Austin Journal of Endocrinology and Diabetes

Open Access

Austin Publishing Group

Case Report

Swyer's Syndrome: Discordance between Genetic and Biological Sex - Case report

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Received: January 02, 2023; **Accepted:** February 10, 2023**; Published:** February 17, 2023

Abstract

Swyer's syndrome is a rare condition in which a disorder of the sex chromosomes produces a defective gonadogenesis with total absence of functional gonadal tissue, resulting in pure gonadal dysgenesis and discordance between genetic and biological sex. The gonads appear as rudimentary bands and the risk of developing gonadal tumors is significant. The etiology is not clear: one of the possible causes is the absence or mutations of the SRY gene located on the Y chromosome. This gene is considered to be the most important, although it is known that there are other genes involved in the cascade of sexual differentiation.

This article reports the case of a 17-year-old female phenotype patient who was studied for primary amenorrhea and presented laboratory findings compatible with hypergonadotropic hypogonadism, 46XY karyotype, who was diagnosed with Swyer Syndrome.

Keywords: Gonadal dysgenesis; Primary amenorrhea; SRY gene; Swyer's syndrome

Introduction

Gonadal dysgenesis encompasses a group of disorders of the sexual development with there is incomplete or defective formation of the ovaries or testicles due to structural or numerical abnormalities of the sex chromosomes or to mutations in the genes involved in sexual development [1,2]. Gonadal dysgenesis can be complete or partial.

Complete XY gonadal dysgenesis (complete failure of testicular development) occurs in phenotypically female individuals with the absence of secondary sexual characters, usually, due to a mutation of the SRY gene.

At birth, these individuals present a normal female phenotype but nor develop secondary sexual character in puberty. The present amenorrhea and an increased risk of gonadal tumor [3].

Clinical Case

Female patient, 17 years old, with no outstanding personal or family history, with primary amenorrhea. She presented pubarche at 15 years of age and the larche at 16 years of age. She has never received oral contraceptives and denies the use of estrogen cream. The patient doesn't have hirsutism acne or galactorrhea. She had no elements of hypercortisolism, headache, or visual disturbances. She didn't present symptoms of thyroid dysfunction, eating disorders or stress. Physical examination highlights: weight 51,8 kg, height 161.5 cm, Body Mass Index (BMI) 20 kg/m², female phenotype without dysmorphia and sexual infantilism, Tanner Stage II breasts, Tanner stage III pubic hair, and female external genitalia. Presented a soft abdomen, depressible, painless with no palpable tumors. Diagnostic tests from the hormonal profile, the following stand out: very decreased estradiol levels, low testosterone levels, FSH and LH increased levels and normal prolactin and TSH levels (Table 1). Therefore, the patients were diagnosed with hypergonadotropic hypogonadism. The evaluation was completed with a karyotype and SRY gene and a karyotype in peripheral blood lymphocytes that reports 46XY. No presence of SRY gene was detected by FISH. There was discrepancy between chromosomal sex and biological sex. Gynecological ultrasound did not show uterus or ovaries. Magnetic resonance imaging of the abdomen and pelvis reported the absence of uterus and ovaries and a hypoplastic vagina. Other structures were reported as normal.

Citation: Aldao G, Mintegui G and Agüero P. Swyer's Syndrome: Discordance between Genetic and Biological Sex - Case report. Austin J Endocrinol Diabetes. 2023; 10(1): 1097.

Table 1: Relevant hormone dosages in he reported clinical case.

Hormone	Foundvalue	Reference interval
FSH	51,2 mU/mL	3,5- 12.5 mU/mL
LH	20,8 mU/mL	2.4- 12.6 mU/mL
Estradiol	5 pg/ mL	12,4 – 233 pg/mL
total testosterone	2,5 ng/dL	15-70 ng/dL
Prolactin	14,5 ng/mL	6-29.9 ng/mL
TSH	4,48 µUI/mL	0,27-4.20 µUI/mL

Discussion

Gonadal dysgenesis are rare congenital disorders in which gonadal development is atypical and consequently the phenotype and karyotype are discordant [4]. In the dysgenesis there is defective gonad genesis, where gonadal development is arrested in early stages and ovaries or testicles cannot be differentiated.

