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Rokitanski Association and Fragile X Syndrome: A Case Report and Review of the Literature

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Abstract

Background: Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare congenital disorder characterized by agenesis or hypoplasia of the uterus and upper vagina due to Müllerian duct anomalies. Fragile X syndrome (FXS), a leading cause of inherited intellectual disability, is caused by CGG repeat expansions in the FMR1 gene and has been associated with premature ovarian insufficiency (FXPOI). **Objective:** We report a unique case of co-occurrence of MRKH syndrome and a premutation in the FMR1 gene, raising the question of a possible link between FMR1-related genomic instability and Müllerian developmental anomalies. **Case Presentation:** A 25-year-old woman with a history of delayed psychomotor development and familial intellectual disability presented with primary amenorrhea. Clinical evaluation revealed hypergonadotropic hypogonadism, absent pubertal development, neuropsychiatric symptoms, and bilateral sensorineural hearing loss. Pelvic MRI confirmed the diagnosis of MRKH syndrome. Molecular testing revealed a premutation in the FMR1 gene. **Conclusion:** This rare association between MRKH syndrome and FMR1 premutation highlights the potential role of FMR1 or related loci in embryonic morphogenesis beyond its known neurological and ovarian functions. Further studies are needed to explore the possible pathogenic link between genomic instability and Müllerian tract development.

Keywords

MRKH Syndrome, Mayer-Rokitansky-Küster-Hauser, Fragile X Syndrome, *FMR1* Gene, Premutation, Genetic Association

1. Introduction

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare congenital mal-

formation resulting from agenesis or hypoplasia of Müllerian duct-derived structures, primarily the uterus and the upper third of the vagina. The clinical presentation varies depending on the degree of developmental involvement and is typically classified into types [1]-[3].

Fragile X syndrome (FXS), on the other hand, is the most common monogenic cause of intellectual disability and serves as a prototypical example of trinucleotide repeat expansion disorders. It is associated with several clinical manifestations, including an increased risk of premature ovarian insufficiency (FXPOI) [4].

Although MRKH and FXS are traditionally considered distinct clinical entities, we report here the case of a patient presenting with both MRKH syndrome and a premutation or full mutation in the *FMR*1 gene.

This rare co-occurrence raises important questions: is it merely coincidental, or could it reflect an underlying genomic instability affecting both neural and Müllerian development? Alternatively, could *FMR*1 or other related loci play an as-yet unrecognized role in embryonic morphogenesis?

2. Case Report

We report the case of a 25-year-old female patient with a personal history of delayed psychomotor development and a family history of intellectual disability among siblings. She was admitted to our endocrinology department for investigation of primary amenorrhea.

Initial clinical examination revealed a complete absence of pubertal development, with Tanner staging assessed at P1 S1. Notably, the patient also exhibited significant hearing loss, suggesting associated sensorineural impairment, which was confirmed during further evaluation. Additionally, she presented with neuropsychiatric features, including marked hyperactivity and behavioral disturbances.

A comprehensive psychological assessment was conducted by a mental health specialist to further explore the patient's neuropsychiatric profile. This evaluation revealed behaviors and traits consistent with autism spectrum disorder (ASD), characterized notably by difficulties in social interactions, repetitive behaviors, and impairments in nonverbal communication. These findings complement the initial clinical picture marked by pronounced hyperactivity and behavioral disturbances, highlighting the complex neurodevelopmental features associated with this case.

Hormonal assessment demonstrated a hypergonadotropic hypogonadism profile, with elevated FSH and LH levels at 76 mIU/mL and 30.47 mIU/mL, respectively, and a markedly low estradiol level of 12.33 pg/mL, persistent over time. This longstanding estrogen deficiency resulted in severe osteoporosis, reflecting the chronic nature of the hypoestrogenic state.

A standard karyotype analysis was performed as an initial step in the diagnostic workup to investigate the patient's primary amenorrhea and suspected genetic abnormalities. The analysis revealed a normal female chromosomal complement of

46, XX, with no evidence of chromosomal anomalies such as Turner syndrome or mosaicism, which are common causes of gonadal dysgenesis and hypogonadism in females. Given the normal karyotype, further molecular genetic testing was pursued to explore other potential causes of the patient's clinical presentation. Subsequent analysis identified a premutation in the *FMR*1 gene, characterized by an abnormal expansion of CGG trinucleotide repeats within the gene's 5' untranslated region. This finding confirmed the diagnosis of Fragile X syndrome, a well-known genetic disorder associated with intellectual disability and, in some cases, gonadal dysfunction. The identification of this premutation provided a crucial genetic explanation for the patient's phenotype and guided further clinical management and genetic counseling.

