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CASE REPORT

Female with XY chromosome: Swyer syndrome

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Abstract

We report a case of pure 46,XY gonadal dysgenesis (Swyer syndrome) in a 27-year-old Malay lady. Swyer syndrome is rare and occurs in approximately 1 in 80,000. This syndrome is characterised by normal female genitalia at birth; however, the affected individuals have symptoms which usually becomes apparent in adolescence presenting with delayed puberty and amenorrhea. Besides primary amenorrhea, there is a presence of female internal genital tract and bilateral streak gonads in a phenotypic female. The genetic background of this syndrome includes mutations of several genes involved in the testis differentiation cascade. The patient was a 27-year-old lady who was referred for endocrinological evaluation because of primary amenorrhea. Physical examination revealed a phenotypic female, height 159 cm and weight 66.5 kg. She was noted to have widely spaced nipple, poor breast development, short stature, webbed neck and puffiness of the hands and feet. She had female external genitalia. Pelvic magnetic resonance imaging showed a hypoplastic uterus and ovaries at both sides measuring 5×9 mm in size. Chromosomal analysis revealed 46,XY karyotype. Analysis of the *SRY* gene showed the presence of the *SRY* gene. Serum follicle-stimulating hormone and luteinizing hormone were elevated.

Keywords: Swyer syndrome; 46,XY; primary amenorrhea

Introduction

Disorders of sex development (DSD) are congenital conditions in which the development of chromosomal, gonadal or anatomical sex is atypical. It is estimated that overall incidence of DSDs is one in 5,500 (Blackless *et al.*, 2000; Sterling and Sax, 2017). There are many types of DSD such as Congenital Adrenal Hyperplasia (CAH), Testosterone Biosynthesis Defects, Klinefelter Syndrome, Turner Syndrome and many more. Swyer syndrome is a type of DSDs where the patients exhibit female features but their sex chromosome is XY, instead of XX. Here we report a case of Swyer syndrome in 27-year-old Malay lady.

Case Report

The patient is a 27-years old Malay lady, apparently no past medical history noted. Both her parents are of Malay ethnicity; her father is 54 years old and the mother is 48 years old, with non-consanguineous marriage and they appear to have normal physical characteristics. She has a physically normal male twin. She is the second child from eight (8) siblings. The other siblings do not show any similar features or symptoms as the index case and they are considered as normal. The patient came with her parents to the hospital for complaint of primary amenorrhea.

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Physical examination of patient revealed a phenotypic female, height 159 cm, weight 66.5 kg, and breast and pubic hair development were Tanner I and II, respectively. She had female external genitalia, she was also noted to have widely spaced nipple, poor breast development, short stature, webbed neck and puffiness of the hands and feet.

Pelvic magnetic resonance imaging showed a hypoplastic uterus and ovaries at both sides measuring 5×9 mm in size. Serum follicle-stimulating hormone and luteinizing hormone were elevated. Serum tumor marker concentrations were normal.

Chromosomal analysis was done for further investigation of her chief complaint. Patient's leucocyte sample was collected fresh from her peripheral blood sample and Giemsa banding was done. All metaphases were captured and analysed using Cytovision 6.0 software and final analysis showed 46,XY in 72 metaphases examined with 400-550 ISCN bphs resolution (Figure 1). The finding was confirmed with the presence of *SRY* gene by PCR analysis (Figure 2).

Hormone replacement therapy was initiated for this patient and had resulted in a development of secondary sexual characters. After about a year and half (1.5) of treatment, the patient had menarche and responding well to treatment on subsequent follow-ups.

