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CASE REPORT

Swyer's Syndrome: In a Fifty-Year-Old Female

Culha Cavit · Ozkaya Mesut · Serter Rustu · Sahin Ibrahim · Aydin Bayram · Aral Yalcin

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Introduction

Disorders of sexual differentiation may be classified into two categories; 1-disorders of gonadal differentiation; and 2-disorders of genital development. Here we present a case with complete 46, XY gonadal dysgenesis (Swyer's syndrome) which is one of the female phenotype sexual differentiation disorders resulting from abnormal gonadal differentiation. It is well known that the risk of gonadal neoplasia is increased in gonadal dysgenesis. Swyer's syndrome should be differentiated from syndrome of complete androgen insensitivity (Testicular feminization) and from Leydig cell agenesis. In the latter two disorders phenotype is female, karyotype 46, XY, the gonads are testes, while uterus and tubes are absent. On the contrary, the patients with Swyer's syndrome have uterus and cervix which are hypoplastic.

Culha C. (✉) · Ozkaya M. · Serter R. · Sahin I. · Aral Y.
Department of Endocrinology and Metabolism, Ankara Education and Research Hospital Ankara, Yavuzevler Sok. No: 30/16, Buyukesat, 06610 Ankara, Turkey
e-mail: cavitculha@hotmail.com

Aydin B.
Department of Obstetrics and Gynecology, Ankara Education and Research Hospital, Ankara, Turkey

Case Report

A 50-year-old phenotypically female patient presented with complaints of headache and excessive perspiration and history of primary amenorrhea. Considering her female phenotype we presented the patient as "she" in our manuscript. She was 155 cm in height at 15 years of age when she got married to a man. The patient had never had normal menses. She was put on cyclic hormone replacement (estrogen–progesterone) therapy for primary amenorrhea. Around 2 years ago she stopped the treatment herself. She declared a history of left oophorectomy due to gonadal cyst at 24 years of age. Patient's height continued to increase till 35 years of age. According to the testimony of her husband, when the patient married at 15, she was at the height of her husband's shoulder, when she was referred to us (at the age of 50), her husband was not even at the height of her shoulders. Her family history was negative for described ambiguous genitalia or sex reversal.

On physical examination, the patient had female phenotype with eunuchoid habitus. Her body weight was 90 kg, height 188 cm, arm span 201 cm, vertex–pubis 93 cm, pubis–heel 95 cm, and vertex–pubis/pubis–heel ratio: 0.97. Hands and feet appeared bigger than normal. Breast development, axillary and pubic hair was compatible with Tanner's grade B 4–5 and P 4–5, respectively.

The appearance suggesting acromegaly led to further investigation. Growth hormone (GH) levels were suppressed by oral glucose administration, excluding

acromegaly. Sella X-ray and magnetic resonance imaging (MRI) of the pituitary gland were normal. Ovaries were atrophic and uterus hypoplastic on ultrasonographic examination. Hormonal characteristics of the patient are demonstrated in Table 1. Our patient had elevated gonadotropins, low estradiol (E_2) and normal testosterone levels, Karyotype analysis of the patient revealed a 46, XY genotype (pure) without evidence of structural abnormalities. Right gonad was streak while the left one could not be demonstrated on transvaginal endosonography. In addition, the absence of the left gonad and the right gonad in a streak form were verified by laparoscopic evaluation. Right gonadectomy was performed and the histopathological examination of biopsy specimens from this streak gonad revealed fragments of mesothelial tissue with fibrotic stroma (no follicles) and calcifications without evidence for malignancy. Laboratory evaluation was normal for AFP and CA 125 and β-HCG. Three months after her stay in our hospital, when we tried to contact the patient for the analysis of *SRY* gene mutation, we learned that she lost her life in a traffic accident together with her husband. Based on these data, the patient was diagnosed to be complete 46, XY gonadal dysgenesis (Swyer's syndrome).

Discussion

Swyer's syndrome was first described by Dr. G. Swyer in the 1950's. Complete 46, XY gonadal dysgenesis (Swyer's syndrome), is a sexual differentiation disorder with female phenotype. Patients have female external genitalia, normal or tall and eunuchoid stature, bilateral streak gonads, sexual infantilism and 46, XY karyotype [1, 2]. Phenotypic difference between complete and incomplete forms depends on the level of differentiation of testicular tissue and on the production of testosterone and antimullerian hormone (AMH) by the fetal testis [1].

Table 1 Hormonal characteristics of the patient

Hormone	Serum level	Normal range
FSH (mIU/ml)	90.40	(2.5–10.2) female (1.4–18.1) male
LH (mIU/ml)	52.04	(1.9–12.5) female (1.5–9.3) male
E_2 (pg/ml)	2.48	(10–165) female (0.0–52) male
Progesterone (ng/ml)	0.18	(0.15–1.40) female (0.28–1.22) male
Testosterone (ng/ml)	41	(14–76) female (241–827) male
Free Testosterone (pg/ml)	2.0	(0.3–3.9) female (10–30) male
PRL (ng/ml)	15.73	(2.8–29.2) female (2.5–17) male
GH (ng/ml)	0.7	(0–14.0)
Cortisol (μg/dl)	26.56	(7.0–29.0)
IGF-1 (ng/ml)	185	(94–210)

