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An odd study case of primary amenorrhea: Swyer syndrome

Abstract

Introduction: Usual sex determination and differentiation occurs progressively during the period of embryonic development, involving chromosomal differentiation, gonadal differentiation, and somatic or genital differentiation. Swyer syndrome is a disorder of sex chromosomes and sexual differentiation characterized by 46, XY pure gonadal dysgenesis in a phenotypically female person with primary amenorrhea, and a complete absence of functioning gonadal tissue. Gonadal malignancy occurs in 10-30% of cases, so gonadectomy is indicated at the time of diagnosis. The treatment includes, in addition to the gonadectomy, hormone replacement therapy, and psychological support.

Objective: To present a case diagnosed and managed in our institution, in addition to reviewing the recent literature about this rare condition, but with a strong physical, psychological and social impact.

Methods: Analysis of clinical history of a patient with Swyer's Syndrome, diagnostic and therapeutic management. Bibliographic review.

Presentation of the clinical case: An 18-year-old patient attends our hospital presenting primary amenorrhea. She presents BMI: 22; Tanner stage PH III BD III, gynecological examination with vulva and vagina with normal characteristics. Hormone profile requested: FSH 96.8 mU/ml, LH 32.9 mU/ml, Estradiol <25 pg/ml; Total testosterone 0.15 ng/ml. TV ultrasound shows a hypoplastic uterus of 23x11x29 mm, ovaries are not visualized, and a heterogeneous solid image of 22x23x24 mm in the left adnexal region. 46XY karyotype. In the presence of these results, a diagnosis of Swyer's syndrome is made, so an MRI was requested, which shows a uterus of 14x20x26 mm, ovaries are not visualized, a solid lobulated oval image of 23x33x47 mm poorly vascularized standing out in the left adnexal region and free inguinal canals. It was decided to perform exploratory laparoscopy and gonadectomy. The intraoperative findings were: intrapelvic hypoplastic uterus, uterine tubes without any particularities, enlarged left gonad of approximately 3x4 cm pearly white with a hard elastic consistency, and a fibrous band in the right adnexa. Bilateral adnexectomy was performed, obtaining as a histological result well-differentiated left dysgerminoma SALL4 +, OCT3/4 +, negative Inhibin and CD 117 +, and right streak gonad.

Conclusions: In the presence of a person with primary amenorrhea and absence or poor development of secondary sex characteristics, Swyer's syndrome should be suspected, and pertinent studies should be requested to arrive at the diagnosis. It is essential to perform gonadectomy at the time of diagnosis due to the risk of malignant transformation. The importance of a multidisciplinary approach and psychological accompaniment of patients and relatives is highlighted.

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Introduction

Sex determination is established by multiple molecular events that direct the development of germ cells, their migration to the genital ridge, and the subsequent formation of testes in the presence of a Y chromosome (46 XY) or an ovary in its absence (46 XX). Sex determination sets the stage for sex differentiation: the specific response of tissues to hormones released by the already differentiated gonads. Usual sex determination and differentiation occurs progressively during the period of embryonic development, and involves chromosomal differentiation, gonadal differentiation, and somatic or genital differentiation.[1,2]

Disorders of sexual development (DSD) encompass those conditions noted at birth or in childhood and adolescence where the genitalia of an individual are atypical in relation to their gonads or chromosomes. Swyer syndrome belongs to the broad group of XY DSDs,[3] being a disorder of sex chromosomes and sexual differentiation characterized by a 46 XY pure gonadal dysgenesis in a phenotypically female individual with primary amenorrhea, and total absence of functioning gonadal tissue. It was first described by Swyer in 1955[4] From that moment, until a new review by Guidozzi et al. in 1994, 62 cases were reported, of which only 39 presented all the diagnostic criteria: 46 XY karyotype, external genitalia: vulva, hypoplastic internal genitalia, absence or poor development of secondary sex characteristics, streak gonad, and testosterone levels in normal female values.[5,6] Several cases have been reported, but to date there are no large series in the literature. For this reason, the exact incidence is unknown but can be estimated at 1/80,000.[7]

Although sex is genetically determined since fertilization, the morphological characteristics associated to feminine and masculine are only acquired after 7-8 weeks of development. All embryos initially have 2 pairs of genital ducts: the mesonephric (Wolff) and the paramesonephric (Müller). Genital and ductal differentiation occurs once gonadal development has been established, and is directly influenced by the presence or absence of certain factors involved.

Only 10-20% of reported cases of Swyer syndrome present a deletion in the SRY gene, which strongly suggests that there are other

genes involved in determining testicular development such as SOX-9 and WT-11.[3,7,8] The SRY gene is located in the distal region of the short arm of the Y chromosome (Yp 11.3) and encodes a transcription factor for a protein with a regulatory function that could be involved in the initiation of sex determination. The presence of the SRY gene causes the activation of a cascade of mechanisms that culminate in the development of Wolffian ducts. In cases where this gene is not expressed properly, the development of the Müllerian ducts takes place. The existence of other genes involved, other than SRY, trigger a cascade of phenomena involving HMG (high motility group) proteins that modify the DNA structure and thus the expression of regions involved in sexual differentiation.[9–11] In sum, the already differentiated gonad secretes factors that lead to the development and evolution of the ducts. In the gonad differentiated into the testis, Sertoli cells secrete anti-Müllerian hormone (AMH), without which the Müllerian ducts evolve to form fallopian tubes, the uterus, and the upper third of the vagina. And the Leydig cells secrete testosterone, responsible for maintaining the Wolffian ducts to give rise to the vas deferens, seminal vesicles, and epididymis.

