

A rare and atypical female pseudohermaphroditism with phallic urethra, bicornuate uterus and persistent Cloaca

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Abstract

A girl aged 16 years with ambiguous genitalia was referred for confirmation of sex by karyotyping. She had an enlarged phallus, accessory phallic urethra and bicornuate uterus. The vaginal and urethral openings were absent and the perineum was fused like the males. She uses to defecate, micturate and menstruate through the only opening at the anal site i.e. the persistent cloaca. Chromosomal analysis confirms normal female, Karyotype-46, XX. The case is presented with its genetic, hormonal and embryological etiogenesis.

Key Words: Female pseudohermaphroditism, Phallic urethra, Bicornuate uterus, Persistent cloaca
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Introducion

Molecular cascades of sex determination and sexual differentiation is enigmatic. Female pseudohermaphroditism is interesting and intriguing. Female pseudohermaphroditism blending with bicornuate uterus and 'persistent cloaca' is rare and only a few reports are seen in the literature [1]. The female pseudohermaphrodites have typically female internal genitalia with female karyotype(46,XX) but the external genitalia are masculinized [2]. The degree of abnormalities varies from simple clitoral enlargement to partial or complete fusion of the labio-scrotal folds into a scrotum like structure with only opening at the perineum, i.e. the persistent cloaca [3].

Case report

A girl aged 16 years came to Gynecology OPD with ambiguous genitalia and irregular menses. On physical examination, it was found that she had an enlarged phallus with phallic urethra through which urine was dribbling while micturating. Her breasts were well developed (Fig.1A). In the perineum there was a single opening at the anal site through which she used to defecate, micturate and menstruate (Fig.1B).

She was referred to our Cytogenetic lab for the confirmation of sex by karyotyping. Sonography revealed that she was having a bicornuate uterus with collection of blood in the uterus.



Figure 1. A: Girl with well developed mammary glands and ambiguous genitalia.
 B: Presence of phallus and absence of vaginal and urethral openings.

Both the ovaries, kidneys and rest of the abdominal structures were normal. Magnetic resonance imaging (MRI) confirmed the presence of bicornuate uterus (Fig. 2) and also found the duplication of urethra, one opening in the persistent urogenital sinus and another at the tip of the phallus traversing the phallus as accessory phallic urethra. Hormonal analysis revealed normal levels of 17-Hydroxyprogesterone, Dehydroepiandrosterone (DHEA), Estradiol, Free testosterone and Progesterone: Karyotyping confirmed the patient having normal female chromosomes; 46, XX (Fig.3).

