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Mayer-rokitansky-kuster-hauser syndrome with pituitary hypoplasia: A rare case report from Pakistan

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Abstract

Mayer-Rokitansky-Küster-Hauser Syndrome (MRKH) is a rare disorder characterized by congenital absence of the uterus and upper two-thirds of the vagina in individuals with normal secondary sexual characteristics. We present a unique case of a 15-year-old female from Pakistan with primary amenorrhea. Through comprehensive clinical evaluation and diagnostic imaging, we identified a combination of factors contributing to her condition, including 46, XX gonadal dysgenesis, MRKH syndrome type 1, and hypogonadotropic hypogonadism secondary to pituitary hypoplasia. This case sheds light on the intricate relationship between ovarian and pituitary anomalies in the context of MRKH syndrome and highlights the importance of hormonal replacement therapy for the development of secondary sexual characteristics and prevention of complications. The rarity of such co-occurrence emphasizes the need for continued research and collaboration in the field of reproductive disorders. This is the first of its kind presentation of MRKH.

Keywords: Mayer-Rokitansky-Küster-Hauser Syndrome; Mullerian agenesis; Primary amenorrhea; MRKH syndrome type 1; Pituitary hypoplasia; Reproductive tract anomalies; Congenital reproductive disorders.

Introduction

Disorders of Sex Development (DSD) are a heterogeneous group of rare conditions characterized by an abnormality of the chromosomal, gonadal, or phenotypic features that typically define sex development [1]. According to the Chicago consensus, DSDs are classified as 46, XX, 46, XY, and sex chromosome DSDs [1]. One of the DSDs in females with 46, XX karyotype is Mullerian agenesis or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, characterized by congenital aplasia of the uterus and the upper two-thirds of the vagina in a woman with normal secondary sexual characteristics affecting 1 in 5000 live female births [2].

They are of two types: Type 1 having only uterovaginal agenesis and type 2 having uterovaginal agenesis with anomalies in the fallopian tube, kidney, spine, heart and other organ amenorrhea and painful sexual intercourse [3]. The exact etiology of MRKH syndrome is not known. Previously, drugs like Diethylstilbestrol (DES) and thalidomide were said to have teratogenic causes for MRKH syndrome [4].

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Case presentation

A 15-year-old female from Pakistan presented with the chief complaint of primary amenorrhea. She is a non-smoker, non-alcoholic and consumes a mixed diet. She had no past medical history and has not undergone surgery. There was no history of amenorrhea in the first and second-degree relatives. She is a child of consanguineous parents. Her mother reported that all developmental milestones were achieved timely and had above average educational performance. She has no libido and is not sexually active. Her mother confirmed no known exposure to any medication or maternal illness during pregnancy. Other parts of the history included no visual symptoms, no headaches, no hearing loss, no significant weight changes, no postural dizziness, no polyuria, and no polydipsia.

General physical examination findings were normal. Her body weight was 40 kg, height was 140 cm, and all other vital signs were stable, i.e., the blood pressure was 110/70 mmHg, and pulse rate was 86 per minute at the time of presentation. She had no secondary sexual characteristics and had short stature. Breast examination revealed Tanner stage 1 in both breast and limited axillary hair, which is not typical for her age. Her genitalia examination revealed a prepubertal female genitalia without any ambiguity noted while urethral and vaginal orifices were seen. No facial dysmorphism or syndromic facies were observable. The patient had no features of turner syndrome like webbing of the neck or wide carrying angle. There was no skeletal abnormality and the gait was perfectly normal. Cardiovascular and neurological examination was also unremarkable and showed no abnormalities.

The complete blood count, renal, liver function tests, and serum electrolytes were within the normal range. Serum calcium and serum phosphate were also normal. And peripheral blood karyotype 46, XX with no significant copy number change on the sex chromosomes. Rest of the laboratory parameters are shown in Table 1. Hormonal levels of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), prolactin, progesterone, and testosterone levels were all measured.

Magnetic Resonance Imaging (MRI) of the pelvis revealed the uterus and ovaries were not visualized, the distal vagina appears normal. Ultrasonography was done where we came to know that she had no uterus and vagina. MRI of the pituitary gland was undergone and many significant findings were there. The MRI indicated a small sized sella with a hypoplastic pituitary gland measuring 3 cm x 4 cm and the pituitary stalk was found to be in the midline.

The diagnosis of Mayer-Rokitansky-Küster-Hauser syndrome and hypogonadotropic hypogonadism secondary to pituitary hypoplasia was made. She was started on conjugated estrogen and counseling therapy was done. Hormone replacement therapy remains the only therapeutic option. Given her young age, it was aimed at triggering the development of secondary sexual characters and prevent osteoporosis. Counselling of the patient as well as her mother's counselling was done.

Table 1: Biochemical levels with those out of range marked bold.