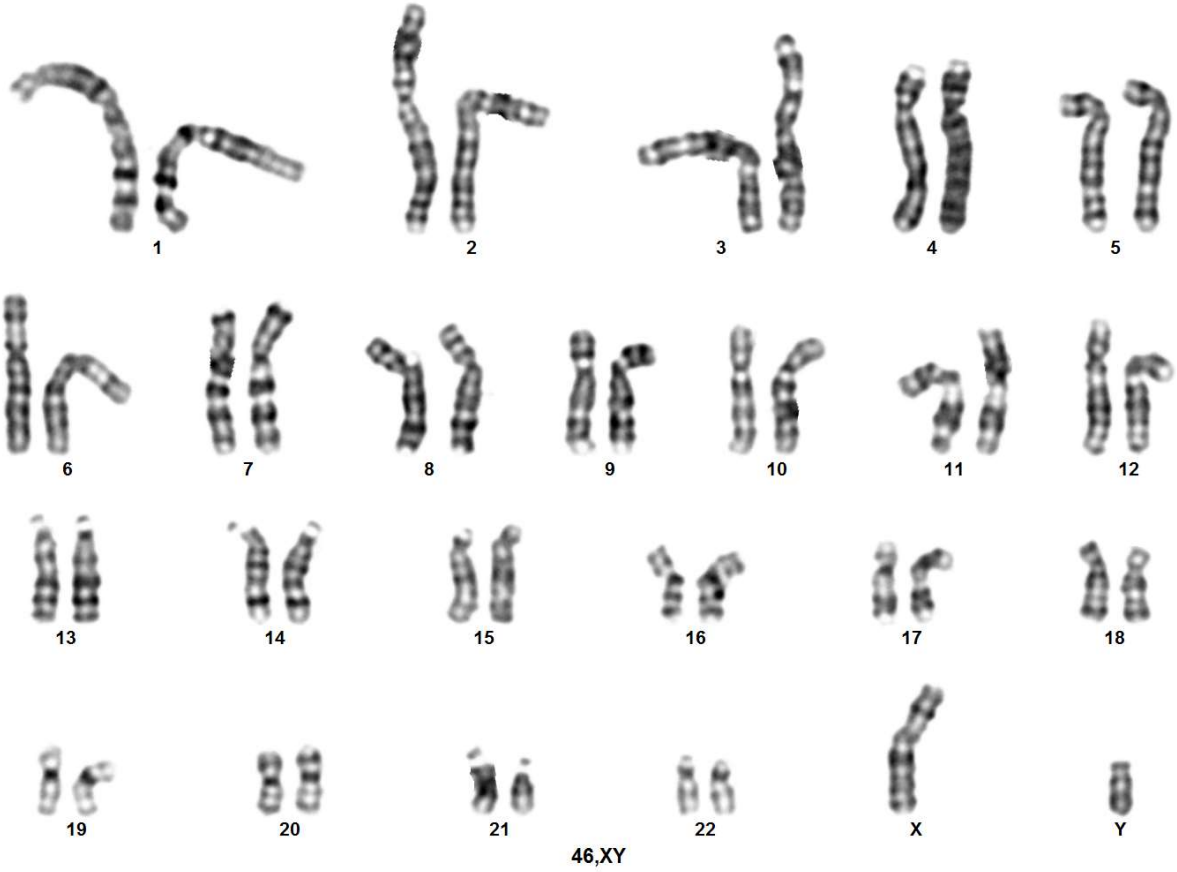

Figure 1. Karyogram of the patient's karyotype depicting 46, XY examined with 400-550 ISCN bphs resolution.

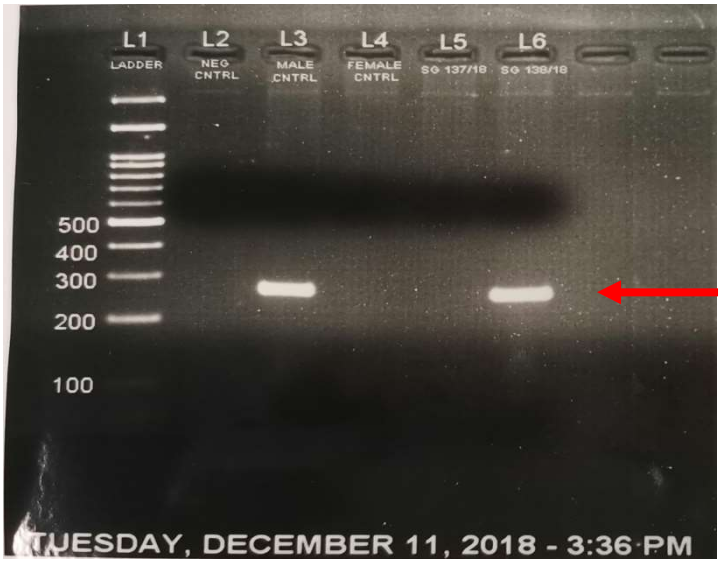

Figure 2. PCR analysis and results confirm the presence of *SRY* gene in the patient (red arrow). Band size for *SRY* gene is 270bp.

Discussion

The male and female reproductive systems develop initially as embryonically "indifferent". Male sex determination is due to the presence of *SRY* gene located on the chromosome Y, which initiates the formation of testis. In the early stage of sex development, testis secretes anti-Mullerian hormone (AMH) from the sterol cells that causes regression of the Mullerian ducts, fallopian tubes and uterus and therefore prevents the formation of female internal genitalia (King and Conway, 2014; Patel; and Gondal, 2021).

