Case Report
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Exploring 17q12 Deletion Syndrome: A Case Report of Neurodevelopmental, Endocrine, and Genital Anomalies

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Abstract

Objective – 17q12 deletion syndrome is a rare genetic disease characterized by neurodevelopmental disorders, genital and renal abnormalities, and maturity-onset diabetes of the young type 5 (MODY5). **Case Report** – This case report details the case of a 13-year-old female with moderate intellectual disability, Mayer-Rokitansky-Küster-Hauser syndrome, multicystic dysplastic kidneys, and MODY5. Genetic testing revealed a 1.52-megabase heterozygous deletion on chromosome 17q12, encompassing the *HNF1B* and *LHX1* genes, which was found to be inherited from the mother. **Conclusion** – This case underscores the importance of early genetic testing and multidisciplinary approach in managing the multisystemic manifestations of 17q12 deletion syndrome. Early diagnosis and appropriate management are crucial for improving the outcomes and quality of life for affected individuals.

Key Words: 17q12 Deletion Syndrome ▪ Intellectual Disability ▪ Mayer-Rokitansky-Küster-Hauser syndrome ▪ Maturity-Onset Diabetes of the Young type 5.

Introduction

17q12 deletion syndrome is a rare genetic disease characterized by variable combinations of neurodevelopmental or neuropsychiatric disorders, kidney and urinary tract abnormalities, and maturity-onset diabetes of the young type 5 (MODY5) (1). Genital malformations, such as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, have also been reported (2). Less frequently, other features, such as seizures, hyperparathyroidism, and hepatopathy, can also be present (3).

This syndrome results from a recurrent 1.4-megabase (Mb) heterozygous deletion at chromosome 17q12, which can be inherited in an autosomal dominant manner or, as it most often occurs, appear *de novo* (3). This deletion involves at least 15 genes, two of which are of particular interest as they seem to explain the syndrome's major clinical manifestations: *Hepatocyte Nuclear Transcription Factor 1 homeobox b* (HNF1B) and *LIM Homeobox 1* (*LHX1*) (4, 5). Despite its high pathogenicity and penetrance, the phenotypic manifestations of 17q12 deletion syndrome are highly variable, often complicating and delaying the diagnosis. Moreover, the lack of established guidelines further challenges the management of these patients, necessitating individualized, multidisciplinary care (3).

This case report aims to provide a comprehensive clinical description of this rare genetic disorder and discuss the diagnostic and management challenges it presents.

Case Report

A 13-year-old girl was referred to a Pediatrics Neurodevelopmental consultation due to suspected

intellectual disability. The patient was born full-term via cesarean section due to non-reassuring fetal status after an otherwise normal pregnancy, except for a prenatal diagnosis of left urinary tract dilation (UTD). At birth, she required resuscitation, with Apgar scores of 4, 7 and 8 at 1st, 5th, and 10th minutes of life, respectively. The remainder of the neonatal period was uneventful, and the prenatal UTD diagnosis was not confirmed in the postnatal renal ultrasonography. No other significant past medical history was reported, except for a probable mixed receptive-expressive language disorder that was addressed with speech therapy since the age of 5.

She was the second child of two unrelated parents with significant learning disabilities. Their first child, born after a 9-year struggle with infertility, died from multiple congenital anomalies shortly after birth. The mother supposedly had type 2 diabetes and reported having her menarche only at 24-years-old. On clinical evaluation, the patient exhibited a thin appearance (<5th percentile for weight and height) and subtle dysmorphic features, including a prominent forehead, thin upper lip, winged ears, downslanted palpebral fissures, tapered fingers, and dystrophic nails. She had poor fine and gross motor skills, language and speech problems, and low tolerance to frustration. Formal cognitive assessment confirmed moderate intellectual disability (Wechsler Intelligence Scale III-R Full scale IQ score of 47). The patient had a normal karyotype (46, XX), and X-fragile syndrome was excluded.

At 15 years of age, the patient underwent an abdominal and pelvic ultrasonography due to primary amenorrhea, revealing a small rudimentary uterus, normal-appearing ovaries, and multiple bilateral renal cysts. Besides the absent menarche, the patient had complete pubertal development. The hormonal assessment (LH, FSH, testosterone, estradiol) showed a normal gonadal axis. A magnetic resonance imaging (MRI) of the abdomen and pelvis confirmed the presence of a rudimentary uterus and the absence of the superior two-thirds of the vagina, leading to the MRKH syndrome diagnosis (Fig. 1).

