a variety of manifestations in addition to early-onset diabetes. These include pancreatic atrophy, which may be evident on computed tomography (CT) scan, and abnormal renal development, which may be visible as renal dysplasia on ultrasonography in the fetus. There may be single or multiple renal cysts, glomerulocystic disease, oligomeganephronia (a form of renal hypoplasia) and slowly progressive renal insufficiency. Other abnormalities may include hypomagnesemia, elevated serum aminotransferases, and genital abnormalities, such as epididymal cysts, atresia of vas deferens, and bicornuate uterus (4). Almost half of patients diagnosed with MODY5 (*HNF1B* mutation) harbor a whole gene deletion (5). 17q12 microdeletion syndrome, also known as 17q12 deletion syndrome, is a rare chromosomal anomaly caused by the deletion of a small amount of material from a region in the long arm of chromosome 17. It is typified by deletion of more than 15 genes, including *HNF1B*, resulting in kidney abnormalities and the renal cysts and diabetes syndrome, with neurodevelopmental or neuropsychiatric disorders (6).

Here, we report a patient presenting with MODY5 diabetes who was eventually diagnosed with 17q12 deletion syndrome identified by microarray analysis.

Case Report

A 12-year-old girl was referred to our clinic, after high blood sugar was detected in the hospital where she attended because of polyuria and polydipsia of one month standing. She was born at term weighing 2250 g [-2.5 standard deviation (SD)] by normal spontaneous vaginal delivery. There was no family history of diabetes mellitus (DM). On physical examination, her body weight was 45 kg [0.29 SD score (SDS)], height 149 cm (-0.81 SDS), body mass index (BMI) 20.0 kg/m^2 (0.18 SDS), and vital signs were stable. There was no acanthosis nigrigans. On admission, random blood glucose level was 429 mg/dL, blood ketone was 2.2 mmol/L with normal blood pH. Of note, serum magnesium (Mg) level was low at 1.5 mg/dL (normal value 1.6-2.6 mg/dL). Her hemoglobin A1c was 14% (normal value 3.6-5.8%) and her C-peptide was within the normal range at 1.54 ng/mL (normal value 0.8-4 ng/mL). She was initially treated with basal-bolus insulin regimen and oral Mg treatment. Subsequently, her Mg level increased to 1.9 mg/dL. Type 2 DM was not considered because the patient did not have obesity and there were no signs of insulin resistance, such as acanthosis nigricans, hypertension, or hirsutism. Early-onset DM or MODY were considered in the differential diagnosis. Anti-GAD antibody was negative. Although there was no family history of diabetes in three generations, based on the other findings, MODY5 was suspected. Her DNA was extracted and tested on a next generation sequencing (NGS) gene panel including *ABCC8, BLK, CEL, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEURODD1, PAX4, PDX1, RFX6, ZFP57, GLIS3, FOXP3, NEUROG3,* and *G6PC2*. However, no abnormality was detected on this screening panel. The patient was followed up with 1 U/kg/day basal bolus insulin therapy. When she was 16 years old, she developed morbid obesity (BMI 39.1 kg/m^2). Physical examination revealed clinical signs of insulin resistance, including acanthosis nigricans and hypertension. Her C-peptide level remained normal at 3.04 ng/mL when postprandial blood sugar level was 391 mg/dL. Her mother had been diagnosed with type 2 DM one year previously. Therefore, metformin was started (500 mg/day) considering type 2 DM, but she could not tolerate the treatment due to abdominal cramps. When she was 17 years old, the patient complained of numbness in the hands and feet. Her serum Mg level was found to be low (1.2 mg/dL) and her urinary Mg excretion was high at 172.5 mg/day. *HNF1B* gene mutation was again considered in this patient with chronic hypomagnesemia with increased basal C-peptide level. Targeted diagnostic work up with abdominal CT and magnetic resonance imaging (MRI) revealed a 43 mm diameter, cystic lesion in the head of the pancreas, accompanied by agenesis of the pancreatic neck, trunk and tail (Figure 1). There were no renal or urinary anomalies on imaging and liver function tests were normal. Although fecal elastase was not available, there were no symptoms of malabsorption. As the earlier NGS screening panel had not detected any variant in the *HNF1B* gene, microarray analysis was performed and a heterozygous deletion of 1.63 Mb of DNA at chromosomal location 17q12, including *HNF1B*, was detected (Figure 2). No mutation was detected in her parents. In terms of accompanying anomalies, an arcuate uterus anomaly was found on pelvic MRI. When she was evaluated

