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TURNER SYNDROME: DIAGNOSIS AND TREATMENT CHALLENGE IN A DEVELOPING COUNTRY.

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ABSTRACT

Turner syndrome is one of the rare genetic diseases when there is a partial or complete missing of the X chromosome in females. Short stature and late puberty are the most common manifestations and the main target of treatment. However, not all Turner syndrome patients can get both treatments. We herein report the challenges in treating Turner syndrome patients in a developing country with a chief complaint of short stature and whose breasts had not grown. The patient was diagnosed late because the parents thought her short stature was normal. The patient denied growth hormone therapy because the treatment was expensive and the government's insurance program did not cover it. Therefore, we optimized her treatment in another aspect, which was inducing her puberty with low-dose estrogen. In developing countries, late diagnosis, expensive treatment, and no insurance coverage are challenges in treating patients with rare diseases such as Turner syndrome.

Keyword: Chromosomes, Diagnosis, Developing countries, Treatment, Turner syndrome.

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Turner syndrome is one of the rare genetic diseases when there is a partial or complete missing of the X chromosome in females. Short stature and late puberty are the most common manifestations and the main target of treatment. However, not all Turner syndrome patients can get both treatments. We herein report the challenges in treating Turner syndrome patients in a developing country with a chief complaint of short stature and whose breasts had not grown. The patient was diagnosed late because the parents thought her short stature was normal. The patient denied growth hormone therapy because the treatment was expensive and the government's insurance program did not cover it. Therefore, we optimized her treatment in another aspect, which was inducing her puberty with low-dose estrogen. In developing countries, late diagnosis, expensive treatment, and no insurance coverage are challenges in treating patients with rare diseases such as Turner syndrome.

Keyword: Chromosomes, Diagnosis, Developing countries, Treatment, Turner syndrome

INTRODUCTION

Turner syndrome occurs when there is a partial or complete missing of the X chromosome in females. This syndrome occurs in about 25–50 per 100,000 females. The most karyotype that the patient had is 45,X.[1] Short stature is one of the most common manifestations of Turner syndrome. However, sometimes the parents do not think that short stature is a problem and ignore the signs, causing a late diagnosis of Turner syndrome.[2,3] Another common manifestation is the loss of ovarian function, causing a delay in puberty in patients with Turner syndrome.

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Additional symptoms and signs of Turner syndrome include webbed neck, low posterior hairline, broad chest, wide space nipple, short fourth metacarpal, multiple pigmented naevi, and lymphedema.[1] Turner syndrome is related to several organ abnormalities. Congenital heart defects are one of the most common congenital malformations in Turner syndrome and have become the most common cause of death.[4] Other abnormalities that can be found are skeletal abnormalities, sensorineural hearing loss, renal anomalies, neurocognitive, etc. The definitive diagnosis of Turner syndrome is by karyotype examination. After the Turner syndrome diagnosis has been made, screening for related abnormalities must be done. The primary treatment of Turner syndrome is treating short stature and inducing puberty.[1] Growth hormones are effective in increasing the height in Turner