Array comparative genomic hybridization (Array-CGH) testing identified a 1.52-Mb heterozygous deletion on chromosome 17q12 (Fig. 2). This deletion encompasses several genes, notably

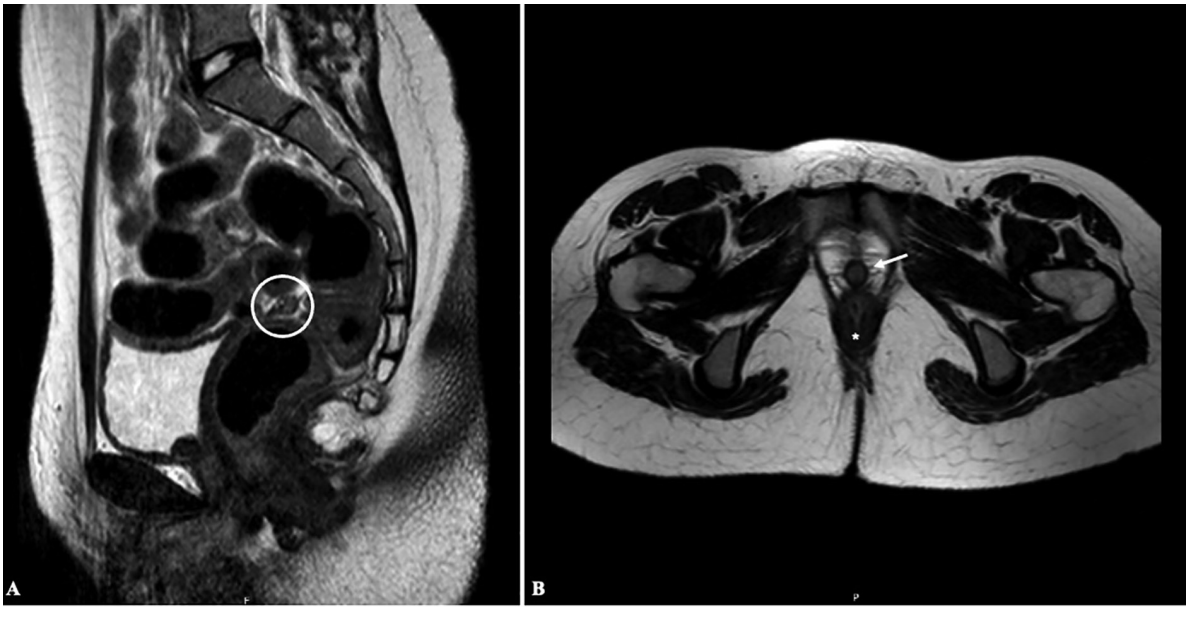

Fig. 1. *Abdomen and pelvis magnetic resonance imaging of the patient. A: Anterior to the rectum, a rudimentary uterus (circle) is apparent. B: Anterior to the rectum (asterisk), only the urethra (arrow) is evident, compatible with the absence of the superior two-thirds of the vagina.*