The *SRY* gene encodes for a testis-specific transcription factor (TDF, testis determining factor) that plays an important role in sexual differentiation and development in males. 15–20% of familial and sporadic cases have a mutation in high mobility group (HMG) box-related sex-determining region on chromosome Y (*SRY* gene mutation) XY gonadal dysgenesis can result from deletions on the short arm of chromosome Y, mutations on *SRY* gene, mutations of autosomal genes (9p and 10q deletions), or from duplications of X chromosome. Duplication on Xp21, 2 and p22, 11 region of X chromosome has been reported in more than 20 patients with Swyer's syndrome (duplicating DAX1) [1, 3]. Although any mutation on *SRY* gene hasn't been established in some clinical studies, Midro and coworkers [4] have reported that normal structure of this gene does not exclude the possibility of Swyer's syndrome. Scherer and colleagues [5] had reported *SRY* gene mutation in 10–15% and gene deletion in another 10–15% of patients with Swyer's syndrome while there was no clear etiologic factor in the remaining 70–80%. Zenteno and coworkers [6] also reported a patient with 46, XY gonadal dysgenesis caused by a de novo mutation within SRY HMG box. In studies reported from Italy, Salehi and colleagues [7] showed a new mutation in HMG box of *SRY* gene in a female with 46, XY karyotype and gonadal dysgenesis. They identified a new protein which is truncated as consequence of a stop codon at the position 103 due to a single nucleotide insertion at codon 89 and recently, Gimelli et al. [8] demonstrated a familial mutation caused by substitution of leucine for serine in N-terminal domain of SRY protein. They suggested that this mutation may prevent the normal function of SRY protein. Although many SRY mutations reduce DNA-binding/bending activity, it is not clear how SRY mutations lead to disease. High-mobility group domain of SRY harbors two nuclear localization signals (NLSs). Harley and collaborators [9] examined SRY from four XY females with missense mutations in these signals. They concluded that SRY normally requires the two distinct NLS-dependent nuclear import pathways to reach sufficient levels in the nucleus for sex determination. The results of their study indicated impaired ability of mutant SRY protein to accumulate in the nucleus. Steroidogenic factor-1 (SF1) is a nuclear transcription factor that plays an important part in adrenal and gonadal development, steroidogenesis and reproduction. Lin et al. and Reuter et al. [10, 11] demonstrated that SF1 mutations (SFl/AdBP4/FTZF1, NRSA1)

may cause inadequacy in testis development and sexual differentiation without any disturbance in adrenal functions in the patients with gonadal dysgenesis and 46, XY karyotype.

Recently, mutations in genes other than *SRY* gene were also discovered in patients with complete pure gonadal dysgenesis. Canto and colleagues [12] firstly described the mutations of Desert hedgehog (*DHH*) gene associated with the presence of 46, XY complete pure gonadal dysgenesis. Hence, the genetic origin of this entity seemed to be heterogeneous and the genes other than *SRY*, might also be involved in the testis-determining pathway implicated in abnormal testicular differentiation [12].

Vagina, uterus and uterine tubes are completely female but hypoplastic in patients with 46, XY gonadal dysgenesis. In addition, breast development is either absent or weak. Eunuchoidal habitus is usually obvious. Gonads are composed of fibrous stromas (i.e. streak gonad). Gonadotropins are elevated while estrogens are low, and androgens are normal or high for female range [1–4]. When differential diagnosis is considered, complete androgen insensitivity syndrome (CAIS) may be suspected based on the clinical features. It is important to give special attention to the differences in clinical features and hormonal profile between complete 46, XY gonadal dysgenesis and CAIS: both entities present a female phenotype in spite of a 46, XY karyotype. However, breast development in CAIS is normal contrary to complete 46, XY gonadal dysgenesis in which there is no breast development; In CAIS patients the testes are usually well formed and located in the inguinal canal, labia or abdomen while in complete XY gonadal dysgenesis they are replaced by fibrous streaks which don't secrete testosterone or AMH. On the other hand, testosterone serum levels are normal or high in CAIS but low in XY gonadal dysgenesis when considered in the male range. Therefore, demonstration of the presence of testis-like masses in a phenotypically female patient before puberty suggests the diagnosis of CAIS. The patients with CAIS after puberty exhibits primary amenorrhea, normal breast development, and sparse or absent of pubic or axillary hair. Pelvic examination or ultrasound confirms the absence of a cervix and uterus. Whereas elevated levels of plasma LH, testosterone (for male range) and estradiol are expected in this disorder [1–4], our patient had elevated gonadotropins, low estradiol and normal testosterone levels of female range. Also, Leydig cell agenesis (aplasia) must be considered in differential diagnosis. These patients may present in infancy with variable degrees of genital ambiguity. Alternatively, they may appear as normal phenotypic females and escape detection until adolescence, when they present with primary amenorrhea, with or without normal breast development. The gonads (testes) are usually located in the inguinal canal. The axillary and pubic hair may be sparse. Serum gonadotropins are elevated and testosterone levels are within the low normal range for females [1].

The risk of development of malignancy, i.e. gonadoblastoma, dysgerminoma, and hilar cell adenoma, is increased in the presence of streak gonads. Because of this increased risk, removal of gonads is fundamental in the treatment of disease [13–15]. All germ cell tumors including gonadoblastomas and dysgerminomas have been frequently demonstrated in patients with Swyer's syndrome and cases of gonadal dysgenesis with a Y chromosome [14]. It has been suggested that SRY may play a role in the formation of gonadal tumours in pure gonadal dysgenesis patients [15].

In conclusion, in addition to testicular feminization syndrome and Leydig cell agenesis, Swyer's syndrome must be kept in mind in differential diagnosis of phenotypically female patients with primary amenorrhea, tall eunuchoid stature, and 46, XY karyotype. Interestingly, the patient presented here got married to a man at the age of 15 and strongly wished to have a baby for years. Probably, the patient was referred to a specialist too late. The conservative characteristics of the individuals, especially in rural areas, should be the contributing issue in this situation. Although the diagnosis of this patient was made very late, early diagnosis of Swyer's syndrome and the surgical removal of streak gonads seemed to be essential for avoiding risk of malignancy.

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