A Rare Case of Coexistence of Pituitary Stalk Interruption Syndrome and Mayer-Rokitansky-Küster-Hauser Syndrome

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Case report

Keywords: Pituitary Stalk Interruption Syndrome, Mayer-Rokitansky-Küster-Hauser syndrome, hypogonadotropic hypogonadism, estrogen replacement therapy

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Abstract

Background Pituitary stalk interruption syndrome (PSIS) is a rare congenital pituitary anatomical disorder. Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is characterized by congenital absence of the uterus, cervix, and part of the vagina in phenotypically normal 46, XX females.

Case presentation A young woman was initially diagnosed as MRKH syndrome based on primary amenorrhea, 46, XX karyotype, and absence of uterus or vagina. Further investigation revealed breech delivery, short stature, hypogonadotropic hypogonadism, interrupted pituitary stalk on pituitary MRI, which led to the diagnosis of PSIS. After a 12-month treatment with estradiol, no signs of uterus or vagina were found on pelvic computed tomography.

Conclusions We highlight the importance of considering PSIS in the differential diagnosis of suspected MRKH syndrome in prepubertal girls or girls with delayed or absent puberty, when no uterus is visualized on imaging.

Background

Pituitary stalk interruption syndrome (PSIS, ORPHA 95496) is a rare congenital pituitary anatomical disorder, characterized by thin or interrupted pituitary stalk, ectopic posterior pituitary, and aplastic anterior lobe [1]. Its pathogenesis remains unclear with prevalence of approximately 0.5/100000 [1].

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, also referred to as Müllerian agenesis, is characterized by primary amenorrhea, congenital absence of the uterus, cervix, and the upper part of the vagina in 46, XX females [2]. The structure and function of the ovaries are usually normal [2]. Its incidence is about 1 in 4,500-5,000 newborn females. The association between PSIS and MRKH syndrome has not been reported previously. We herein report the first case of a rare coexistence of PSIS and MRKH syndrome.

Case Presentation

A 29-year-old woman was referred to the Obstetrics Department of Peking Union Medical College Hospital, with complaints of reproductive tract malformation for 15 years and primary amenorrhea. She was diagnosed as having growth hormone deficiency (GHD) at the age of 11 and recombinant human growth hormone was administered for 2 years. Physical examination showed height of 1.37 m and weight of 36 kg. Her breast development stage was B1 and pubic hair development stage was P1 according to the Tanner stage. She had no vaginal opening and had naive vulva and normal external urethral opening. Muscle strength of the upper and lower limbs was normal. Repeated karyotype tests showed 46, XX. Pelvic enhanced magnetic resonance imaging (MRI) and uterus ultrasound showed absence of uterus or vagina, which was consistent with the diagnosis of MRKH syndrome (Figure 1). Bilateral ovaries were seen on MRI and ultrasound. Ultrasound for heart, thyroid gland, and urinary system showed no obvious abnormalities. Spine X-ray did not show any skeletal malformation. Hearing
test was normal. MRKH syndrome was diagnosed by a gynecologist. Further investigation by an endocrinologist revealed that the patient had a history of breech delivery. Her father was 1.70 m tall and her mother was 1.65 m tall. Further physical examination showed proportionate short stature and no signs of syndromic facial appearance: no hypertelorism, normal posterior hairline, and no moles on the face. Pituitary MRI showed absence of pituitary stalk, ectopic posterior pituitary, and anterior pituitary dysplasia, leading to the diagnosis of PSIS (Figure 2). Bone age was 14-15 years with nearly closed epiphysis (Supplementary Figure 1).

Laboratory examinations were carried out. Blood count, urinalysis, and liver and kidney function were normal. Triptorelin stimulation test showed that luteinizing hormone (LH) (60 min) and follicle-stimulating hormone (FSH) (60 min) were increased to 3.75 IU/L and 8.39 IU/L 60 minutes after 100 ug triptorelin was administered. Other laboratory assessments are shown in Table 1. Dual emission X-ray absorptiometry (DXA) showed that the bone mineral density value for the lumbar spine 2-4 (L2-L4) was 0.678 g/cm$^2$ (Z value -2.7 T value -3.7) and that for the femoral neck was 0.516 g/cm$^2$ (Z value -2.7 T value -3.3). Whole Exome Sequencing, including genes related to PSIS and MRKH syndrome, was carried out and no pathogenic mutations were identified which has been reported to be associated with MRKH syndrome. A benign homozygous mutation c.61G>A, p.G21S(rs2275558) in PBX1 was detected.