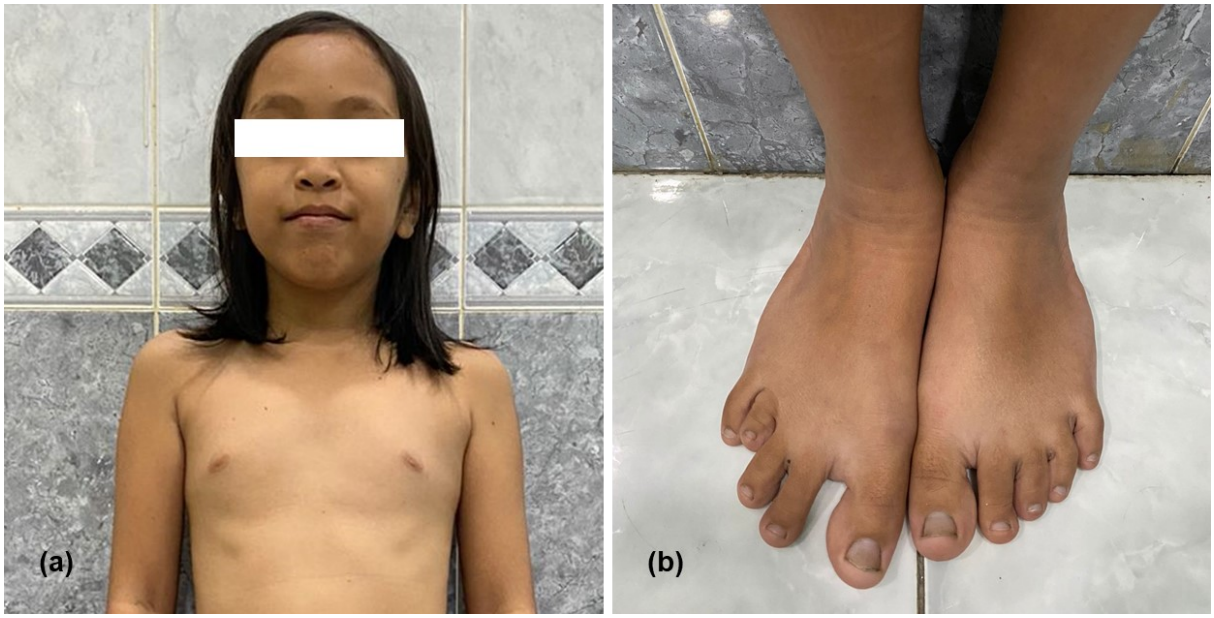

Figure 1: (a) The clinical presentation of the patient: low posterior hairline, short neck, wide space nipple, puberty status A1M1P1 (b) Brachymetatarsia

syndrome patients.[5] Estrogen replacement therapy is the choice of therapy to induce puberty and prevent infertility.[1] However, not all patients with Turner syndrome can be treated for both main complaints. This case report shows physicians' challenges in treating Turner syndrome in developing countries.

CASE REPORT

A 13-years-3-months-old girl came to the hospital with a chief complaint of short stature, and her breasts had not grown. The patient was embarrassed because she was the shortest student at her school. The parents noticed that their child looked shorter than their peers since she was four years old. However, the parents delayed taking the patient to the doctor because they thought that after puberty, she would have a normal height. She was also embarrassed because her breast had not grown, and she had not got her first period. The patient was healthy, with no history of headache, projectile vomiting, or blurred vision. The patient had a normal development. There was no significant history in the family and her siblings were healthy. During pregnancy, the mother was healthy and had no complications.

The patient's height was 120 cm (Height/Age CDC 2000 <P3) and her weight was 21 kg (Weight/Age CDC 2000 <P3), while in the Turner Syndrome growth chart both her weight and her height were < -2 SD. Her height age was 6 years and 9 months old. Her upper segment body length was 58 cm and the ratio of upper/lower was 0.9. Her father's height was 165 cm, and her mother was 150 cm. The mid-parental height was 149 cm, with a potential genetic height of 140.5 – 157.5 cm. The patient showed a low posterior hairline, short neck, no webbed neck, wide space nipple, and short fourth metacarpal and brachymetatarsia (Figure 1). The pubertal status of the patient was A1M1P1.

Laboratory findings showed high luteinizing hormone (LH) 9.95 mIU/mL (normal: 2.39-6.6 mIU/mL), high follicle-stimulating hormone (FSH) 84.47 mIU/mL (normal: 3,03-8.08 mIU/mL) and low estradiol <9.0 pg/mL (normal 18–147 pg/mL). Her bone age examination showed an 8-year-10-months-old girl and 78.4% of the mature height.

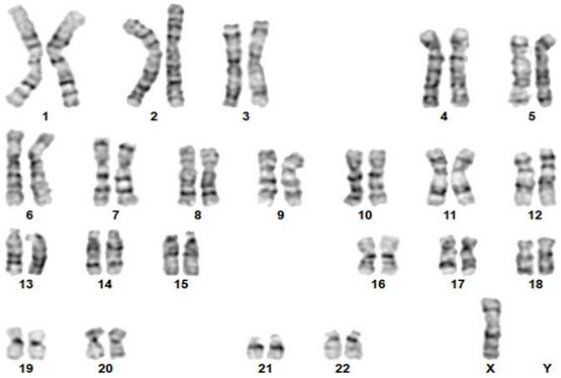

Figure 2: Chromosome analysis result of the patient (45,X)

The patient chromosome analysis result showed 45,X, in line with Turner Syndrome (Figure 2). Her ultrasonography pelvis showed a hypoplasia uterine and ovaries were not visualized. The IGF-1 result was lower than the normal range, 98 ng/mL (normal 183–850 ng/mL).