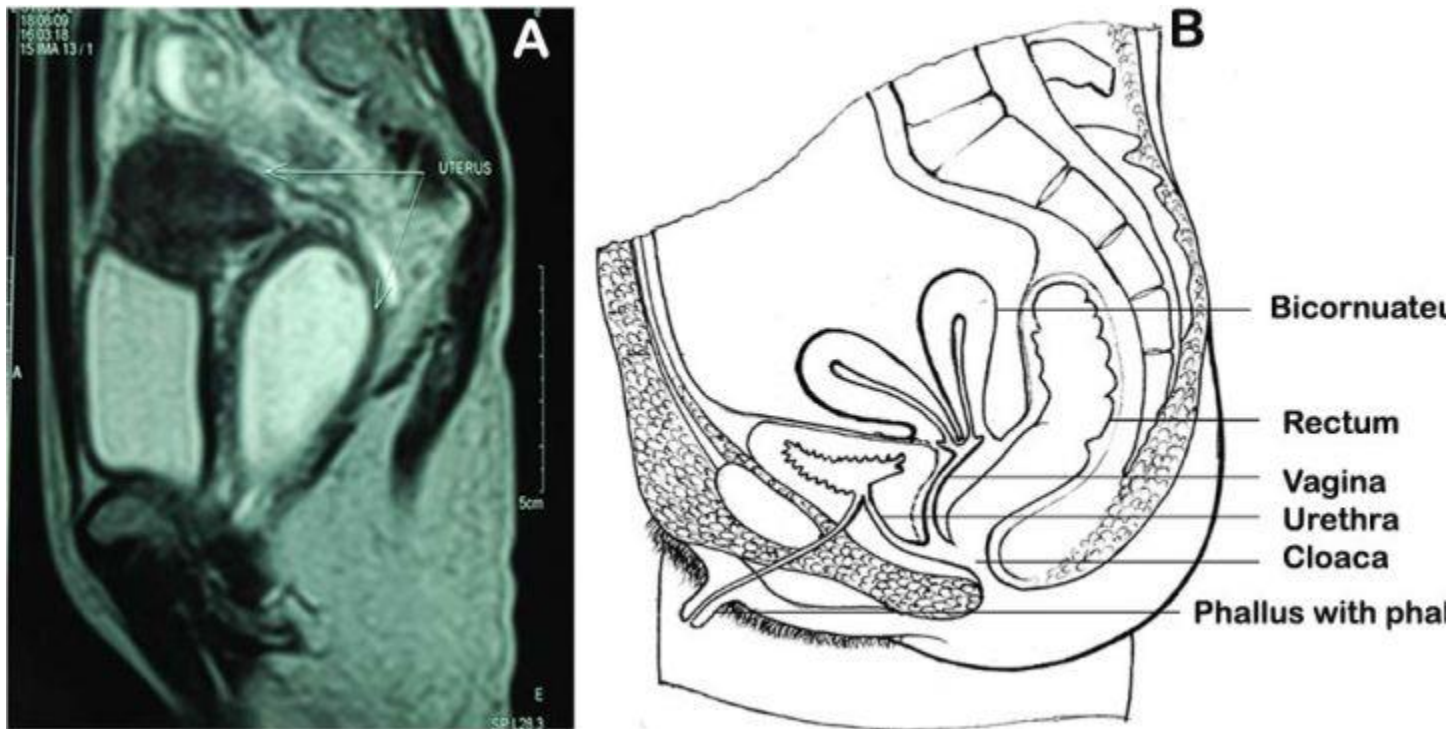


Figure 2. A: MRI showing bicornuate uterus.
 B: Schematic diagram of the pelvic organs of the subject.