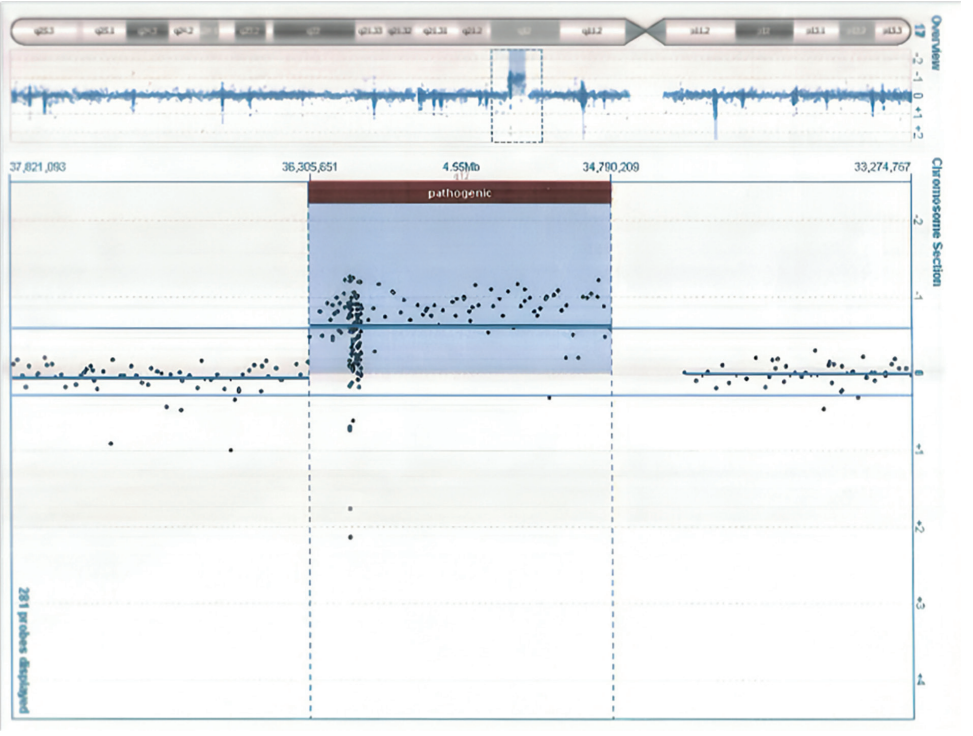

Fig. 2. *Detailed view of array comparative genomic hybridization testing highlighting a 1.52-Mb heterozygous deletion on chromosome 17q12 classified as pathogenic. The karyotype according to the International System for Human Cytogenetic Nomenclature (ISCN), 2016, is 17q12(34790209_36305651)×1.*

HNF1B and *LHX1*, and was later confirmed to be the same one carried by her mother by subsequent Array-CGH testing.

NGS genetic panel testing confirmed a heterozygous deletion of the entire *HNF1B* gene, consistent with the diagnosis of MODY5. The patient had normal fasting glucose levels but impaired glucose tolerance, leading to treatment initiation with sulfonylureas. Throughout this period, the patient maintained stable renal ultrasounds, normal kidney function, and normal arterial pressure with no other organ involvement identified.

Discussion

17q12 deletion syndrome is a rare genetic disorder that can present with a wide range of clinical features, including neurodevelopmental, endocrine, renal, and genital anomalies (6). Its estimated prevalence ranges from 1 in 14.000 to 1 in 50.000 individuals in the general population, though the syndrome may be underdiagnosed or misdiagnosed due to the variability of its phenotypic manifestations (3, 7). Table 1 summarizes the most frequently reported clinical features of 17q12 deletion syndrome in the literature (3, 6), illustrating its variable expression and situating the presented case within its known clinical spectrum.

Kidney abnormalities, often attributed to *HNF1B* haploinsufficiency, are the most commonly reported manifestations of 17q12 deletion syndrome, with multicystic dysplastic kidneys being the most frequent finding (3, 6). Other possible kidney and urinary tract abnormalities include poor corticomedullary differentiation and collecting system abnormalities, such as UTD (6). The spectrum of severity of the 17q12 deletion syndrome-associated kidney disease can range from normal kidney function never requiring kidney

Table 1. Key Clinical Features of 17q12 Deletion Syndrome

Frequency	Clinical Features	Examples
Most common (>50%)	Structural kidney and urinary tract abnormalities	Multicystic dysplasia; renal hypoplasia or agenesis; urinary tract dilation
	Functional kidney disorders	Hypomagnesemia; hyperuricemia; hypercalcemia; chronic kidney failure
	Neurodevelopmental and neuropsychiatric disorders	Intellectual disability; speech and motor delay; autism spectrum disorder; schizophrenia
	Mild dysmorphic features	High forehead; deep-set eyes; highly arched eyebrows; epicanthal folds
	Endocrine abnormalities	MODY5 slowly progressive, insulin-dependent; pancreatic hypoplasia or aplasia
	Hyperparathyroidism	
Common (25-50%)	Female & male genital malformations	MRKH syndrome; bicornuate uterus; uterus didelphys; bilateral or unilateral cryptorchidism
	Structural & functional liver abnormalities	Asymptomatic elevation of hepatic transaminase enzyme levels; intrahepatic cholestasis
	Eye abnormalities	Strabismus; hypermetropia; cataracts
Less common (<25%)	Congenital cardiac anomalies	Tricuspid/aortic insufficiency; coarctation of the aorta; ventricular septal defect
	Musculoskeletal features	Short stature; hip dysplasia; joint laxity; kyphoscoliosis
	Seizures	