Oral estrace was given for 3 months at a dose of 0.5 mg per day, and it was continued for another 9 months at 1.5 mg per day. Growth hormone, 2 U per day, was subcutaneously injected. Calcitriol, 0.25 ug per day, and carbonic calcium, 600 mg per day, were given. After 12 months of treatment, her breasts gradually developed to B3 stage according to the Tanner stage. Her LH was 0.51 IU/L, FSH was 2.88 IU/L, estradiol was 37 pg/ml, and progesterone was 0.24 ng/ml. Repeated pelvic ultrasound, at an interval of three months, found no uterus enlargement after estradiol replacement therapy. Repeated pelvic computed tomography (CT) confirmed the absence of uterus or vagina after 12 months. Therefore, we considered that the patient may be suffering from PSIS combined with MRKH syndrome. Vaginoplasty was recommended.

Discussion

In our case, the patient was initially diagnosed as having MRKH syndrome due to absence of uterus or vagina on pelvic MRI and ultrasound, and 46, XX karyotype. But her short stature and hypogonadotropic hypogonadism (HH) were not coherent with the usual MRKH syndrome. Patients with MRKH syndrome usually present with normal stature and secondary sexual development [3-4]. LH and FSH are in normal range due to normal function of the pituitary-ovary axis [4]. A few cases of MRKH syndrome coexisting with Turner Syndrome, which presented with short stature and hypergonadotropic hypogonadism, have been reported [4]. However, our patient, who had normal karyotype and HH, was against the diagnosis of Turner syndrome. Additionally, MRKH syndrome coexistence with 46, XX gonadal dysgenesis has been reported [3]. However, 46, XX gonadal dysgenesis often presents with hypergonadotropic hypogonadism and absence of ovaries, as well as uterus and vagina [5], which did not support our case.
Therefore, we investigated deeper into her history and found that she experienced breech delivery at birth, which gave us a clue for PSIS. Many PSIS patients present with breech delivery and may show no uterus on ultrasound due to lack of estrogen during pubertal development [1]. The laboratory results of hypopituitarism and pituitary MRI confirmed the diagnosis of PSIS. Estrogen was then prescribed for pubertal development and development of the uterus. However, after 12 months of estrogen replacement, no uterus could be detected on pelvic CT. Therefore, we diagnosed the patient with PSIS and MRKH syndrome. Literature review revealed that PSIS coexisting with MRKH syndrome has not been reported.

Patients with HH show a small uterus on ultrasound initially, which may grow after estrogen replacement therapy. Misdiagnosis of HH as MRKH syndrome has been reported, since pelvic ultrasonography may reveal no uterus or ovaries initially [6]. The findings of pelvic ultrasound can be misleading in the evaluation of primary amenorrhea as no visualization of uterus on ultrasound can occur in delayed puberty, and it can be imprudent to establish a premature diagnosis of MRKH syndrome. Further physical examination and hormone assessment may contribute to the final diagnosis [6]. The size of uterus needs to be re-evaluated after estrogen replacement therapy for at least 6-12 months [3].

It is difficult to identify the mechanism for coexistence of these two anomalies in this patient. The mechanism behind PSIS is still under debate. Damage to the pituitary area connecting to the hypothalamus, such as breech delivery, and abnormal pituitary development caused by genetic factors are widely accepted hypotheses. Breech delivery may cause the break of pituitary axis and interruption of hormone transportation from hypothalamus to pituitary [7]. Single pituitary-specific genes, including PROP1, HESX1, OTX2, ARNT2, CHD7, PAX6, ROBO1, LHX4, and PROK2, have been reported in less than 5% of PSIS patients [1]. In our patient, no abnormal mutations related to PSIS were identified in whole exome sequencing, indicating that the cause of PSIS may arise from breech delivery.

MRKH syndrome is the second most common cause of primary amenorrhea. It is characterized by congenital absence of uterus, cervix, and upper part of vagina in normal 46, XX females. It is generally divided into two subtypes, including MRKH type 1 (OMIM 277000) featuring absence of the upper vagina, cervix, and the uterus, and MRKH type 2, associated with other additional malformations, such as renal and skeletal abnormalities [2]. MRKH type 2 also includes the subtype MURCS (Müllerian duct aplasia, unilateral renal agenesis, and cervical-thoracic somite anomalies; OMIM 601076) [2]. Our patient showed no renal or skeletal malformation; thus, she may be classified as MRKH type 1.