Swyer´s syndrome is characterized by the presence of undifferentiated gonadal striae with total absence of functioning gonadal tissue in female phenotype patients with female genitalia hypoplastic [5].

The exact incidence is unknown but it is estimated at 1:80,000 births [6]. It was described by first time in 1955 by G.L. Swyer with primary amenorrhea [7]. Most women with pure 46 XY gonadal dysgenesis have normal physical characteristics until the onset of puberty where a delay in pubertal development occurs [8]. They are usually tall due to late closure of the growth plates (8) and their internal genitalia have little or no development, with the presence of bilateral fibrous bands that occupy the space of the gonads [7].

Case reports in the literature have mentioned the difficulty of identifying the uterus during the initial clinical evaluation,

As it may be hypotrophic due to lack of estrogen stimulation.

For this reason, it is recommended to repeat the pelvic ultrasound to assess for the development of an “occult uterus” before starting hormone therapy [9].

Laboratory findings confirm that the hypergonadotropic hypogonadism occurs due to a deficit in the synthesis and

action of necessary hormones for male genital differentiation: the factor Mullerian channel (AMH) inhibitor,

testosterone synthesized by Leydig cells, and dihydrotestosterone (DHT) synthesized in target tissues with 5α-reductase

enzyme [10]. The etiology of this pathology is not completely clear but the most probable cause is the molecular

alteration of the expression of major testicular determinants (TDF). SRY is the most promising gene to be TDF [7].

The SRY gene is located at the distal end of the short arm of the Y chromosome. It is responsible for the initiation of the genetic cascade that causes the undifferentiated gonad to develop into testicles; the absence of SRY could alone explain the cause of this disorder.

Although, up to now, the SRY gene has been attributed to be the most important in male sexual differentiation, it is not the only one. A homologous gene, SOX9, has been found located on chromosome 9. Both genes are co-expressed in the male. SOX9 activates the transcription of the Mullerian inhibitory substance, therefore, it is believed that it has a fundamental role in male sexual differentiation.

In other cases, there may be alterations in the SRY promoter gene or intrinsic disorders of the SRY gene that are not yet known. Genetic study is important especially in the SRY [7,10,11].

As to whether these are inherited or sporadic mutations, it is considered that some cases of Swyer´s syndrome are caused by a genetic mutation during development, isolated and without a clear cause, which is known as a de novo mutation. Although some clinical cases report about Swyer syndrome in whom a mutation was detected in the SRY gene on the Y chromosome who had relatives of first degree with SRY gene mutation but who did not develop the syndrome [12].

Accurate diagnosis of Swyer syndrome is usually delayed. An early diagnosis is important for several reasons: the risk of gonadal malignancy, early substitution of therapy with estrogens for puberty induction and to protect bone mineral density [6].

The risk of developing gonadal tumors in Swyer´s syndrome is significant where an incidence of 20 to 30% is reported. The most common tumor is gonadoblastoma, often bilateral. The incidence of neoplasia in patients with gonadal dysgenesis is surely wider than reported, but there are little case reports published on dysgerminoma in female patients with a pure dysgenetic gonad.

However, all agree in recommending the oophorectomy due to high risk of malignant transformation. A positive rate of CA125 has been seen greater than 50 % in all cases of gonadal tumors, therefore this tumor marker is useful for the screening of malignant germ cell tumors. The treatment of the patient with dysgerminoma is primarily surgical, including resection of the primary lesion and appropriate surgical staging. Chemotherapy or radiation therapy is given to patients with metastatic disease [13].

On the other hand, 5% of cases of dysgerminoma present XY karyotype, so in adolescents with dysgerminoma presenting primary amenorrhea or secondary amenorrhea, the karyotype test should be performed. Menstrual function may be associated with estrogen secretion from tumor lesions and investigation of the gonads is recommended [13].

Treatment of Swyer syndrome includes estrogen replacement at puberty to achieve the development of secondary sexual characteristics, in addition to preventing the loss of bone mass [7].