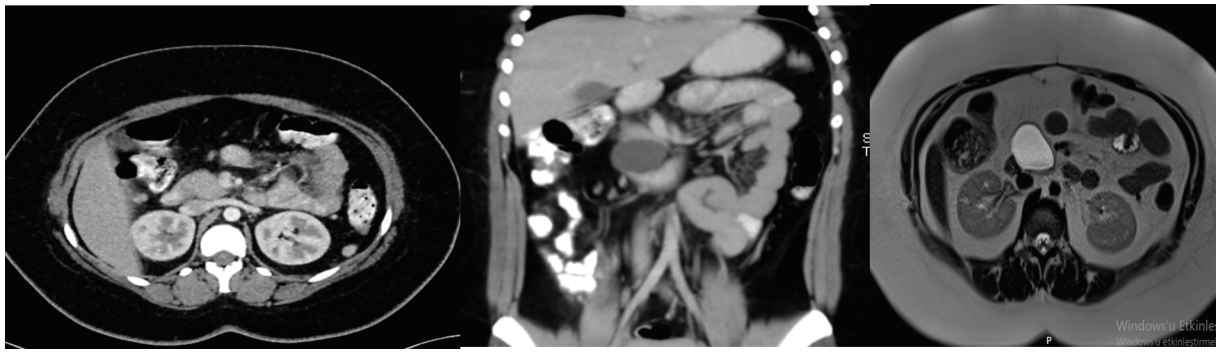

Figure 1. Abdominal computed tomography and magnetic resonance images demonstrating a cystic lesion in the head of the pancreas, and agenesis of the pancreatic neck, trunk and tail

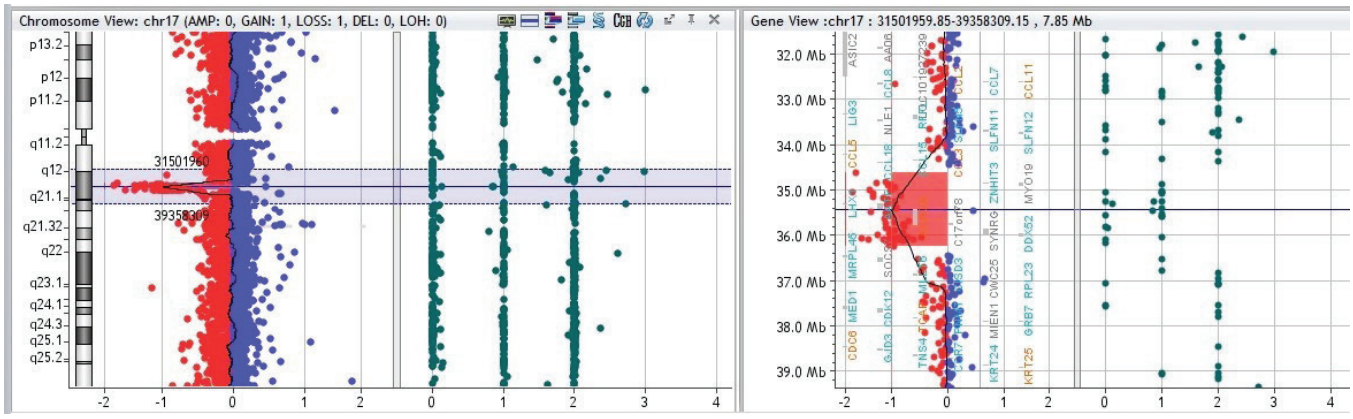

Figure 2. Microarray analysis demonstrated a prominent, heterozygous deletion of a 1.63 Mb-spanning DNA sequence at chromosomal location 17q12, which included the *HNF1B* gene

in terms of neuropsychiatric disorders that may accompany 17q12 deletion, the pediatric psychiatry clinic diagnosed anxiety disorder and obsessive compulsive disorder.

