

Absent Visualization of a Hypoplastic Uterus in a 16 Year Old with Complete 46 XY Gonadal Dysgenesis (Swyer Syndrome)

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Abstract

Case: A 16-year-old female presented with primary amenorrhea, absent breast development, Tanner V pubic hair, sparse axillary hair and female appearing external genitalia without clitoromegaly. Further workup revealed: 46 XY karyotype with detectable SRY (sex-determining region of the Y chromosome), elevated follicle-stimulating hormone and luteinizing hormone, testosterone and androstenedione in the female range, normal dehydrotestosterone. Estrogen, estrone and ultra sensitive estradiol were in the prepubertal range. HCG stimulation did not result in an increase in testosterone levels, and the inhibin B level was undetectable; suggesting absent testicular function. Anti-Mullerian hormone level was <0.1. On trans-abdominal pelvic ultrasound, no ovaries, uterus or gonads were visualized. After the initiation of hormonal replacement therapy with an estrogen patch, MRI of the pelvis revealed a hypoplastic uterus and no definitive ovaries. Laparoscopic bilateral gonadectomy was performed. The pathology report showed some fallopian tissue on the left gonad with cystic changes. On the right gonad there was some ovarian stromal tissue without follicles. There was no evidence of gonadoblastoma.

Summary and Conclusion: Swyer syndrome with XY complete gonadal dysgenesis may present with absent genitalia and an "absent" uterus on pelvic ultrasound. However, a uterus is in fact present and may be visualized on MRI, particularly after treatment with estrogen. It is important to correctly diagnose these patients because of the reported increase of gonadoblastoma. In addition they have the option of pregnancy (*in vitro* fertilization of donor egg by donor sperm, followed by embryo transfer).

Keywords: Swyer syndrome; Gonadal dysgenesis; Gonadal tumors; Primary amenorrhea; Hypoplastic uterus

Introduction

In humans, genetic females and males are characterized by the presence of an XX and XY karyotype, respectively. Patients with complete androgen insensitivity syndrome and complete gonadal dysgenesis have an XY karyotype but absent external male genitalia and hence are usually raised as females. They do not develop true breast tissue or undergo spontaneous menarche, and are thus brought to medical attention.

Complete gonadal dysgenesis is characterized by bilateral streak gonads, normally developed Mullerian structures, female appearing external genitalia, and hypergonadotropic hypogonadism. These patients have a low testosterone level using a male range and absent breast development, on the other hand, in patients with androgen insensitivity, the testosterone levels are high and conversion to estrogen results in breast development. A high incidence of gonadoblastoma and germ cell malignancies has been reported in cases of gonadal dysgenesis and the current practice is to perform gonadectomy of any gonadal tissue visualized during surgery. The management of puberty in complete gonadal dysgenesis is similar to other causes of ovarian failure i.e. initiation of estrogen to induce the development of secondary sexual characteristics, and long term combined replacement therapy with estrogen and progesterone.

Case

A 16 year old female was referred to our endocrinology practice after initial evaluation by the primary care physician for primary amenorrhea. She also had delayed puberty and absence of breast development. On our physical examination, her height was 161 cm (41%); weight was 45.7 kg (10%), with a body mass index of 17.6 (9%). She was Tanner stage I for breast development, scant axillary hair was present, and Tanner stage IV for pubic hair. An external genital exam revealed normal labial folds. Bone age was 13.6 years for female and 14.6 years for male. On vaginocopy a viable cervix

was found. Pelvic sonographic examination revealed no identifiable uterus or ovaries. Chromosome analysis showed a 46 XY karyotype in 100% of the cells examined. FISH analysis demonstrated the male sex-determining region of the Y chromosome was present in each cell examined i.e. no deletion of SRY was detected. Initial hormonal assays showed elevated serum follicle stimulating hormone (128.5 mIU/ml) and elevated luteinizing hormone (56.4 mIU/ml). Estradiol (81 pg/ml). Total testosterone (13 ng/dl) and free testosterone (0.3 ng/dl) were in the female range. The initial labs were all adult assays. Repeat laboratory examination with pediatric assays revealed a total estrogen level of 39.9 pg/ml, estrone level of 9 pg/ml, low estradiol level of 9 pg/ml, dehydrotestosterone level of 4.2 ng/ml, total testosterone level of 14 ng/ml, free testosterone level of 1.0 pg/ml, free percent testosterone of 0.73 %, Sex hormone binding globulin level of 52 nmol/l, undetectable Inhibin B (<30 pg/ml), undetectable anti Mullerian hormone (<0.1 ng/ml). BHCG stimulation test showed no response suggesting absent testicular tissue. ACTH stimulation test mounted an appropriate normal adrenal response. Electrolytes, complete blood count, TSH and Free T4 were normal. A bone density was performed prior to the institution of estrogen replacement therapy and after correcting for the bone age, it was normal for the age and ethnicity. Cystoscopy and vaginocopy under general anesthesia were performed and a viable cervix was found.