The etiology of MRKH syndrome is unknown. Endocrine hormone disturbance has not been reported. Although it is mainly sporadic, familial cases indicate that it may be an inherited disorder. Chromosomal abnormalities have been reported affecting chromosomes 1-7, 10-18, 22, and chromosome X. Five recurrent deletions/duplications at chromosomal regions 1q21.1, 16p11.2, 17q12,22q11.21, and Xp22 have been reported [8]. Mutations in genes, encoding anti-Müllerian hormone receptor (AMH-R) and estrogen receptors, have been hypothesized to cause MRKH syndrome [3]. Only the WNT4 gene has been confirmed to be associated in a few MRKH patients with hyperandrogenism, and most of the MRKH cases were diagnosed without genetic testing. Gene mutations, including LHX1, HNF1B, TBX6, WNT4,
WNT5A, WNT7A, and WNT9B, were candidates for MRKH syndrome [2]. Our patient showed no mutation of the above genes on whole exome sequencing, but a benign homozygous mutation c.61G>A, p.G21S(rs2275558) in PBX1 was discovered, which was reported to be associated with MRKH syndrome risk in the Chinese Han population [9]. The allele frequency of the variant is 0.2869 in the total population and 0.6329 in the East Asian population, which makes it a less convincing pathogenic mutation.

To date, we could not identify the direct genetic link between PSIS and MRKH syndrome. We suppose that PSIS was caused by breech delivery, while the cause for MRKH syndrome remains unknown.

**Conclusions**

We therefore report the first unusual coexistence of PSIS and MRKH syndrome to provide more evidence for the understanding of these two rare diseases. We highlight the importance of considering PSIS in the differential diagnosis of suspected MRKH syndrome in pre-pubertal girls or girls with delayed or absent puberty or short stature, when no uterus is visualized on imaging.

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

**Availability of data and material**

Not applicable

**Competing interests**

The authors declare no competing financial interests.

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**Authors' Contributions**
Methodology and original draft preparation, Ma Wanlu; Data collection and follow-up, Ma Wanlu and Wang Xi; Writing—review and editing, Wang Xi, Mao Jiangfeng, Nie Min and Wu Xueyan; Conceptualization and funding acquisition, Wu Xueyan. All authors have read and agreed to the published version of the manuscript.

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Tables

Table 1. Laboratory assessments before treatment and 12 months later
| Hormones                  | Baseline | 12months later | Reference range   |
|---------------------------|----------|----------------|------------------|
| LH(0min) (IU/L)           | 0.71     | 0.51           | 1.2-8.6          |
| FSH(0min) (IU/L)          | 3.69     | 2.88           | 1.3-19.3         |
| LH (60min)(IU/L)          | 3.75     | -              | 12.6-48.8        |
| FSH (60min)(IU/L)         | 8.39     | -              | 11.8-24.3        |
| Estradiol (pg/ml)         | 23       | 37             | 47               |
| Progesterone (ng/ml)      | 1.0      | 0.24           | 0.10-0.84        |
| Testosterone (ng/ml)      | 0.2      | 0.19           | 1.75-7.81        |
| Prolactin (ng/ml)         | 6.8      | 7.7            | 2.6-13.1         |
| β-HCG (IU/l)              | 0.16     | 0.32           | 5.0              |
| FT4 (ng/dl)               | 0.97     | 0.70           | 0.81-1.89        |
| FT3 (pg/ml)               | 2.25     | 2.78           | 1.80-4.10        |
| TSH (uIU/ml)              | 1.386    | 1.571          | 0.38-4.34        |
| IGF1 (ng/ml)              | 36       | 117            | 101-267          |
| Growth hormone (ng/ml)    | 0.1      | 0.1            | < 2.0            |
| F (8am) (ug/dl)           | 22.1     | -              | 4.1-22.3         |
| 17a-OHP (ng/ml)           | 0.86     | -              | 0.31-2.17        |
| Fasting insulin (uIU/ml)  | 6.6      | 4.3            | 5.2-17.2         |
| TC                        | 6.26     | 5.26           | 2.9-5.7          |
| TG                        | 0.79     | 0.80           | 0.45-1.81        |
| LDL-C                     | 3.91     | 3.14           | 2.07-3.12        |

LH: luteinizing hormone; FSH: follicle-stimulating hormone; LH(60min) and FSH(60min): gonadotropins levels 60 minutes after triptorelin stimulating test;

β-HCG: β-chorionic gonadotropin; FT3: free triiodogonine; FT4: free thyroxine; TSH: thyrotropin; IGF-1: insulin-like growth factors-1; F: serum free cortisol; 17a-OHP: 17a hydroxyl-progesterone; TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol.