Primary amenorrhoea caused by Turner syndrome: A case series

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ABSTRACT

Background: Amenorrhoea is a condition where women do not experience menstruation or the cessation of menstrual cycles at reproductive age. Amenorrhoea is divided into primary and secondary. Turner syndrome is one example of gonadal dysgenesis that cause the most common primary amenorrhoea. It is represented by the absence of all or part of the normal second sex chromosome and physical features including short stature, webbed neck, cubitus valgus, pterygium colli, low hairline, edema of the hands and feet, and shield chest. Clinical pictures and karyotype of Acehnesse patients with Turner syndrome are presented in this study. The patients involved in the study were those who came to an endocrinology clinic in a tertiary care center.

Case Presentation: We reported four cases of Turner syndrome which were confirmed from anamnesis, physical examination and chromosomal analysis at the Department of Obstetrics and Gynecology in the Fertility, Endocrine and Reproductive Division of RSUD Dr. Zainoel Abidin Banda Aceh.

Conclusion: All patients with Turner syndrome had amenorrhoea, short stature, bone deformity and underdeveloped primary dan secondary sexual characteristic. Only one case has monosomy X (45, XO), a mosaic chromosomal component was present in the rest of them (45, X with mosaicism).

Keywords: Turner Syndrome, Primary amenorrhoea, Gonad dysgenesis.


INTRODUCTION

Menstrual problems are more common in younger people, especially in developing countries. This problem puts pressure on a person's social, emotional and psychological life along with the emergence of gynecological problems.1 Women experiencing mensturation for the first time (called menarche) is a sign of entering puberty, an early sign of functioning of the reproductive system and entering the maturity stage of the sexual organs in the body, many changes appear including physical and mental changes which usually occur in the range of age 10-16 years or at early adolescence before entering the reproductive period. About 5.2 % of children's menarche occurs in 17 provinces in Indonesia under the age of 12. The difference in each country for the age of menarche is influenced by environmental conditions, nutritional status, physical activity and genetic factors.2

Amenorrhoea is the absence of menarche in women of reproductive age. Amenorrhoea is classified into two, namely: (1) Primary amenorrhoea, defined as circumstances that have never experienced menstruation at age 14 with secondary sexual characteristics absence, or at age 16 with normal growth and development of secondary sexual characteristics. (2) Secondary amenorrhoea is defined as the ceasing of menstruation for at least 3 consecutive months in women who have previously had regular menstruation.3 In Rebar R (2018), some physicians will consider to start the evaluation of a girl with primary amenorrhoea at age 14, especially if it has been more than 5 years since the first sign of pubertal development. Women who are menstruating less than nine times in 12 months (defined as oligomenorrhoea) should be evaluated like women who experience secondary amenorrhoea. These women usually experience oligo or anovulation. Primary and secondary amenorrhoea that occur as a result of artificial action, for example, medicinal amenorrhoea/iatrogenic amenorrhoea, cannot be included in the evaluation results of women for amenorrhoea.4

The prevalence of amenorrhoea without pregnancy, breastfeeding, or menopause is 3-4%. Amenorrhoea reflects the failure of the hypothalamic-pituitary-gonadal to induce

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cyclic changes in the endometrium that usually causes menstruation and can also occur due to lack of the presence of secondary sex organs or their obstruction tool genitalia. Amenorrhoea can result from abnormalities at any level of the reproductive tract.6

World Health Organization (WHO) estimates amenorrhoea is the 6th cause of infertility worldwide and affects women of childbearing age as much as 2-5%.3 Even so, amenorrhoea is not a diagnosis and is only a sign of a disease. Normally, menstruation occurs at 28 ± 3 day intervals with a normal range of 18–40 days in two-thirds of women. The three causes that need to be considered in categorizing amenorrhoea are: (1) Anatomical condition, including pregnancy, which almost can be detected by physical examination alone; (2) Ovarian failure; (3) Chronic anovulation as a result from various endocrine disorders.4

Research on amenorrhoea has been conducted since a long time ago, stating that gonadal dysgenesis is the most common cause of primary amenorrhea. Turner syndrome by 43%, followed by Agenesis Mullerian as much as 15% and Delayed puberty as much as 14%. These three causes are the most common causes of gonadal dysgenesis that cause primary amenorrhea.6