The patient initially refused an exploratory laparoscopy. Hormonal

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replacement therapy (estradiol-17beta [patch]) was initiated. Six months after estrogen replacement therapy, an MRI of the pelvis showed a uterus measuring 6x2.2 cm in depth and 3.5 cm in width, but no definitive ovaries were found. After this finding the patient and parents consented to surgery to remove any present gonadal tissue because this may have the potential for malignancy. Pathology reports were compatible with bilateral streak gonads. The left had some cystic changes with fallopian tissue, on the right gonad there was ovarian stromal tissue with no follicles, and no germ cells or tumors were found. At 7 months postoperative follow up, she was well and reported some breast development. The estrogen patch dose was increased and after menses were established, the therapy was changed to a combined oral contraceptive pill. She has been evaluated by a psychiatrist and has a female gender identity. We discussed the option of pregnancy (*in vitro* fertilization of donor egg by donor sperm, followed by embryo transfer) [1-3].

Discussion

Multiple mutations in the SRY gene are believed to account for approximately 10%-20% of all cases with complete gonadal dysgenesis and the retention of Mullerian ducts in a genetic XY male. Mutations in other genes, such as ZFY, SOX9, SF1, WT1, DYZ1, and DAX1, are possible causes in the interference of sex determination. Swyer syndrome was first described in 1955, since then a number of cases have been reported [4]. The incidence is believed to be 5:100,000 births. Most of the women with complete gonadal dysgenesis were accurately diagnosed several years after the initial presentation of their problems. Early diagnosis is of crucial importance for different reasons including the risk of gonadal malignancy, early institution of hormonal replacement therapy for induction of puberty and to improve bone mineral density. At birth and during childhood the patients are phenotypically females. They are brought to medical attention for delayed the larche or primary amenorrhea [5]. The initial test is often a karyotype analysis, followed by ultrasound. Upon diagnosis of complete gonadal dysgenesis the clinician must be aware that there are at least four possibilities of XY females: Androgen insensitivity syndrome, complete gonadal dysgenesis, mixed gonadal dysgenesis and partial gonadal dysgenesis. Distinguishing between these categories can often be quite challenging.

Complete gonadal dysgenesis is associated with an absence of testicular differentiation in a phenotypic female with a 46XY karyotype

[6,7]. Normally, anti Mullerian hormone is synthesized by Sertoli cells, which are activated by the SRY gene found on the Y chromosome. Anti Mullerian hormone then causes regression of Mullerian structures. If anti Mullerian hormone secretion fails to occur by six to eight weeks of intra uterine life, because of a defect in testicular differentiation or a mutation of the SRY gene, external female genitalia form. Female internal genitalia development varies according to the exact timing of secretion of anti Mullerian hormone. Women with complete gonadal dysgenesis have an overall smaller uterus size when compared to normal controls, and the small uterine size does not appear to have an adverse effect on fertility outcome. The presence of a hypoplastic uterus implies a deficiency of anti Mullerian hormone in utero (absent functional testicular tissue). In addition it remains hypoplastic due to a lack of estrogenic stimulation (absent functional ovarian tissue). On account of the high incidence of malignancy (5% at 15 years old, and as high as 50% at 30 years of age) gonadectomy is performed. Hormonal replacement therapy is given to induce the onset of breast development, uterine development, menses and to prevent osteoporosis. Bone health and fertility options are important issues to discuss with these patients.

Our case illustrates that a uterus may be present in a patient with gonadal dysgenesis, even if the initial ultrasound suggests an absent uterus. The presence of a uterus has important diagnostic and therapeutic implications in these patients.

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