Gonadal malignancy occurs in 10-30% of cases, so gonadectomy is indicated at the time of diagnosis. Among them, the most frequent are dysgerminoma and gonadoblastoma. Gonadoblastoma is a rare lesion composed of a combination of germ cells and sex cords that occurs in dysgenetic gonads, with an estimated risk of occurrence of about 30%.[12–14] It is a poorly invasive tumor and generally has a good prognosis, but it can develop into dysgerminoma (50%), endodermal sinus tumor (20%), immature teratoma (20%), embryonal carcinoma, and rarely choriocarcinoma.

The treatment includes, in addition to gonadectomy, hormone replacement therapy, prevention of osteopenia and osteoporosis, and cardiovascular disease, fertility treatments with egg donation if fertility is desired, and psychological support. Treatment with estrogen therapy to increase uterine size prior to fertility treatment has been described based on patients with Turner syndrome, probably due to its greater frequency, but it could be extrapolated to other dysgenesis such as the case of swyer syndrome.[7]

Objective

To present a case diagnosed and managed in our institution, in addition to reviewing the recent literature about this rare condition, but with a strong physical, psychological and social impact.

Methods

Analysis of clinical history of a patient with Swyer's Syndrome, diagnostic and therapeutic management. Bibliographic review.

Clinical case

An 18-year-old patient attends our hospital presenting primary amenorrhea. She denies personal and family medical history. On physical examination, she weighed 54 kg, height 1.57 m, BMI: 22; scant pubic and axillary hair, Tanner III breast exam (Figure 1), gynecological examination with vulva and vagina with usual characteristics, according to age. Vaginal examination: small uterine body and cervix, adnexa cannot be delimited. In the presence of primary amenorrhea, the following are requested: hormonal profile: FSH 96.8 mU/ml, LH 32.9 mU/ml, Estradiol <25 pg/ml; Total testosterone 0.15 ng/ml. TV ultrasound shows a hypoplastic uterus of 23x11x29 mm, ovaries are not visualized, and a heterogeneous solid image of 22x23x24 mm poorly vascularized in the left adnexal region. 46XY karyotype. In the presence of these results, a diagnosis of Swyer's syndrome is made, a Magnetic Resonance Imaging is requested, which shows a uterus of 14x20x26 mm, ovaries are not visualized, a solid lobulated oval image of 23x33x47 mm standing out in the left adnexal region and free inguinal canals. It was decided to perform laparoscopy and gonadectomy. The intraoperative findings were: intrapelvic hypoplastic uterus, uterine tubes without any particularities, enlarged left gonad of approximately 3x4 cm pearly white with a hard elastic consistency, and a fibrous band in the right adnexa (Figure 2). Bilateral adnexectomy was performed, obtaining as a histological result well-differentiated left dysgerminoma SALL4 +, OCT3/4 +, negative Inhibin and CD 117 +, and right streak gonad.

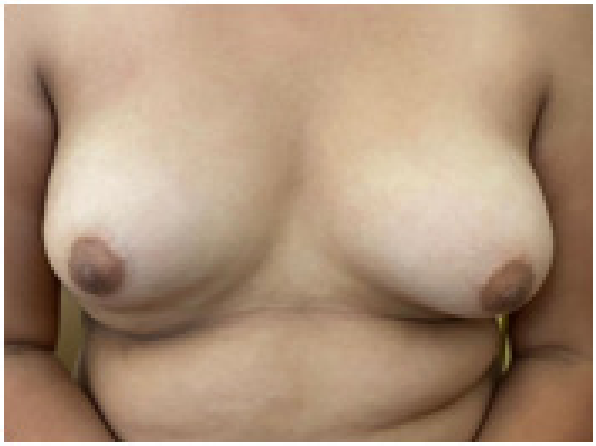

Figure 1 Patient's breast examination: Tanner III

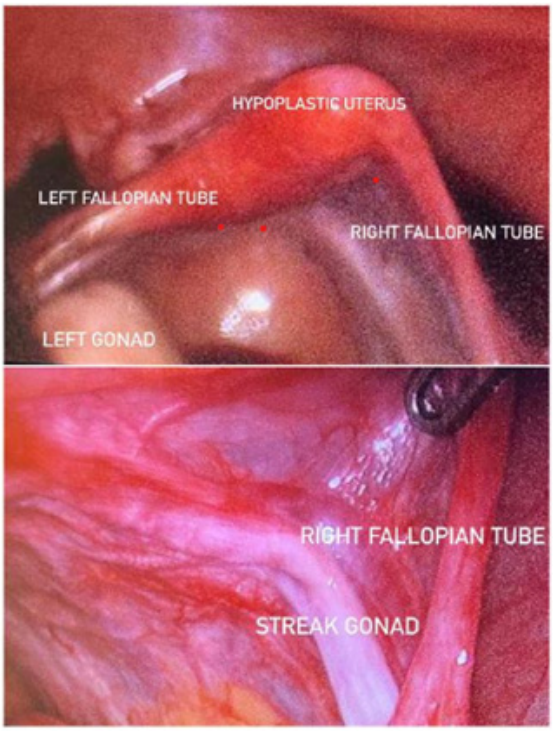

Figure 2 Intraoperative findings: intra pelvis hypoplastic uterus, uterine tubes without particularities, enlarged left gonad, and a fibrous band in the right adnexa

Conclusions

In the presence of a person with primary amenorrhea and absence or poor development of secondary sex characteristics,

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Swyer's syndrome should be suspected. A battery of studies should be requested to arrive at the diagnosis: complete hormonal profile, imaging studies, karyotype. It is essential to perform gonadectomy at the time of diagnosis due to the risk of malignant transformation. The importance of a multidisciplinary approach and psychological accompaniment of patients and relatives is highlighted. The treatment includes, in addition to the gonadectomy, hormone replacement therapy, and psychological support.

Acknowledgments

None.

Conflicts of interest

The authors declared no conflicts of interest.

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