The initial pelvic ultrasound examination failed to visualize the uterus, prompting the need for further evaluation using pelvic magnetic resonance imaging (MRI). The MRI revealed absence or hypoplasia of the Müllerian duct-derived structures, characteristic of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. These findings confirmed the diagnosis by demonstrating specific anatomical anomalies, such as the absence of the uterus and the upper third of the vagina, which are typical features of this congenital malformation.

Although this diagnosis was supported by imaging, a targeted genetic analysis to investigate known mutations or chromosomal microdeletions commonly associated with MRKH syndrome (e.g., deletions at 17q12 or mutations in genes such as *WNT*4, *LHX*1, or *HOXA*13) could not be performed due to limited resources. Therefore, the precise genetic etiology underlying the MRKH phenotype in this patient remains undetermined.

3. Discussion

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare congenital malformation, with an estimated prevalence of approximately 1 in 4500 to 5000 female births [1]. It results from agenesis or hypoplasia of structures derived from the Müllerian ducts, which are primarily responsible for the development of the uterus, cervix, and the upper two-thirds of the vagina [2].

MRKH syndrome was first described in 1829 by Mayer, who reported cases of partial or complete vaginal duplication in four stillborn infants. In 1838, Rokitansky expanded upon this description by documenting 19 cases of uterovaginal agenesis observed during autopsies of adult women, three of whom also presented with unilateral renal agenesis.

Later, in 1961, Hauser and Schreiner emphasized the importance of differentiating MRKH syndrome from testicular feminization syndrome (now known as complete androgen insensitivity syndrome), highlighting the value of karyotype analysis in this distinction.

From a genetic standpoint, the etiopathogenesis of MRKH remains only partially understood. Several studies have suggested the involvement of mutations in genes related to embryonic development (e.g., *WNT*4, *HOXA*13, *LHX*1), as well

as submicroscopic chromosomal abnormalities, such as microdeletions on chromosome 17q12. However, in the majority of cases, no identifiable genetic factor is found, suggesting a likely complex multifactorial origin [3].

The clinical presentation of MRKH syndrome may vary. It is classically classified into two types: type I (isolated form) and type II (syndromic form), which is associated with renal, vertebral, and sometimes auditory or cardiac anomalies [5].

The sensorineural hearing impairment observed in our patient is considered a secondary manifestation of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. This association can be explained by common embryological anomalies affecting not only the development of the Müllerian structures, which give rise to the uterus and vagina, but also the inner ear, leading to sensorineural hearing loss.

Congenital anomalies of the female reproductive tract encompass a broad spectrum of malformations resulting primarily from defects in the development, fusion, or resorption of the Müllerian (paramesonephric) ducts during embryogenesis. The clinical expression of these anomalies varies significantly depending on the extent of Müllerian involvement. It may range from partial or complete agenesis of the upper two-thirds of the vagina to uterine malformations such as uterine agenesis (complete absence), hypoplasia (underdevelopment), bicornuate uterus, didelphys uterus (double uterus with double cervix), or septate uterus. These anomalies may occur in isolation or in conjunction with an absence of communication between the uterus and the vagina, thereby preventing menstrual outflow through the introitus.

Moreover, due to the shared embryological origin of the genital and urinary tracts, renal anomalies are frequently associated. These may include unilateral renal agenesis, ectopic kidney, or duplication of the urinary collecting system [6].

Moreover, the ovaries are generally anatomically present and functionally normal. This can be explained by their distinct embryological origin: while uterovaginal structures arise from the Müllerian ducts, the ovaries develop from the intermediate mesoderm, specifically the urogenital ridge, making them independent from anomalies affecting Müllerian structures. As a result, the development of secondary sexual characteristics typically occurs normally, with complete pubertal progression—including thelarche and pubic hair development—despite the absence of menstruation or a functional uterus [7].

The association of MRKH syndrome with hypergonadotropic hypogonadism is rare, although it has been reported in the context of known syndromes such as Turner syndrome. To date, over 15 such cases have been described in the literature. However, no reported case has established a connection between MRKH syndrome and hypogonadism related to Fragile X syndrome, apart from the present case [8].