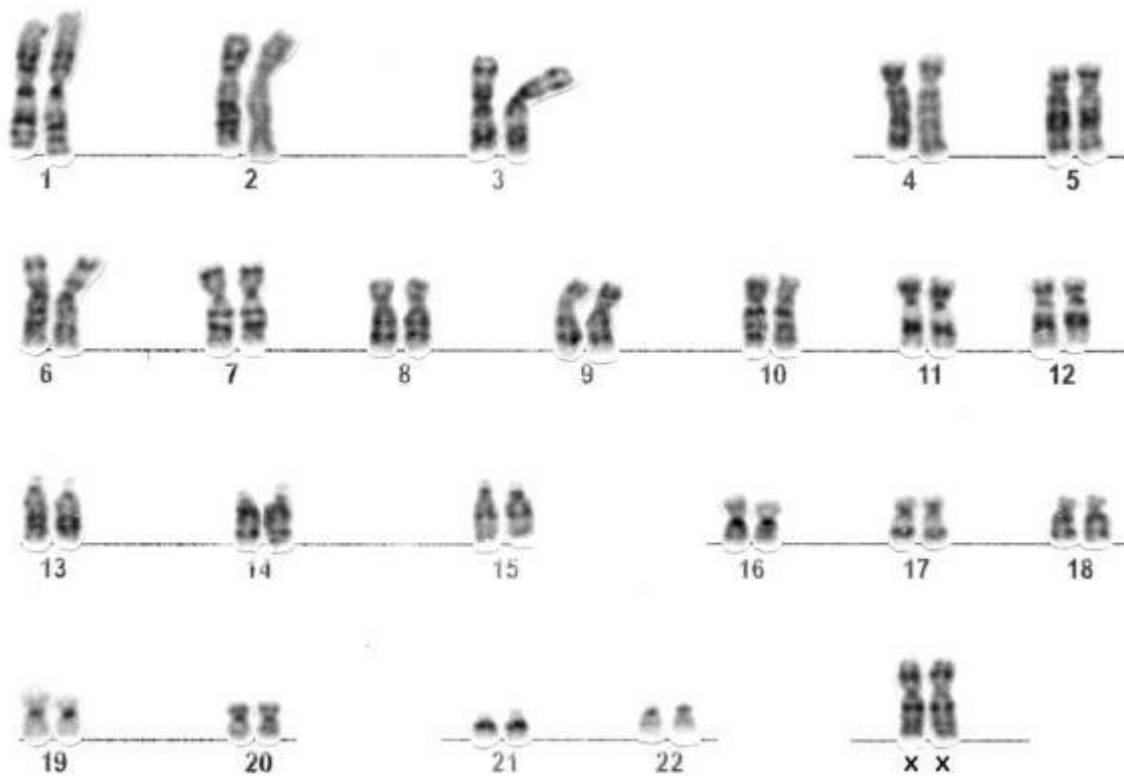


Figure 3. Karyotype: 46, XX.

Discussion

The cloaca is limited caudally by the cloacal membrane, cranial to the cloacal membrane the cloacal folds unite to form the genital tubercle which forms clitoris, under the influence of the androgens it gets enlarged to form phallus [1,2]. In the 7th week of the intrauterine life the cloaca is divided into a dorsal primitive rectum and ventral uro-genital sinus by urorectal septum. In the present case, there is incomplete partition of the cloaca by the urorectal septum. Urogenital sinus opens into anterior wall of primitive rectum which has opened exterior as a common channel for urethral and vaginal and anal openings i.e. the persistent cloaca. The phallic part of the urogenital sinus has grown along the enlarged phallus to form the phallic urethra which is normally formed in the males [1-4].

The paramesonephric ducts forms the uterine tubes and meets with similar duct of opposite side to form the uterovaginal canal. The cranial part of the uterovaginal canal forms uterus, partial fusion of the ducts in cephalic part forms bicornuate uterus [2].

The Wnt-1, Wnt-4, SOX-9 and DAX-1 genes are normally expressed during the embryogenesis of the genital ridges in both the sexes. In the absence of SRY gene on Y chromosome Wnt-4 upregulates the DAX-1 which induces the differentiation of the genital ridges as ovary (female gonad) [4,5]. Another type of Wnt gene, Wnt-7a seems to be involved in maintaining the expression of a sequence of Hox genes that regulate the development of the female reproductive tract, e.g. (i) Hox-9: Uterine tubes, (ii) Hox-10: Uterus, (iii) Hox-11: Uterus and cervix, (iv) Hox-12: Upper vagina, (v) Hox-13: Lower vagina [6]. Mutations in the above mentioned genes lead to the anomalous formation of the urogenital system. It has also been reported that mutations in the Hoxa-13 and Hoxd-13 lead to incomplete partition of the cloaca by the urorectal septum [7].

From the above discussion it seems that some genetic mutations might have taken place during the organogenesis that disrupted the genetic circuit related to affected organs of the subject and ultimately lead to bicornuate uterus and incomplete partition of the cloaca by the urorectal septum leading to persistent cloaca.

Pseudohermaphroditism is always caused by the abnormal levels of the sex hormones or by abnormalities in the sex hormone receptors [2]. In the female pseudohermaphrodites the müllerian duct derivatives are normal and the anatomic abnormality is limited to the external genitalia. The female fetus is masculinized only if exposed to the androgens and the degree of masculinization is determined by the stage of differentiation at the time of exposure. Before the 12th week of gestation high fetal androgen levels lead to a varying degree of masculinization from simple clitoral enlargement to complete labioscrotal fusion with single perineal opening, and after 12th week androgens cause only clitoral enlargement [8].

