CASE REPORT

Case Report: A Delayed Diagnosis of Turner's Syndrome in Aboriginal Adolescence in Primary Care

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ABSTRACT

Turner syndrome is a genetic disorder characterized by a partial or complete loss of one X chromosome in females. This case report describes a 16-year-old Aboriginal adolescent who presented with amenorrhea and developmental challenges in primary care on a community visit. The patient's medical history revealed a delay in speech development, poor academic performance, and limited literacy skills. Physical examination demonstrated characteristic Turner Syndrome features such as slanted eyes, a flat nasal bridge, a webbed neck, cubitus valgus, short metatarsals, and atrophic genitalia. Karyotyping confirmed the diagnosis of Turner Syndrome (45, X). In addition, the patient exhibited growth retardation, with height and weight measurements below the 3rd centile. Management included a referral to obstetrics and gynaecology for growth hormone therapy, aortic aneurysm and bone marrow density monitoring, and genetic counselling for the family. This case emphasizes the importance of early diagnosis, the challenges in diagnosing TS in rural areas and multidisciplinary care for patients with Turner Syndrome to address the condition's medical and developmental aspects.
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INTRODUCTION

Turner syndrome (TS), one of the most common genetic diseases that occurs in girls, is caused by a missing or abnormal X chromosome. TS has a prevalence of 1 in 2500 female live births (1). TS is associated with multi-systemic medical complications such as congenital heart defects (e.g., bicuspid aortic valve), skeletal anomalies, hearing impairment, ophthalmologic abnormalities, and kidney structural anomalies. Conditions such as osteoporosis, celiac disease, hypertension, and autoimmune thyroiditis are also associated with TS. Short stature, a broad chest, a webbed neck, cubitus valgus, edema of the hands or feet, gonadal dysgenesis, and delayed puberty are some dysmorphic features of TS. The diagnosis of TS can be suspected during pregnancy by ultrasonography, and it can be confirmed by genetic testing from chorionic villous sampling and amniocentesis. Realizing the complications of TS, early diagnosis necessitates thorough follow-ups to detect multi-systemic problems. Also, early detection of TS is important as it affects the final height, sexual health, and psychological development of patients (2). In this study, we report a case of late diagnosis of TS and highlight the challenges in the diagnosis of TS in rural areas.

CASE REPORT

A 16-year-old aboriginal adolescent presented to a primary clinic due to amenorrhea. Her last menstrual history was 2nd January 2020. Neither she is sexually active nor has she tested positive for pregnancy in her urine. It was reported by her mother that she began menstruating at the age of 12, with spotting and minimal, soaked a quarter of a pad at first, then reduced to spotting from the first to third day, regular cycle, and no blood clot. It is her mother who keeps track of her daughter's periods since she is unable to read and count. There is no domestic abuse, either sexual or physical. During the consultation, she answered only simple questions and was mostly silent. According to her mother, she does poorly in school and cannot read, count or read A to Z, but can write her name. She rarely does her homework. Her primary language is their native language, and she speaks a moderate amount of Malay. Her antenatal and postnatal care were uneventful. She was born to term in a tertiary hospital with a normal birth weight. After day three of delivery, she was discharged from the hospital and continued her follow up in a healthcare clinic. She has completed her immunization schedule up to the age of 13. Only her mother could remember that her speech

development was delayed compared to her siblings, as she did not start speaking until more than two years old. They were not consanguineous and neither parent knew if there was a family history of dysmorphic disorder. The parents completed primary school education. The father works for self-sufficiency and the mother is a housewife. She is the fourth of six siblings. At seven years old, the second sister died of measles complications, and the fifth brother died from acute gastroenteritis and severe dehydration at one year old. She has two brothers, the eldest of whom is twenty-one and the second of whom is eighteen. The two of them stopped their studies after Form 3, both working as fishermen. The youngest sister is 7 years old, healthy, and in standard one primary school. On physical examination, she maintains good eye contact, sitting quietly, with slanted eyes and a flat nasal bridge, a high arched palate, a webbed neck, and cubitus valgus, short metatarsal. (Figure 1 and 2)

Figure 1: Childhood photo (slanted eyes, flat nose bridge, webbed neck).