Informed consent was granted by the parents of the patient for publication.

Discussion

The presented patient was eventually found to have 17q12 microdeletion, harboring more than 15 genes, one of which was *HNF1B*. The 17q12 deletion syndrome consists of MODY5 type DM, renal malformation, impaired renal function, pancreatic malformations and neurodevelopmental/neuropsychiatric disorders. HNF1B is known to play an important role in the development of the kidney, liver, pancreas and urogenital tract during the embryonic period (7).

Renal dysfunction and anatomical malformations frequently accompany *HNF1B* mutation (8). Multicystic dysplastic kidney is the most common renal cystic disease. Apart from cystic renal disease, other renal abnormalities reported include solitary kidney, renal hypoplasia, and horse-shoe kidney (9). In the present case there were no structural renal anomalies evident. However, serum electrolyte imbalances, including hypokalemia, hyperuricemia, and hypomagnesemia are also common in patients with *HNF1B* mutations. *HNF1B* is essential for the expression of *FXYD2*, a subunit of Na^+/K^+-ATPase and is involved in the reabsorption of Mg in the distal convoluted tubule (10). These electrolyte imbalances develop with age and became apparent in late childhood. The present case had hypomagnesemia, hyperuricemia (uric acid 7,9) (normal value 2,6-6,0) with normal serum potassium levels. The low Mg level only became evident in late adolescence.

HNF1B mutation-related MODY5 DM has been reported in 63% of patients with 17q12 deletion syndrome (9). Since *HNF1B* is related to pancreatic organogenesis, variants in this gene are often associated with pancreatic malformations (11). In these cases, DM is caused by insulin deficiency due to pancreatic hypoplasia (12). However, hepatic insulin resistance also plays a role in the pathogenesis. Patients are diagnosed in adolescence and early adulthood. In a UK study, it was reported that around 24% of patients with *HNF1B* gene mutations developed DM at a median age of 12 (10,11,12,14) years (13). The presented patient was not

diagnosed with diabetes until the age of 12.5 years. In a study, it was reported that patients with 17q12 deletion syndrome had lower BMI and a greater insulin requirement at diagnosis compared to patients with intragenic *HNF1B* mutations (14). In the present case, her BMI was in the normal range at the time diagnosis, but morbid obesity developed during follow-up despite receiving high-dose insulin treatment (1 U/kg/day basal-bolus insulin at the time of diagnosis). Although diagnostic imaging demonstrated pancreatic neck, trunk and tail agenesis, there was no clinical sign or symptoms of exocrine pancreas disorder. Unfortunately, fecal elastase testing was not available.

Liver function test abnormalities including elevation of transaminases and mild hyperbilirubinemia may be seen in patients with *HNF1B* gene mutation or 17q12 deletion syndrome (15). However, the mechanism causing these abnormalities is not completely clear. Liver biopsy histology has reported increased steatosis, periportal fibrosis and hypoplastic bile duct (16). In the presented patient, there were no remarkable liver function test abnormalities.

Autism, cognitive disorders, neuropsychiatric and neurodevelopmental disorders have been reported in patients with 17q12 deletion syndrome, in contrast to patients with *HNF1B* intragenic mutations (17). Clissold et al. (17) detected neurodevelopmental disorders in patients with 17q12 deletion/without *HNF1B* mutation. On the other hand, Lim et al. (7) reported that three (21%) patients had neurologic findings of 14 patients with intragenic *HNF1B* mutations, one of which was a whole gene deletion, and the other two had missense mutations.