Turnersyndromeisa common condition in which a woman with a chromosomal abnormality originating from the absence of a second sex chromosome, either partial or total, with or without cell line mosaic, becomes X monosomy (45, X).7,8,9 This chromosomal abnormality affects approximately 1 in 2500 female patients.10 Typical abnormalities in Turner Syndrome include short stature, gonadal dysgenesis (usually reflecting ovarian failure), characteristic facial shape, webbed/short neck, short hair, wide chest with sparse nipple spacing, nevus throughout the body, shorter IV metacarpals, small nails, shield-shaped chest, unfavorable breast development, and cardiovascular anomalies. Many patients develop coarctation of the aorta, cardiovascular abnormalities, lymphedema during fetal life leading to cystic hygroma, and primary or secondary amenorrhoea. People with Turner Syndrome also experience abnormalities in the urinary system such as a malformation of the koliigentes duct in the nephron system and a hoof-like kidney shape that occurs in 30–40% of patients. There are eye disorders such as epicanthus, ptosis, strabismus and hyperopia, abnormalities in the hearing system (chronic otitis media and deformed ears) and immune disorders (autoimmune thyroiditis). Turner Syndrome patients with epilepsy have also been reported to be associated with developing cortical malformations.5,11

In Turner Syndrome, when the germ cells in the ovarian epithelium undergo migration which is then followed by a normal mitotic division process but the next process is not followed by normal meiotic division, it will cause rapid oocyte cell loss. About 70-80% of sufferers do not experience puberty development and 90% of sufferers experience primary amenorrhoea.6 Cyclic replacement of estrogen and progesterone is required to induce the development of puberty starting at the age of 11 years. At the age of 13-14 years, adolescent girls with Turner Syndrome should undergo a process of counseling regarding options for fertility and other patients who have a mosaic karyotype and who experience spontaneous puberty accompanied by no increase in FSH or decrease in AMH.
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CASE REPORT

CASE PRESENTATION

Case 1
A 28-year-old woman came with a complaint that she had never experienced menstruation until 1 year ago after using contraceptive pills which were obtained by an obstetrician and gynecologist when she was 27 years old. Every time she took birth control pills, she got menstruation for 6 days and changes sanitary napkins once a day. No history of menstrual disorder in her family. On physical examination, the patient's body weight was 50 kg, height 138 cm, BMI 26.2 kg/m2 (short stature). Her forearm was angled out away from the body when the arm was fully extended (cubitus valgus). She also had a shield chest and a low hairline.

Assessment of maturation in secondary sexual development recognized by Sexual Maturity Rating or Tanner Stage which is used to document and track the development and sequence of secondary sex characteristics during puberty, adolescence and adult. Tanner's stage evaluates the growth of pubic hair and breast development. This patient had Tanner Stage 2 (breast bud only) for breast development and also Tanner Stage 1 for pubic hair (no hair, figure 1a). The blood laboratory on July 4 2019 obtained Haemoglobin 14.6 gr/dl, Haematocryte 39%, leukocytes 7,400/m3, platelets 279,000 /m3, blood sugar levels at 111 gr/dl. Ultrasound examination revealed a rudimentary uterus. From laboratory finding, the Anti Mullerian Hormone (AMH) level results were <0.01 ng/mL (normal value: 1.2-4.6 ng/ml). Her low AMH level showed a premature ovarian failure. Her abnormal chromosome result was mosaicism of 45X with another cell line: 45, X [19] / 46, X, i (X) (q10) [21] (figure 1b). Based on the history, physical examination and investigations, the patient was diagnosed with primary amenorrhoea e.c. Turner Syndrome.

Case 2
A 22-year-old woman came complaining that she had never had a period. The patient also complained of the absence of secondary sex growth. Physical examination of the patient found:

a. Posture short stature (height 140 cm, body weight was 30 kg) accompanied with lumbar scoliosis, webbed neck, chest-shaped shield (shield-like chest).

b. Undeveloped breast glands and areola follow the contour of the chest skin (Tanner stage I).

c. No pubic hair was found (Tanner stage I).

Gynecological examination found vulva urethra within normal limits, but the vaginal opening was not found. On ultrasound examination (USG) with a difficult impression of the uterus to be assessed, the right and left ovaries are difficult to assess. From the karyotypic examination results are 46, X, r? (X) [28] / 45, X [12] (figure 2a and 2b).