The main management of the patient was to treat growth problems, induction of puberty, and finding other related abnormalities to Turner syndrome. The patient was recommended to undergo a growth hormone treatment to treat her growth problem. However, the patient declined the treatment because growth hormone treatment was expensive, and the insurance did not cover this treatment. Estradiol valerate 1x0.5 mg daily was given to the patient to induce her puberty. Echocardiography was performed, ultrasonography examination of her renal and bladder, ear and eye examination. The patient's heart, renal, and bladder were normal. No abnormal finding was found on the ear examination. However, ocular hypertension was found in both eyes and the patient was administered timolol maleate and oxymetazoline hydrochloride as treatment[DFA1].

DISCUSSION

This case report highlights the challenges faced by physicians in developing countries in treating rare diseases like Turner syndrome. This patient had two main presenting features of Turner syndrome, namely, short stature and delayed puberty. She was diagnosed late at the age of 13 years, even though her parents had noticed that she was shorter than her peers since she was 4 years old. A cohort study by Swauger et al. showed that most of their patients were diagnosed prenatally, the median age for delayed diagnosis in the study was 7 years old.[6] Apperley *et al*. also found similar findings: 54% of their patients were diagnosed during childhood (1 – 12 years).[2] Late diagnosis of Turner syndrome affects the maximum treatment effect in the patient because the patient has missed the opportunity of early growth hormone treatment and induction of puberty at an appropriate age.[2]

Previous studies found that girls diagnosed at age more than 12 years old had the greatest height deficit.[2] Thus, it is particularly concerning that our patient was diagnosed at 13 years old. The late diagnosis of this patient was because her parents thought her short stature was normal and the patient would reach her normal height during puberty. Parents with lower education backgrounds, lower income levels, and no private insurance have lower median height expectation thresholds.[7] In developing countries, those conditions were common. Therefore, clinicians must take notes on how the parents see short stature as a problem, so there would be no more late diagnoses of Turner syndrome. The height screening program for children is also important. Thus, even though the parents did not bring the children because of their short stature, they can still get diagnosed and treated early. The aim of our patient’s treatment after being diagnosed with Turner syndrome was to treat her short stature and induce her puberty. Treating these two main symptoms would boost the patient’sconfidence.

Several studies have shown that the administration of growth hormone can significantly increase lifelong height in patients with

Turner syndrome. Thus, growth hormone is still the main treatment choice for treating short stature.[2,8] However, the government's insurance program does not cover growth hormone treatment. Particularly in a rare disease like Turner syndrome, there are lots of limitations because the insurance focuses more on common diseases such as hypertension, diabetes, and cancer. Therefore, even though the patient had insurance, the patient had to get this treatment out-of-pocket. Growth hormone treatment is still expensive in our country, so the growth treatment could not be given to the patient because her parents could not afford it. Therefore, the main goal of the treatment is to induce the patient's puberty and treat the function of the ovary. The patient was given a low dose of estrogen hormone (0.5 mg/day). Estrogen replacement therapy is given to Turner patients to mimic the normal progression of puberty in girls and should begin at age 11-12 years old. Low dose-estradiol is usually given to preserve the child's growth potential due to its role in the fusion of epiphyses, thus stopping bone growth and affecting height.[9,10] Among patients treated with estrogen alone in a controlled trial study by Ross JL *et al.* 32% of them increased their height, and this finding was higher than those treated with double-placebo treatment.[11] Based on these findings, the clinician could also hope that the height increase was achieved in this patient.

CONCLUSION

Height increment and inducing puberty is the main goal of Turner syndrome treatment. However, not all of the patients can get treated for both complaints. Therefore, the clinician must optimize any available treatment for the patient. Late diagnosis, expensive treatment, and no insurance coverage are challenges in treating patients with rare diseases such as Turner syndrome in developing countries.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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