Individual with Swyer syndrome has a typical female external genitalia with a normal fallopian tube and uterus but the gonads (ovaries) are not functional. These gonads are undeveloped and these remaining clumps of tissues are called gonad streaks.

Most individuals with Swyer syndrome do not experience any outward symptoms until they are in their early teens when they do not experience their menses; or exhibit primary amenorrhea. Swyer syndrome patients appear normal physically, tall in height with small or undeveloped breasts but normal axillary and pubic hair development. Usually, the diagnosis of Swyer syndrome of a suspected individual is at younger age group; however, our patient is presented to the clinical department at 27 years of age, most likely after exhausting other non-medical efforts.

The first person to identify and describe this syndrome is a scientist named Swyer. In 1955, Swyer reported two cases of sex reversal that differed from the known forms of what was then referred to as 'male pseudo hermaphroditism' (Swyer, 1955). Swyer described this syndrome to be caused by an error in sex determination during the course of embryogenesis.

Swyer syndrome is caused by mutations in genes related to the development of gonads. The *SRY* gene which is located on chromosome Yp11.3, encodes for testis-determining factor that controls the activation of genes responsible for the development of testis. This gene comprises high mobility group (HMG) box that shares characteristics with other DNA-binding sequences. Deletions in the DNA-binding region of the *SRY* gene accounts for 10 to 20% of women diagnosed with Swyer syndrome (Michala *et al.*, 2008). However, in 80% to 90% of the cases, the *SRY* gene are normal and mutations in other testis determining factors are probably implicated (Michala *et al.*, 2008). For example, the *NR5A1* gene located on chromosome 9q33.3 is another gene that has been implicated in Swyer syndrome (Paliwal *et al.*, 2011; Song, Fan and Gong, 2018). This gene encodes for steroidogenic factor-1 (SF-1) that regulates the development of gonad. Recently, a study revealed 14 novel *NR5A1* mutations in 30 patients diagnosed with Swyer syndrome (Song, Fan and Gong, 2018). Interestingly, 20% of the patients inherited the mutations from their maternal and paternal lines (Song, Fan and Gong, 2018).

Apart from karyotype analysis, fluorescent *in situ* hybridization method can also be used to confirm the presence of Y chromosome (Chand *et al.*, 2020). In the absence of viable evidence through conventional cytogenetics analysis, Sanger

sequencing is another approach to confirm the diagnosis (Paliwal *et al*., 2011; Song, Fan and Gong, 2018). As of time of writing, there are 109 and 183 mutations for *SRY* and *NR5A1* genes respectively, recorded in the Human Genome Database indicating the need for further analysis at the molecular level (*Human Gene Mutation Database*).

The treatment for Swyer syndrome may include hormone replacement therapy to replace estrogen and progesterone hormones in order to induce puberty and reinstate hormonal balance in patients. Furthermore, estrogen therapy should also be established to ensure healthy bone formation followed by cyclic estrogen and progesterone treatment until 50 years of age (Priya *et al*., 2017). The undeveloped gonad streaks have the risk to develop into high risk tumour, which are gonadoblastomas or dysgerminomas (Da Silva Rios *et al*., 2015; Hamed and Hanafy, 2021). Dysgerminomas is germ line tumour occurs in one of three patients with Swyer syndrome (Matsumoto, Shimada and Ida, 2014). Therefore, surgery is recommended to remove the undeveloped gonads (streak gonads) as soon as the diagnosis has been established. However, when the malignant tumour has developed to an advanced stage, a hysterectomy is necessary to prevent the spread of the tumour as shown in a recent report (Da Silva Rios *et al*., 2015).

Conclusion

Patients with Swyer syndrome may have normal female physical characteristics and some may also show abnormal features. Usually for females with Swyer syndrome, they present with primary amenorrhea as they have non-functioning streak gonads. In this report, the patient had undergone genetic counseling with the experts and karyotyping analysis showed 46,XY chromosome with the presence of *SRY* gene. She was later treated with hormone replacement therapy and had menarche.

With this report, we emphasize the importance of performing karyotype analysis, which is diagnostic for Swyer syndrome, in all cases with primary or secondary amenorrhea even in the presence of normal breast development. Upon diagnosis, specific treatment can be instituted to the patient.

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