Clin Pediatr Endocrinol 2019; 28(4), 135–138
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Case Report

Uterus in mixed gonadal dysgenesis was detected by continuous irregular vaginal bleeding

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Abstract. Disorders of sex development (DSD) are a group of congenital conditions presenting with differences in the chromosomal, gonadal, or anatomic sex development. Evaluating the chromosomes, gonads, and internal and external genitalia of the patients is important for understanding DSD. Furthermore, confirming the presence of a uterus is essential for the assessment of the internal genitalia status. Although the uterus can be identified by ultrasonography, magnetic resonance imaging, or laparoscopy, it may be easily overlooked. Here, we report the case of a patient with mixed gonadal dysgenesis, in whom the presence of a uterus could not be confirmed before the initiation of estrogen replacement therapy despite the performance of various tests. The detection of the uterus was prompted by an atypical genital bleeding. This case implies that physicians may have difficulties identifying the uterus in female patients with DSD before the initiation of estrogen treatment.

Key words: disorders of sex development, uterus, mixed gonadal dysgenesis, prepubertal, atypical genital bleeding

Introduction

Disorders of sex development (DSD) represent a group of congenital conditions characterized by atypical development of the chromosomal, gonadal, or anatomic sex (1, 2). DSD primary symptoms include the presence of ambiguous genitalia and the delayed onset of puberty. The evaluation of the internal genitalia by ultrasonography, magnetic resonance imaging (MRI), or laparoscopy is vital for understanding the pathophysiological mechanisms underlying the disorder.

The small size of the uterus in prepubertal individuals can impede its identification. However, endogenous and exogenous estrogens increase the uterus size. Therefore, imaging assessments should be undertaken repeatedly.

The accurate assessment of the uterus is clinically important for young patients receiving estrogen replacement therapy, since the uterus size plays a crucial role in predicting the onset of menstruation. Although rare, in the presence of a cervical stenosis or atresia, the possibility of an acute abdomen should be considered.

Herein, we present the case of a patient with mixed gonadal dysgenesis. During the initial examinations in the early stages of the disorder,

Received: December 12, 2018
Accepted: June 26, 2019
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the uterus was considered absent; however, the uterus was detected after the initiation of estrogen replacement therapy.

Case Report

A neonate with ambiguous genitalia was admitted to a pediatric hospital in Japan. A pelvic ultrasound examination revealed the presence of a streak gonad in the left half of the abdominal cavity and a testis in the right inguinal canal. No uterus was observed. The karyotype was 45,X/46,X + dic (Yp), indicating the definitive diagnosis of mixed gonadal dysgenesis (MGD). The patient was assigned female gender by the physicians, after discussing the condition with the parents (Table 1).

No uterus was detected during the removal of the left gonad by laparoscopic surgery. The patient underwent a right orchiectomy at 1.5 yr of age and a vaginoplasty at 4 yr and 7 mo of age. She was referred to our hospital for a follow-up.

The patient's growth curve is shown in Fig. 1. Her feminizing genitoplasties were performed at 8, 9, and 11 yr of age. An LH-releasing hormone (LHRH) test conducted at 9 yr of age showed peak LH and FSH levels of 36.68 mIU/ml and 53.24 mIU/ml, respectively. Primary hypogonadism was diagnosed, and conjugated estrogen therapy was initiated by a dose of 0.3125 mg weekly at 9 yr of age; the dose was gradually increased to 0.625 mg daily by 16 yr of age. The uterus was not detectable by either ultrasonography or MRI at the initiation of estrogen treatment. Thus, due to the assumed uterus absence, no progesterone derivative was administered (Fig. 1).

An atypical genital bleeding of seven months' duration, starting at 16 yr of age, prompted the performance of a transvaginal ultrasonography, a vaginography, and an MRI, and a uterus was detected (Fig. 2). Estrogen breakthrough bleeding was identified as the cause of the irregular vaginal bleeding and the therapy was supplemented with progesterone. Following this treatment, the patient's menstrual cycle normalized.

Table 1. Disorders of sex development (DSD) assessment of the present case during the neonatal period

	Assessment
Suggested gender	Female
Karyotype	45,X/46,X + dic (Yp)
Gonads	Left streak gonad Right testis in the inguinal canal
Internal genitalia	Uterus (–)
External genitalia	Clitoral length 3 cm Vaginal opening (+)

Discussion

This case highlighted the difficulties associated with uterus identification before puberty in individuals with DSD. The patient's uterus could not be detected during preadolescence by ultrasonography, MRI, or laparoscopy; the diagnosis of breakthrough bleeding was delayed considerably due to the assumption that the patient had no uterus.