MODY5=Maturity-onset diabetes of the young type 5; MRKH=Mayer-Rokitansky-Küster-Hauser.

replacement therapy to chronic kidney failure with gradual progression to end-stage renal disease, which appears to be uncommon in these individuals (3, 6). Affected patients require regular monitoring of renal function and imaging to detect any potential complications (6). Similarly to other case reports (3), this patient had stable kidney function despite multiple bilateral renal cysts.

Neurodevelopmental and neuropsychiatric disorders, including mild to severe intellectual disability, speech and motor delay, learning disabilities and, less frequently, autism spectrum disorder and schizophrenia, are also commonly reported in patients with 17q12 deletion syndrome (3, 8). The exact pathophysiological mechanisms underlying these manifestations are still unknown, but both *HNF1B* and *LHX1* gene deletions may be implicated in this neurocognitive phenotype (4–6). Global developmental delay, with later confirmation of moderate intellectual disability, was the first manifestation of the syndrome in the presented patient, highlighting the importance of genetic testing and thorough evaluation in patients with suspected neurodevelopmental disorders.

MODY5 is a rare autosomal dominant monogenic type of Diabetes Mellitus caused by *HNF1B* gene mutations. The most common mutation, identified in 50% of these patients, is a whole gene deletion, as it occurs in the 17q12 deletion syndrome (9). MODY5 typically manifests as impaired glucose tolerance in early adolescence or young adulthood (before 25 years of age) and sulphonylureas appear to be an interesting first treatment option at diagnosis. As they stimulate insulin secretion from the remaining functional beta cells, they can be effective in early-stages. However, most patients eventually progress to insulin dependency due to progressive beta-cell dysfunction and hepatic insulin resistance (6, 10). The described patient's impaired glucose tolerance was successfully managed with sulfonylureas, and, at the time of publication, this remained the only specific treatment employed. Nonetheless, given the potential limitations of sulfonylureas in MODY5's treatment, close monitoring of glucose levels is essential to adjust therapy as needed.

Genital malformations are seen in about one third of females and one quarter of males with

17q12 deletion syndrome and typically result of failed fusion of the Müllerian ducts, a process where both *LHX1* and *HNF1B* genes seem to play a role (3, 6, 11, 12). In females, the most commonly reported finding, although rare, is the MRKH syndrome, a congenital disorder characterized by the absence or underdevelopment of the uterus and upper portion of the vagina, in an individual with normal secondary sex characteristics and a normal female karyotype (3, 13). This complexity highlights the importance of considering structural anomalies of the genitourinary tract when faced with an adolescent presenting with primary amenorrhea and complete pubertal development (11).

17q12 deletion syndrome may also present with hyperparathyroidism, structural and functional liver abnormalities, and structural and exocrine pancreatic abnormalities, none of which were present in this patient (3, 6).

The diagnosis of 17q12 deletion syndrome is established by chromosomal microarray analysis, revealing a recurrent 1.4-Mb heterozygous deletion at chromosome 17q12 (3, 6). *De novo* deletions are responsible for 70-75% of cases. In the remaining cases, as in the reported one, the deletion is inherited from an affected parent in an autosomal dominant manner with high penetrance, but highly variable expressivity (3).

The follow-up of patients with chromosome 17q12 deletion syndrome typically involves regular clinical, imaging and laboratory monitoring in order to identify and address any potential complications associated with the condition. In order to do that, a multidisciplinary team, involving genetics, endocrinology, nephrology, neurodevelopment pediatrics, and gynecology, as well as supportive services such as physical therapy and occupational therapy, and special education services, is necessary (3).

Conclusion

17q12 deletion syndrome is an extremely rare multisystemic genetic disease. This case highlights the importance of genetic testing and thorough evaluation in patients with neurodevelopmental disorders, as well as the need for comprehensive, long-term multidisciplinary follow-up. Further research is needed to elucidate the pathophysiological mechanisms underlying the syndrome, understand the variability in clinical expressivity, and determine the long-term outcomes for affected individuals.

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