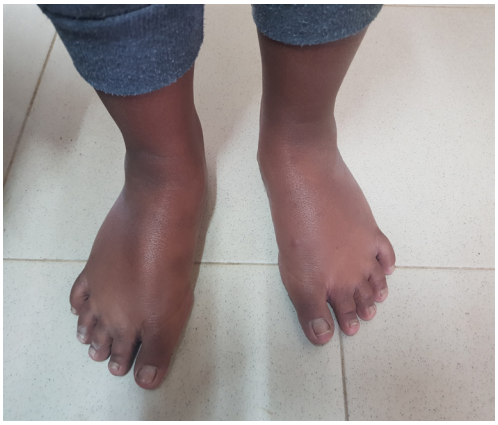

Figure 2: Short metatarsal.

Her height is 128cm (below 3rd centile) and weight 38.2kg (below 3rd centile) with a normal body mass index of 23.3kg/m2 (at 75th centile). Cardiovascular examination reveals no murmur, and no carotid bruit. Abdominal examination soft and non-tender and no mass palpable. She does not have any axillary hair or pubic hair. There were atrophic labia majora, labia minora, and clitoris found during vaginal examination. She also has wide space nipples with Stage 4 Tanner for breast development.

Electrocardiogram showed sinus rhythm and no prolonged QT. Full blood counts, renal and liver profiles, thyroid function tests, FSH, LH, prolactin, and estradiol tests were carried out. The results are summarized in the Table I below. An AP and lateral view of both forearms showed Madelung deformity over the left side. (Figure 3)

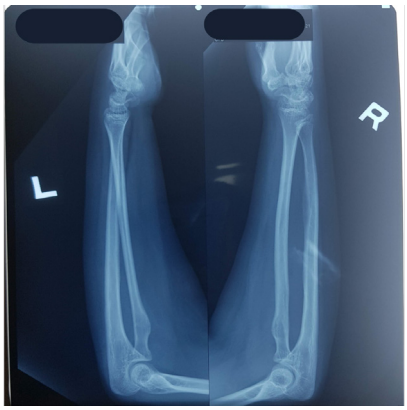

Figure 3: Madelung Deformity.

Ultrasound report indicated her uterus is of normal configuration but bilateral ovaries were absent, associated with minimal pelvic ascites. Her MRI Abdomen and Pelvic report indicated a normal uterus, but bilateral ovaries were absent, with minimal pelvic ascites. Her karyotype was sent outsourced, and it was confirmed that she has Turner's syndrome (45, X). As a result of her coordination and continuity of care, she was referred to obstetrics and gynecology for growth hormone therapy and medical outpatient monitoring of her aortic aneurysm and bone marrow density because she was at risk for osteoporosis. Genetic counseling is also arranged for her family.

Table I: Result of Hormonal Investigation

Test	Result	Unit	Reference value	Interpretation
Luteinizing Hormone	27.4	IU/L	1.18 - 11.78 Follicular 7.59 – 89.08 Mid cycle 0.56 – 14.00 Luteal 5.16 – 61.99 Postmenopausal	Postmenopausal
FSH (July 2021)	114.35	IU/L	3.03 – 8.08 Follicular 2.55 – 16.69 Mid cycle 1.38 – 5.47 Luteal 26.72 – 133.41 Postmenopausal	Postmenopausal
FSH (August 2021)	146.55	IU/L		Postmenopausal
Prolactin	17.05	ug/L	5.18 – 26.53	Normal
Estradiol	<88.1	pmol/L	77 - 921 Follicular 139 - 2381 Mid cycle 77 - 1145 Luteal 0-103 Postmenopausal	Folicular
Free T4	11.43	pmol/L	10.16 – 17.29	Normal
TSH	2.49	mIU/L	0.35 – 4.94	Normal

DISCUSSION

Turner Syndrome (TS) is a chromosomal anomalies

syndrome happens in girls, which is caused by cell division error, resulting in partial or complete X chromosome monosomy. Globally, the prevalence of TS is estimated to be 25-50 per 100000 females (1). TS is characterised by sexual developmental problem such as primary amenorrhea and gonadal dysgenesis. Clinically, TS can present with lymphoedema and dysmorphic features such as short stature, high-arched palate, low hair line, shield chest, webbed neck, cubitus valgus, Madelung deformities of forearm and wrist, nail dysplasia and short 4th/ 5th metacarpals or metatarsals.