The ability to visualize the uterus is limited, even with the assistance of various examinations. A retrospective review of young female patients with the presumed diagnosis of uterine agenesis showed that the uterus identification was delayed (3). In this review, both methods, which initially failed to detect the uterus, and those, which finally enabled its identification, were described; invasive methods, such as laparotomy, were included as initial investigations. In some cases, the presence of a uterus became apparent only after 6 mo of estrogen administration.

Uterine development depends on the presence of endogenous and exogenous estrogen. A previous report demonstrated that estrogen replacement therapy is effective in increasing the uterine size in adult patients with Turner syndrome with primary amenorrhea in a manner resembling the uterine development in spontaneous puberty (4). However, another study reported that most patients with Turner

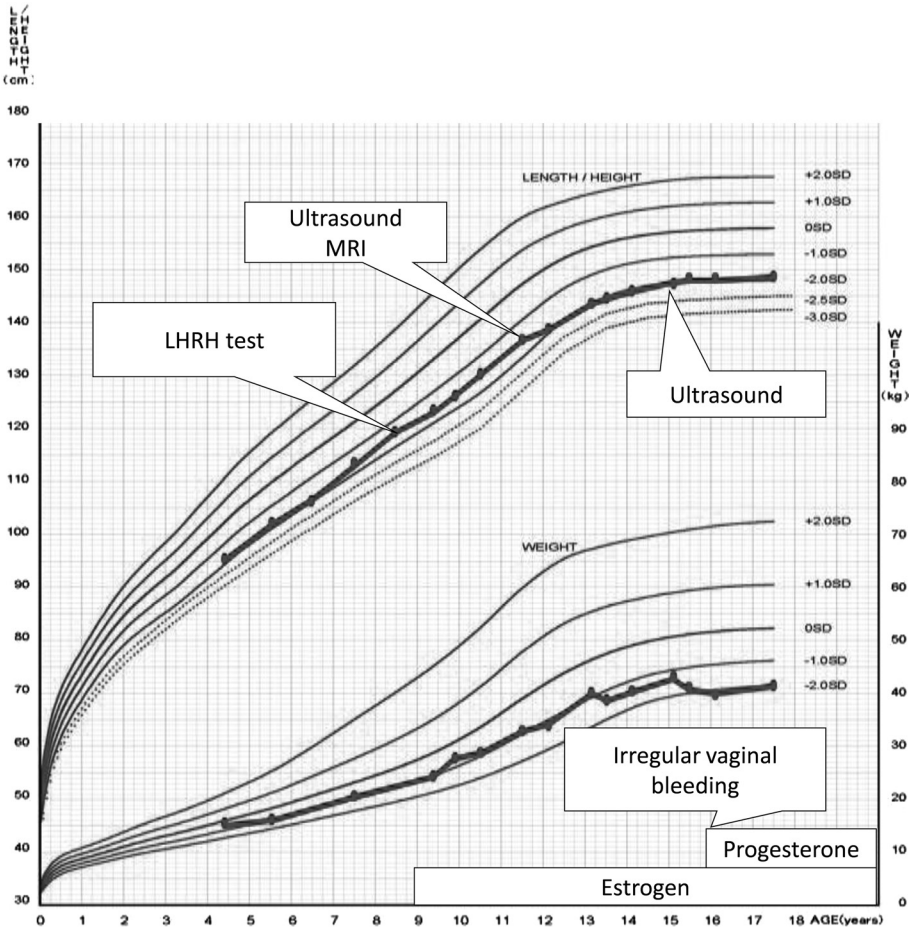

Fig. 1. Growth curve and the process of uterus identification in the patient. A uterus could to be detected during the early stages of the disorder despite the use of ultrasonography, vaginography, and MRI. Primary hypogonadism was diagnosed based on the findings of an LH-releasing hormone stimulation test, and conjugated estrogen treatment was initiated at 9 yr of age. Irregular vaginal bleeding started at 16 yr of age.

syndrome, receiving estrogen replacement therapy, have smaller uterine size than healthy women (5), which was also true for the case described in the current report.

Since the present patient repeatedly underwent surgery, she had an increased risk of hematometra due to vaginal stenosis. Hematometra, a condition characterized by the accumulation of fluid or menstrual products in the uterus, should be considered in the differential diagnosis of abnormal uterine bleeding or abdominal pain in DSD patients who have undergone surgery. Although more rarely, patients with congenital cervical stenosis may develop a uterine rupture as a hematometra complication (6).