Case 3
A 28-year-old woman came with a complaint that she had never had a menstrual period. None of her family members had the same case. On physical examination, the patient's body weight was 50 kg, height 138 cm, BMI 26.2 kg/m2 (short stature). Her forearm was angled out away from the body when the arm was fully extended (cubitus valgus). She also had a shield chest and a low hairline.

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From the results of laboratory tests, the estradiol levels were low (10.1 pg/mL), while the FSH and LH levels were high (FSH: 73.74 mIU/mL, LH: 23.02 mIU/mL). Anti-Mullerian Hormone: <0.13 ng/mL suggests premature ovarian failure. Another examination performed was a karyotype (45, X) indicating Turner Syndrome.

The patient also performed an X-ray of the anterobrachial, lumboasacral, pelvic, and cruris where scoliosis was found in the lumbar spine tilted to the left and the pelvis in the form of an android type. From the MRI examination, it was found that uterine hypoplasia.

The patient also referred to the Eye and ENT department due to eye and hearing problems. From the ENT examination, they found bilateral sensorineural deafness and sclerosis of the tympanic membrane of the left ear, but the sensorineural hearing loss, typical cardiovascular disease, skeletal abnormalities, anomalies of the fingers and kidneys, certain neurodevelopmental profiles, and a constellation of other disorders that are more common in Turner Syndrome, including hypothyroidism and celiac disease. Of all the characteristics above, the ones that stand out are hypothyroidism, diabetes mellitus, hypertension, and osteoporosis.

The other result was the low level of Anti Mullerian Hormone (AMH <0.01 ng/mL in case 1 and AMH<0.13 ng/mL in case 2). Decreasing AMH level was one of the signs of premature ovarian failure for reproductive-age females. Turner Syndrome typically results in the most severe and irreversible premature ovarian failure, often clinically evident before menarche. Premature ovarian failure (POF) is a primary ovarian defect characterized by absent menarche (primary amenorrhea) or premature depletion of ovarian follicles before the age of 40 years (secondary amenorrhea). Typically, in Turner Syndrome, menopause precedes menarche, and there is no evidence of ovarian function. POF is biochemically characterized by low levels of gonadal hormones (estrogens and inhibins) and high levels of gonadotropins (LH and FSH) as shown in case 3: FSH 73.74 mIU/mL, LH 23.02 mIU/mL. The elevation of FSH is usually more marked than that of LH and an FSH value >30 U/L is indicative of ovarian failure. Beyond infertility, hormone defects may

**DISCUSSION**

We reported 4 cases of Turner Syndrome. The most common complaint submitted by patients was amenorrhea and physical examination reveals short stature and underdeveloped secondary sexual development (Table 1).

Turner Syndrome implies the presence of physical characteristics such as short stature, webbed neck, and lymphedema. The clinical manifestations of Turner Syndrome can be extended to include other characteristics. Turner syndrome is associated with a variety of morbidities that can affect nearly every system of the body and become increasingly affected during adult life such as linear growth failure, ovarian insufficiency (delayed puberty), sensorineural hearing loss, typical cardiovascular disease, skeletal anomalies, anomalies of the fingers and kidneys, certain neurodevelopmental profiles, and a constellation of other disorders that are more common in Turner Syndrome, including hypothyroidism and celiac disease. Of all the characteristics above, the ones that stand out are hypothyroidism, diabetes mellitus, hypertension, and osteoporosis.

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**Table 1.** The 4 cases of Turner Syndrome

<table>
<thead>
<tr>
<th>Case</th>
<th>Complaint</th>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amenorrhea</td>
<td>138, No, No, Yes, No</td>
</tr>
<tr>
<td>2</td>
<td>Amenorrhea</td>
<td>140, Yes, Scoliosis, Yes</td>
</tr>
<tr>
<td>3</td>
<td>Amenorrhea</td>
<td>120, Yes, Scoliosis, Yes</td>
</tr>
<tr>
<td>4</td>
<td>Amenorrhea</td>
<td>132, Yes, Scoliosis, Yes</td>
</tr>
</tbody>
</table>

**Table 2.** Karyotypic examination results

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yo)</th>
<th>Karyotype</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>45, X [19] / 46, X, i (X) (q10) [21]</td>
<td>Mosaic</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>45, X</td>
<td>Monosomi</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>45, X [30] / 46, X, i (X) (q10) [10]</td>
<td>Mosaic</td>
</tr>
</tbody>
</table>

**Case 4**

A 37-year-old woman came complaining that she never had menstruation. This patient also had hearing problems (deafness). On physical examination, she had a short stature with a body height of 132 cm, a webbed neck, and a shield-like chest with a wide gap between the nipples, scoliosis of the lumbar, and cubitus vagus.