	Results	Reference range
FSH	0.10 mIU/ml	1.4-15.4
LH	0.36 mIU/ml	1.7-15
Estradiol	22.93 pg/ml	30-300
IGF-1	228.40 ng/ml	107-246
PRL	20.5 ng/ml	3.8-23
Cortisol	9.8 µgm/dl	5-25
TSH	2.63 mIU/L	0.4-4.2
FT4	1.1 ng/ml	0.89-1.79
Vit D	11 ng/ml	>30 ng/ml

Discussion

Primary amenorrhea is clinically defined as the non-appearance of menstruation by the age of 14, when secondary sexual traits are lacking, or by the age of 16, irrespective of the presence of appropriate growth and maturation of secondary sexual features [5].

Gonadal dysgenesis stands as a prevailing etiological factor in primary amenorrhea and concurrent absence of secondary sexual traits. Subsequently, the MRKH syndrome emerges as the subsequent contributor, characterized by uterovaginal atresia, specifically in 46, XX karyotypic females [6].

MRKH in itself is a rare condition, the frequency of type I and type II MRKH syndrome is 56-72% and 28-44%, respectively [7]. These frequency have varied in different studies between different populations. According to Deng et al, Chinese population (28.1%) had a lower type 2 MRKH Syndrome than caucasian populations (46.2%) [8]. They came to the conclusion that the spectrum of type I and type II MRKH syndrome varies across different races and geological locations.

In our case, ovarian dysgenesis, MRKH syndrome type 1, and hypogonadotropic hypogonadism all can be the cause of primary amenorrhea. The existence of pituitary hypoplasia with absence of ovaries and uterus suggests that our patient can be classified as a type 1 MRKH syndrome patient.

The co-occurrence of gonadal dysgenesis and MRKH syndrome is uncommon, evidenced by the sparse literature reporting such cases. Within these reports, individuals exhibiting 46, XX gonadal dysgenesis along with Mullerian agenesis showcased a typical female phenotype, primary amenorrhea, lack of pubertal progression, and hypergonadotropic hypogonadism. Somatic anomalies, although infrequent, were observed in a limited number of instances.

In our patient the pelvic MRI finding is suggestive of type 1 MRKH syndrome with non-visualized ovaries, the latter attributed to 46, XX gonadal dysgenesis, explaining the absence of secondary sexual characteristics.

It's worth acknowledging that for absolute certainty regarding the absence of ovaries, conducting a laparoscopic assessment would have been an ideal approach, despite the general effectiveness of MRI in evaluating their structure conclusively, it might be crucial to assess anterior pituitary function in MRKH syndrome cases. This could shed light on whether these hormone deficiencies are more prevalent or simply coincidental.

In light of the patient's proportionate short stature and po-

tential origins, such as plausible growth hormone deficiency stemming from pituitary hypoplasia, the administration of human growth hormone therapy emerges as a recommended course of action. This approach is particularly advisable for individuals with short stature attributed to growth hormone deficiency, particularly when identified at a younger age.

Given the patient's early presentation, hormone replacement therapy stands as the sole viable avenue for fostering the development of secondary sexual characteristics in our scenario. In the extended term, it would be prudent to consider the necessity of vaginal dilatation and surgical vaginoplasty. Additionally, a close monitoring of the response to estrogen therapy is warranted, with a potential adjustment of the dosage if indicated.

The diagnosis of MRKH syndrome imposes a significant psychological burden on patients because of the associated medical, psychological, and infertility issues. Assisted reproductive techniques and surrogacy can be options concerning fertility [6]. Counseling and management of psychosocial issues should be well addressed.

Numerous studies have been conducted on MRKH, yet only a single previous study has documented pituitary hypoplasia. Notably, this sole study also encompassed thyroid hypoplasia. However, in our instance, we observed normal thyroid hormone levels, setting our case apart from the entirety of existing literature. This distinction positions our case as unprecedented and pioneering in nature.

Given the numerous cases within this field, it's plausible that our case could harbor a range of plausible underlying causes. These factors might encompass relatively straightforward scenarios like mutations or deletions affecting well-known genes crucial to germ cell development and the formation of Mullerian derivatives. Alternatively, a more precise mutation, such as a microdeletion in a segment of the X-chromosome, could potentially lead to the absence or dysfunction of a critical protein. This interruption might, in turn, impede the proper development of gonadal and Mullerian structures, warranting further investigation. Moreover, considering the diverse organ involvement in our case, the influence of endocrine disruptors cannot be discounted.

Conclusion

Ovarian dysgenesis, MRKH syndrome, and hypogonadotropic hypogonadism all can be the cause of primary amenorrhea. However, 46, XX gonadal dysgenesis and pituitary hypoplasia are characterized by significant heterogeneity, and their rare coexistence poses a challenge to understanding the underlying etiology. The intricate interplay between pituitary anomalies and ovarian agenesis in these conditions raises questions about whether these manifestations stem from ostensibly pleiotropic gene (s) or closely linked genetic factors.

However, we report a rare association between 46, XX gonadal dysgenesis, Mullerian agenesis, and hypogonadotropic hypogonadism secondary to pituitary hypoplasia. To our knowledge, this is the first case reported of such a combination. The etiopathogenesis of these associations needs to be investigated. This lays down the need of a closer look into MRKH patient's pituitary size and a correlation between the two, if any.

Declarations

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest: There are no conflicts of interest.

Data availability: The reports and imaging of the patient can be accessed by emailing the corresponding author on the above-mentioned email address.

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