Fragile X syndrome was suspected in our case given the significant family history of intellectual disability affecting the patient's brother. This condition, caused by a mutation in the *FMR*1 gene, is recognized as the most common monogenic cause of inherited intellectual disability in males. Its identification is crucial in the

context of primary amenorrhea in a young woman presenting with a hypogonadotropic hypogonadism profile, as it may explain both the neurodevelopmental impairments and endocrine abnormalities observed. Differential diagnosis with Turner syndrome must be systematically excluded through standard karyotyping, thereby guiding further genetic investigations toward detecting a mutation or premutation in the *FMR*1 gene [9].

The diagnosis of Fragile X syndrome in our patient was further supported by the presence of behavioral disturbances consistent with autism spectrum disorder (ASD). This association is well documented in several meta-analyses, which have demonstrated a significantly increased prevalence of ASD among individuals with Fragile X syndrome, particularly females. These studies highlight a broad range of social difficulties, repetitive behaviors, and neurodevelopmental features, although specific clinical profiles may vary between individuals. This comorbidity underscores the importance of thorough neuropsychiatric assessment in patients with Fragile X syndrome to optimize therapeutic man The leading hypothesis suggests that anomalies in the *FMR*1 gene may directly influence the migration and embryonic development of Müllerian duct-derived structures, which are essential for the formation of the uterus, cervix, and upper third of the vagina. Disruption of this process could explain the occurrence of congenital malformations such as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome observed in some patients carrying *FMR*1 mutations [10].

Furthermore, an alternative but complementary hypothesis is that the presence of a premutation or full mutation in the *FMR*1 gene may induce genomic instability. This instability might extend beyond the *FMR*1 locus itself, affecting the function or regulation of other genes critical to reproductive tract development. Such genomic perturbations could contribute to the complex phenotypic manifestations combining neurodevelopmental disorders and congenital anomalies of the genital tract [11].

These hypotheses emphasize the importance of further research into the genetic and molecular pathways linking *FMR*1 mutations to Müllerian developmental defects. A better understanding of these mechanisms could provide crucial insights into the pathophysiology of syndromes that combine neuropsychiatric features with congenital malformations. Ultimately, this knowledge could enhance diagnostic strategies and therapeutic approaches tailored to patients presenting with these complex and multifaceted associations [12].

The leading hypothesis suggests that anomalies in the *FMR*1 gene may directly influence the migration and embryonic development of Müllerian duct-derived structures, which are essential for the formation of the uterus, cervix, and upper third of the vagina. Disruption of this process could explain the occurrence of congenital malformations such as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome observed in some patients carrying *FMR*1 mutations [13].

4. Conclusion

The rare association between Mayer-Rokitansky-Küster-Hauser (MRKH) syn-

drome and mutations in the *FMR*1 gene provides new insights into the genetic and embryological mechanisms underlying these conditions. The leading hypothesis suggests that anomalies affecting the *FMR*1 gene may disrupt cell migration or embryonic development of the Müllerian structures, thereby contributing to the pathogenesis of MRKH syndrome. Furthermore, the presence of a premutation or full mutation in *FMR*1 may induce broader genomic instability, potentially impacting other genes critical for the morphogenesis and differentiation of reproductive tissues. This genomic instability could play a pivotal role in the multisystemic manifestations observed in some patients, combining neurodevelopmental disorders with congenital malformations of the internal genital organs.

These findings emphasize the importance of an integrated approach that combines clinical, genetic, and embryological analyses to better understand the complex interplay between these factors. They also suggest that the phenotypic spectrum associated with *FMR*1 mutations may be broader than previously recognized, encompassing not only neuropsychiatric disorders, such as Fragile X syndrome and autism but also developmental anomalies of the reproductive tract.

Finally, this case highlights the necessity for further research into the genetic regulation and molecular mechanisms involved in the embryonic development of Müllerian structures, as well as the potential interactions between genes responsible for apparently distinct pathologies. A deeper understanding of these connections could pave the way for earlier diagnoses and targeted therapeutic strategies, ultimately improving the management of patients with such complex associations.

Ethical Considerations

Ethical approval was not required for this study, as it is a descriptive case report (or retrospective study, if applicable) without any interventional procedures. Written informed consent was obtained from the patient for the publication of this article, including any accompanying clinical data and images. The authors affirm that the patient's identity has been protected and all personal information has been anonymized in accordance with the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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