In conclusion, physicians may encounter difficulties identifying the uterus of female prepubertal patients with DSD. Imaging assessments of the uterus should be performed repeatedly after puberty or during estrogen replacement therapy.

Conflict of interest: The authors declare

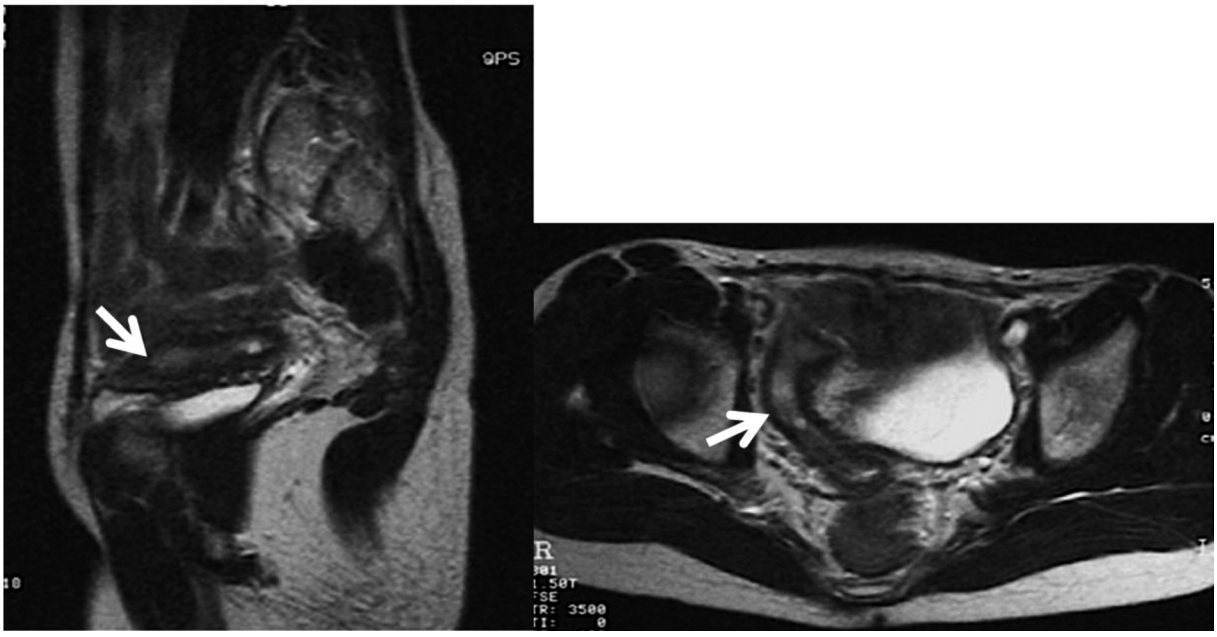

Fig. 2. Identification of the uterus using MRI. The patient underwent an MRI due to irregular vaginal bleeding starting at 16 yr of age. The presence of a uterus (arrow) was confirmed for the first time.

no conflict of interest.

Acknowledgements

We thank the patient for the permission to report on the clinical course of her condition. Furthermore, we acknowledge James R. Valera for his assistance in editing this manuscript.

References

1. Ostrer H. Disorders of sex development (DSDs): an update. J Clin Endocrinol Metab 2014;99: 1503–9. [Medline] [CrossRef]
2. Steven M, O'Toole S, Lam JPH, MacKinlay GA, Cascio S. Laparoscopy versus ultrasonography for the evaluation of Mullerian structures in children with complex disorders of sex development. Pediatr Surg Int 2012;28: 1161–4. [Medline] [CrossRef]
3. Michala L, Aslam N, Conway GS, Creighton SM. The clandestine uterus: or how the uterus escapes detection prior to puberty. BJOG 2010;117: 212–5. [Medline] [CrossRef]
4. Nakamura T, Tsuburai T, Tokinaga A, Nakajima I, Kitayama R, Imai Y, *et al*. Efficacy of estrogen replacement therapy (ERT) on uterine growth and acquisition of bone mass in patients with Turner syndrome. Endocr J 2015;62: 965–70. [Medline] [CrossRef]
5. Bakalov VK, Shawker T, Ceniceros I, Bondy CA. Uterine development in Turner syndrome. J Pediatr 2007;151: 528–31, 531.e1. [Medline] [CrossRef]
6. Yang L, Kanagalingam D. Spontaneous uterine rupture secondary to recurrent haematometra from cervical stenosis. Singapore Med J 2012;53: e114–6. [Medline]