Estradiol can be administered by the transdermal or oral routs. The short-term goal is to achieve the age-appropriate secondary sexual characteristics and lessen the concern of the patient in terms of their appearance in relation to their peers. If the patient presents a hypoplastic uterus and menstruates, progestogens should be added to prevent endometrial hyperplasia [14]. An estradiol therapy is started in gradual doses to mimic puberty and normal breast development [14].

Treatment and follow-up should include psychological support, provided by professionals with experience in gonadal dysgenesis. The patient’s condition should be explained to them, as well as the importance of treatment and prognosis [7].

Sexual life should be normal, without alterations in desire and satisfaction [7]. In case of reproductive desire, they are po-

tential candidates for assisted reproduction by egg donation, although it should be assessing the gestation capacity related to the uterine size since they present uterine hypoplastic. Genetic counseling is recommended for the affected person and their relatives [4].

Conclusions

The diagnosis of Swyer´s syndrome should be suspected in patients with a female phenotype, primary amenorrhea and absence of secondary sexual characteristics. Given this clinical presentation and a hormonal evaluation that reports hypogonadism hypergonadotropic, it is important to perform a karyotype and imaging studies to assess genitalia internal.

The report of this clinical case aids to visualize the scope of this syndrome and the importance of an opportune diagnosis for an adequate sexual development in which therapy of progressive hormone replacement is necessary. It also aids to visualize the high risk of developing gonadal tumors with an indication for early prophylactic gonadectomy.

References

1. Mac Laughlin DT, Donahoe PK. Sex determination and differentiation. N Engl J M. 2004; 350: 367-78.

2. Hughes IA, Houk C, Ahmed SF, Lee PA, Society LWPE. Consensus statement on management of intersex disorders. J Pediatr Urol. 2006; 2: 148-62.

3. Protzel A, Zegarra P, Rojas R. Disgenesia gonadal pura XY. Síndrome de Swyer. Dos caras de la misma moneda RPGO. 2005; 51: 110-3.

4. King TF, Conway GS. Swyersyndrome. CurrOpinEndocrinol Diabetes Obes. 2014; 21: 504-10.

5. Chang S-H, Montvelisky H, Vinocour M. Amenorrea primaria secundaria a disgenesia gonadal pura 46XY (Síndrome de Swyer). Reporte de un caso. Acta Med Costarric. 1998; 40: 1-3.

6. Michala L, Goswami D, Creighton S, Conway GS. Swyer syndrome: presentation and outcomes. BJOG. 2008; 115: 737-41.

7. Villegas JD, Cuevas R, Barón G. Disgenesia gonadal pura: síndrome de Swyer-James. Presentación de un caso y revisión de la literatura. RCOG. 1998; 49: 41-5.

8. Marta Zermiani MBG. Síndrome de Swyer: causas, manifestaciones clínicas y embarazo [updated28 december 2022]. Available from: https://www.reproduccionasistida.org/sindrome-de-swyer-sintomas-causas-y-embarazo/

9. Nunes E, Rodrigues C, Geraldes F, Águas F. Differentiating swyer syndrome and complete androgen insensitivity syndrome: a diagnostic dilemma. J PediatrAdolesc Gynecol. 2014; 27: 67-8.

10. Audi L, Fernández-Cancio M, Pérez de Nanclares G, Castaño L, editors. Disgenesias gonadales y pseudohermafroditismo masculino. An Pediatr. 2006; 64: 23-37.

11. Napal JCP, Drake CTV, Ibarra HG, Martínez BS. Caracterización molecular de dos pacientes 46 xy, fenotipo femenino. síndrome de Swyer. Archivo Médico de Camagüey. 2004; 8: 1-9.

12. Swyer syndrome: NCATS, U.S. National Institutes of Health, Department of Health; Human Services; [updated 19 agosto 2021].

13. Behtash N, KarimiZarchi M. Dysgerminoma in three patients with Swyer syndrome. World Journal of Surgical Oncology. 2007; 5: 1-5.

14. William F Crowley J, Nelly Pitteloud. Approach to the patient with delayed puberty; [updated 28 december 2022].