Most importantly, TS can substantially increase the risk of cardiovascular abnormalities such as coarctation of aorta, aortic dissection, premature aortic stenosis and insufficiency. Besides, TS is also associated with mental retardation, hearing deficits, ocular abnormalities, thyroid disorders, renal malformations and impaired glucose metabolism. In terms of psychosocial aspect, TS patients had equal or higher risk for depression, especially during adulthood. Therefore, TS patients should not miss their golden therapeutic window before 12 years old to minimize complications and negative impacts on their quality of life.

Even so, TS is often diagnosed late. Studies from the United States and Belgium showed that 19% and 22% of the TS diagnosis were made after the age of 12, with mean age at diagnosis of 4.2 and 6.6 years respectively (2). Compared with world-wide, the result acquired from a single center study in Malaysia stated only 17% of the TS diagnosis was delayed, with the median age at diagnosis for 45,X karyotype at 1 month old while those with mosaicism at 11 years old.

Delayed diagnosis will result in more severe short stature by the time of diagnosis. To stop continuous growth failure and enable attainment of height within the normal range, early uninterrupted growth hormone (rhGH) dose of 45-50μg/kg/day, beginning around 4-6 years of age, is recommended provided that there is falling of height velocity below 50th percentile (1). Study also proved that with appropriate treatment for 4.9 years, the growth hormone treated patient was 6.2 cm taller than the control group ($p<0.001$).(3)

Younger age at treatment initiation also found to have greater height gains and enable age-appropriate induction of feminization to reach the final goals of both optimal adult stature and puberty timing. If the diagnosis is delayed, concomitant treatment with oxandrolone can help to achieve higher final adult height as evidenced by a Cochrane review (4).

Reduced bone density is also seen in women with Turner's syndrome with a delay in the onset of estrogen. Turner's syndrome patients had lower median spinal areal bone mineral density (aBMD) than normal (1.026 g/cm2 vs. 1.221 g/cm2). The main strategies for preventing osteoporosis in women with Turner's syndrome include early estrogen replacement therapy beginning between 11 and 12 years of age, quick titration to the adult dose after 2 years, and long-term follow-up to ensure estrogen replacement therapy compliance. (5)

Several challenges exist when diagnosing and treating patients suffering from Turner's syndrome. It is difficult to diagnose and counsel parents with a child with Turner's syndrome with limited health literacy, low education level, and language barriers, especially in rural areas with limited resources. To provide patients with long-term support and continuity of care throughout their life, multidisciplinary approaches are critical, especially when they require genetic counselling before marriage, during pregnancy, or while undergoing treatment. Health awareness should be raised among parents especially during antenatal check-up and parenting skills sessions. In rural areas, more outreach health screening programmes should be implemented. Primary care providers must recognize the red flag when dysmorphic children present with short statutes or learning disabilities. It is important to refer them urgently for genetic karyotyping, which is currently only available in Penang and Kuala Lumpur government hospitals. Growth hormone treatment can be most effective if the diagnosis is made before puberty to maximize the patient's chances of success in growth attainment.

CONCLUSION

This case shows that how deficit in psychosocial support and health literacy might lead to a delayed diagnosis and eventually caused the patient to miss her golden therapeutic window. Many implications such as growth failure and reduced bone density could be mitigated if the diagnosis were made earlier. Language barrier also made the long-term support and genetic counselling much more difficult to be imparted. We hope that by addressing this issue, more attention will be given to this community.

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