In utero the high levels of the androgen can be of fetal, maternal or some unknown origin. Fetal source could be as seen in Congenital adrenal hyperplasia (CAH): In CAH there is defective hydroxylation at C-21 of progesterone and 17 hydroxyprogesterone, in the adrenal gland which results in impaired synthesis of cortisol. It stimulates the adrenals with negative feedback mechanism to secrete excessive amount of cortisol precursors including androgens which accounts for the female Pseudohermaphroditism[8,9]. Mutation of any of the following genes i.e. CYP17,CYP11A1 (chromosome 15q), HSD3B2 and StAR (chromosome 8p) may cause congenital adrenal hyperplasia [8,9].

Acromatase (Gene:CYP19) catalyzes the conversion of testosterone to estradiol and androstenedione to estrone in many tissues including gonads and placenta. This enzyme plays a vital role in protecting the fetus from excess of androgen exposure in uterus. Deficiency of placental acromatase causes female pseudohermaphroditism [10, 11].

Adrenal tumor, ingestion of the virilizing progestine compounds, ovarian tumor, and luteoma of pregnancy (an ovarian pseudotumor which disappears after pregnancy) are some of the factors which cause increased level of androgens in the mother during gestation leading to female pseudohermaphroditism[8,12].

Since the tested biochemical parameters of the subject were all in normal ranges, it is most likely that the sources of excess amount of androgens were not of fetal origin. The subject might have been exposed to excess androgens of maternal or some unknown sources.

It appears from the above discussion that the subject has been exposed to either the maternal or some unknown source of androgens before the 12th week of gestational period with misregulation of the genetic circuit which has culminated into the formation of phallus, phallic urethra, bicornuate uterus and fusion of labioscrotal folds with persistent cloaca.

References

1. Jose R, Sotolongo Jr, Michael E, Gribetz, Richard L. Saphir and Gerald R.Begun. Female Phallic Urethra and Persistent cloaca. J Urol 1983, 130: 1186-1187.
2. Schoenwolf G, Bleyl S, Brauer P, Francis-West P. Uro-genital system. In:Larsen's human embryology. 4th ed. Churchill Livingstone Elsevier; 2009: 479-542.
3. Macarthur M, Mahomed A. Rare association of female pseudohermaphroditism, phallic urethra, and posterior cloaca. J Pediatric surg 2006; 4: 576-579.
4. Sadler TW. Urogenital System. In:Langmen's Medical Embryology.11th ed. Lippincott Williams & Wilkins; 2009: 235-263.
5. Simpson JL. Genetics of the female reproductive tracts. Am J Med Genet 1999; 89: 224-229.
6. Dolle P. Hox -4 genes and the morphogenesis of mammalian genitalia. Genes Dev 1991; 5:1767-1776.
7. Carlson BM. Urogenital system. In: Human embryology and developmental biology.3rd ed.Mosby;2004: 393-428.
8. Melvin M,Grumbach, Felix A. Disorders of sex differentiation. In: Wilson J, Foster D, Kronenberg H, Larsen P (eds).Williams textbook of endocrinology. 9th ed. W.B.Saunders Company; 1998: 1303-1426.
9. White PC, New MI, Dupont B. Congenital adrenal hyperplasia:1. N Engl J Med 1987; 316:1519-1524.
10. Shozu M, Akasofu K, Takenori H, Kubota Y.A new case of female pseudohermaphroditism:placental aromatase deficiency. J Clin Endocrinol Metab 1991; 72: 560-566.
11. Morishima A, Grumbach MM, Simpson ER. Acromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 1995;80:3689-3698.
12. Brunskill J. The effects of fetal exposure to Danazol. Br J Obstet Gynaecol 1992; 99: 212-214.

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