Of note, 17q12 deletion includes the *LHX1* and *ACACA* genes. *LHX1* is expressed in the brain in early development and therefore represents a candidate gene for the neurocognitive phenotype. *LHX1* variants have been reported to be associated with epilepsy, autism, and mental retardation (18). However, Loirat et al. (19) reported that three patients with 17q12 deletion in a large cohort of 86 patients with *HNF1B* gene abnormalities had developed autism, growth retardation and social interaction impairment over time. These patients had negative genetic tests for autism. In these three patients and 32 control patients with autism, no mutation was found in the *LHX1* gene and it was considered that autism might be an additional finding to the *HNF1B* deletion (19). The presented patient had a deletion in the *LHX1* gene and was being followed up by a child psychiatrist with diagnosis of anxiety disorder and obsessive-compulsive disorder. It has been reported that facial dysmorphism may be present in some patients with 17q12 deletion (9). However, there was no facial dysmorphism in the presented case. 17q12 deletion can be inherited as autosomal dominant or *de novo*, with 70% developing as a result of *de novo* mutation. Therefore, the absence of diabetes and other clinical features in the family does not exclude 17q12 deletion syndrome. In the presented patient, because there was no history of diabetes in three generations and no mutation was found on genetic screening panel for analysis of the parents, we strongly suspect that the mutation developed *de novo*.

HNF1B variants may be difficult to diagnose and the resulting syndrome has a large phenotypic variation. Furthermore, most of these mutations occurs *de novo*. Faguer et al. (20) developed an *HNF1B* scoring system to select patients for *HNF1B* gene analysis, based on clinical, imaging and biological variables. This scoring system consists of 17 parameters and a total score of >8 increases the probability of an *HNF1B* variant, in which case genetic analysis is recommended for these patients (20). The presented patient scored 6 points using this scoring system. As has been previously reported and when considering the presented case too, the specificity of the scoring system is low (21). In patients with 17q12 deletion syndrome, genital malformations due to unsuccessful fusion of the Mullerian ducts can be seen. It has been reported to be a risk factor for Mayer Rokitansky-Küster Hauser syndrome (22). It has been suggested that this may be related to *LHX1* mutation (23). Bernardini et al. (22) did not detect a mutation in the *LHX1* gene in the chromosome 17 on CGH array analysis of 20 patients with Mayer Rokitansky-Küster Hauser syndrome. It was reported that genital anomalies might only be seen in patients with *HNF1B* point mutations, and thus an intact *LHX1* gene. Interestingly, despite our patient having no *HNF1B* point mutation, she had arcuate uterus anomaly and an *LHX1* gene mutation.

Finally, it has been reported that *HNF1B* is required in the expression of parathyroid hormone and that *HNF1B* mutation may result in hyperparathyroidism without renal failure (24). There were no findings of hyperparathyroidism in our patient.

Conclusion

In conclusion, findings accompanying diabetes in children and should be carefully evaluated. Since 17q12 deletion is often *de novo*, monogenic diabetes should be considered in the presence of clinical findings, even if there is no family history of diabetes. In case of clinical suspicion, further genetic examination using techniques such as MLPA or CGH array, may be required since deletions and duplications may be missed on NGS panels including the *HNF1B* gene. In addition, patients diagnosed with MODY5 should be screened for 17q12 deletion sydrome, when neurological

developmental delay and/or psychiatric disorders are present.

Ethics

Informed Consent: Informed consent was granted by the parents of the patient for publication.

Authorship Contributions

Concept: Hümeyra Yaşar Köstek, Filiz Tütüncüler Kökenli, Design: Hümeyra Yaşar Köstek, Fatma Özgüç Çömlek, Emine Neşe Özkayın, Filiz Tütüncüler Kökenli, Data Collection or Processing: Fatma Özgüç Çömlek, Hakan Gürkan, Filiz Tütüncüler Kökenli, Analysis or Interpretation: Hümeyra Yaşar Köstek, Fatma Özgüç Çömlek, Hakan Gürkan, Emine Neşe Özkayın, Filiz Tütüncüler Kökenli, Literature Search: Emine Neşe Özkayın, Filiz Tütüncüler Kökenli, Writing: Filiz Tütüncüler Kökenli.

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