Her secondary sexual characteristics were Tanner Stage II for breast growth and the areola widens, darkens slightly, and elevates from the rest of the breast like a small mound. Her pubic hair grew sparse, straight, and only slightly curled,

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cause severe neurological, metabolic, or cardiovascular consequences and lead to the early onset of osteoporosis.

Uterine development is also altered in girls with Turner syndrome. USG examination showed rudimentary uterus in cases 1 and 4, while in case 2 patient uterus was difficult to assess. About half of the cases of primary amenorrhea are due to ovarian dysgenesis, which is revealed by the finding of streak ovaries accompanied by uterine hypoplasia at the ultrasound.

Turner syndrome is associated with multiple skeletal abnormalities. Scoliosis was found in all cases in this study but only one case performed radiological examinations of lumbosacral and pelvic X-rays which found scoliosis of the lumbar vertebrae. Scoliosis occurs in around 10% of adolescent girls with Turner syndrome and may contribute to short stature. Scoliosis screening is therefore usually undertaken. Women with small deletions distal to the short arm on the X chromosome (Xp22.33) where the SHOX (short stature homeobox gene is located, often have short stature and bone anomalies associated with other Turner Syndrome. So far, only one gene on the sex chromosome, SHOX, which is located in the pseudoautosomal 1 portion of the X and Y chromosomes, has been believed to be related to the phenotype in Turner Syndrome. SHOX escapes X inactivation and decreased SHOX expression explains part of the growth deficit associated with Turner Syndrome. Also, SHOX haploinsufficiency is generally associated with scoliosis.13

The severity of clinical manifestations in Turner Syndrome is approximately the same as the magnitude of the deficit in the material making up the X chromosome. The karyotypes in Turner Syndrome can be divided into two main groups; aneuploidy and structural anomalies. Aneuploidies consists of 45, X (missing one X chromosome entirely) and various forms of mosaicism such as 45, X / 46, XX and 45, X / 46, XY. The group of structural anomalies includes deletion of Xq isochromosomes, X rings, Xp, and Xq partials. To add a further level of variation, structural anomalies may exist in the form of mosaics with 45, X, or 46, XX karyotypes. Other more complex karyotypes include chromosomal translocations and mosaics 45, X / 47, XXX.12

In this study, the karyotypic examination that had been performed shows that only one patient had complete monosomy (45, X) while the rest have Turner mosaic (Table 2). In population about 40-50% of women with Turner Syndrome present with karyotype 45, X 15-25% have mosaicism with 45, X / 46, XX about 20% of women have isochromosomes, and the ring chromosome is present in a few women.14 As many as 10-12% of women had a different amount of Y chromosome material, while 3% were present with 45, X / 46, XY.15,16 None of the patients with mosaic karyotype in this study had a Y chromosome, most of the case have 45, X / 46, XX.

All of the patients present to our health facility in Aceh in their post-adolescent age (22 yo to 37 yo). This late age of presentation is a cause for concern as therapy for improving height outcomes is often not possible, and delay in estrogen therapy has a detrimental effect on bone health and social and psychological well-being. Barriers to the achievement of these goals are often seen due to lack of awareness of the problem, late presentation, and financial constraints.

CONCLUSION

Primary amenorrhea is the most common presenting feature in women with Turner Syndrome leading to delayed age of presentation. The most common physical signs of Turner syndrome in Acehness females were short stature, scoliosis, short web neck, and underdeveloped primary and secondary sexual characteristic. Only one patient with Turner Syndrome has been reported who showed chromosomal monosomy X (45, XO). All other cases were a mosaic chromosomal component.

CONFLICT OF INTEREST

The authors have nothing to disclose.

FUNDING

This study uses the author's funds, without support from any sponsors or scholarships.

ETHICAL CONSIDERATION

This case series have obtained the ethical approval from the Health Research Ethics Commission of Faculty of Medicine of Universite of Syiah Kuala – Dr Zainoel Abidin Hospital. All patients and their families have understood and agreed to the publication of this article.

AUTHOR CONTRIBUTION

All authors contributed to the study, including literature research, data collection, data analysis, and manuscript preparation.

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