A Case of Primary Amenorrhoea

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Abstract

**Objective:** To report a case of primary amenorrhoea and to describe an approach to evaluation.

**Methods:** Primary amenorrhoea can be due to diverse causes and needs detailed and astute evaluation. We report the case of a 17 years old individual born and brought up as a female, who was brought to us with primary amenorrhoea. Approach to such a patient with a review of available published literature is described.

**Results:** After detailed history, biochemical testing, imaging and karyotyping, we found that this patient had a XY karyotype with normal uterus, fallopian tubes and vagina, but streak gonads.

**Conclusion:** Swyer syndrome (46,XY gonadal dysgenesis), a sex reversal disorder characterized by a phenotypic female with non-functional streak gonads, poorly developed secondary sexual characters, primary amenorrhoea and 46,XY karyotype was diagnosed. This patient was treated with gonadectomy and sex hormone replacement.

Introduction

Evaluation of primary amenorrhea is always a clinical challenge. We report a case of Swyer syndrome in a 17 year old girl who presented with primary amenorrhea.

Case Report

A 17 year old girl, the only child of non consanguineous parents, presented with failure to attain spontaneous menarche. Her birth and development were normal and her scholastic performance was good. She was evaluated elsewhere and was given estrogen and progesterone combination pills with which she had withdrawal bleeding at age 17.

On examination, her height was 154 cm (mid parental height: 158cm), weight 40 kg and BMI 16.9 kg/ m². Her blood pressure was normal. All the distal pulses were well felt. Systemic examination did not reveal any abnormality. Genital examination revealed Tanner stage III breast development and Tanner stage III pubic hair.

Ultrasound of the abdomen revealed normal uterus and fallopian but the ovaries were not visualized. Serum biochemistry revealed elevated Luteinizing Hormone (LH) 16.9 mIU/ml (normal: 1.1 to 11.6 mIU/ml) & Follicle Stimulating Hormone (FSH) 84.2 mIU/ml (normal: 2.8 to 11.3 mIU/ml) and low Estradiol 0.103 nmol/L & low Testosterone 23.3 ng/dL (normal for women: 50 to 120 ng/dL).

Phytohaemagglutinin - stimulated 72-hour cultures of peripheral blood showed 46, XY karyotype in all 25 cells counted (Figure 1). Interphase fluorescence in situ hybridization (FISH) analysis confirmed the presence of XY and the presence of the SRY gene locus in all the 500 cells examined (Figure 2). The above findings confirmed that this patient with a female phenotype was in fact a genetic male.

She subsequently underwent laparoscopy. At surgery she was found to have normal uterus and fallopian tubes with bilateral streak gonads. The streak gonads and fallopian tubes were excised. Histopathology revealed ovarian tissue with immature stroma and no follicles.

She was advised to continue cyclical estrogen - progesterone replacement therapy. Fertility issues were discussed with her family and the option of assisted reproduction...
using donor oocytes was explained to them. She is doing well on follow up.

**Differential Diagnosis and Approach**

The possible causes of primary amenorrhea include Turner syndrome, mixed or pure gonadal dysgenesis, complete androgen insensitivity syndrome (CAIS), hypo gonadotrophic hypogonadism, and anatomical deformities such as mullerian agenesis, transverse vaginal septum or imperforate hymen.

Detailed history and physical examination will clearly identify patients with Turner syndrome and those with anatomical defects like transverse vaginal septum and imperforate hymen. CAIS is characterized by well developed female external secondary sexual characteristics, palpable inguinal gonads and absent or sparse body hair. Pelvic ultrasound confirms the absence of uterus and fallopian tubes in patients with CAIS and Mullerian agenesis. A low level of gonadotropins is the hallmark of patients with hypothalamic-pituitary dysfunction.

In Swyer syndrome the streak gonads fail to function and hence these patients do not develop secondary sexual characteristics. Estrogen related changes such as breast development, widening of the pelvis and hips, and menstruation do not occur. However, because of adrenal androgens, some development of pubic and axillary hair may be present. Very often, these patients present after having had some form of estrogen treatment which would have resulted in pubertal changes or even withdrawal bleeding as was the case with our patient.

Gonadotropin levels are usually elevated, indicating normal pituitary response to nonfunctioning gonads. Pelvic ultrasound will demonstrate the presence of the uterus; however the streak ovaries cannot be identified on ultrasound. Magnetic resonance imaging (MRI) or computed tomography (CT) of the pelvis are required to confirm the presence of streak gonads. Cytogenetic studies of peripheral blood are critical to confirm the 46, XY karyotype for the diagnosis of Swyer syndrome. FISH analysis will detect the presence or absence of the SRY gene; however, mutations of SRY are not detected by FISH analysis and these require molecular studies.

In our patient FISH analysis confirmed the presence of the SRY gene but further investigations to identify the exact mutation in the SRY gene were not available.

**Discussion**

Until the sixth week of embryonic life, the developing gonad is bipotential, irrespective of whether the inherited chromosomes are XX or XY. Further differentiation is determined by a group of genes. Male sexual differentiation is initiated by expression of the SRY (sex-determining region Y) gene on the Y chromosome, which leads to the gonad developing into a testis. In the absence of the SRY, the bipotential gonad develops into an ovary.

If the SRY gene is mutated, the undifferentiated gonad fails to develop into a testis despite the patient carrying both the XY chromosomes. Because testosterone and Anti- Müllerian hormone (AMH) are not produced, this results in failure of virilization and leads to the female phenotype. As the Wolffian ducts fail to develop, internal male organs are not formed. The absence of AMH leads to the development of uterus, fallopian tubes, cervix and vagina. In utero, the ovaries may contain ova, but they rapidly degenerate and these patients’ presents with primary amenorrhea.

Swyer syndrome or pure gonadal dysgenesis (PGD) was first described in 1955. Its incidence is estimated to be 1 in 100,000 live births. PGD can be either sporadic or familial with X-linked or autosomal recessive patterns of inheritance. Mutations of the SRY gene are seen in 10-15% of cases of PGD. The remainder may be due to mutations of other genes.
involved in the sex differentiation pathway such as the autosomal genes SOX9 & WT1 and the DAX1 gene on the X chromosome.³

Individuals with pure gonadal dysgenesis appear to be normal females at birth. They however do not develop secondary sexual characteristics and have primary amenorrhea. Such individuals have normal stature, normal female external genitalia, normal cervix, uterus, fallopian tubes and streak gonads. The female genitalia may be normal or hypoplastic.⁴ Streak gonads composed of ovarian-like stroma are elongated and whitish in appearance. These gonads have an increased risk of developing into gonadoblastomas and malignant germ cell tumours. Gonadoblastomas are seen in 20-30% in women with Swyer syndrome.⁵

**Management**

In the presence of the Y chromosomes, streak gonads have a high likelihood of developing into gonadoblastomas and malignant germ cell tumours. Therefore, these streak gonads must be removed within a year of diagnosis since cancer can begin even during infancy. Following surgery these patients require cyclical estrogen and progesterone replacement. Fertility is a problem in the absence of functioning gonads. In vitro fertilization with donor oocytes may be required if pregnancy is desired.

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**Potential Conflicts of Interest**

None

**Individual Author Contribution**

Anulekha Mary John : Data collection, manuscript preparation, literature search, article submission.

Vasanthi Natarajan: Patient care, clinical diagnosis.

Vivi Srivastava: cytogenetic and FISH analysis, proof reading.

Alice George : surgical treatment of the patient

Simon Rajaratnam : Overall guidance in diagnosis and patient care, intellectual input, manuscript proof reading and editing.

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