

## Late Diagnosis of Turner Syndrome-Rare Genetic Disease: A Case Report

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### ABSTRACT

Turner syndrome (TS) is a rare genetic disease that occurs only in girls and is the result of the complete or partial absence of the X chromosome. TS has often delayed diagnosis in late childhood or adolescent age and is rarely identified during the neonatal period. The clinical features are primary amenorrhea, short stature, infertility, and characteristic dysmorphic features. Late diagnosis is the main problem because early detection and appropriate management can improve the final height, sexual health and psychological development of patients. We report a case of turner syndrome in a 16-years and 4-months old female adolescent. The patient had specific clinical features of turner syndrome such as amenorrhea, absence of secondary sex growth and posture short stature since 14 years old. This case was confirmed from anamnesis, physical examination and chromosomal analysis, which demonstrated a gene karyotype of 45, X monosomy.

**Keywords:** Turner syndrome; Delayed Diagnosis; Amenorrhea; Karyotype



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## Introduction

Turner syndrome is a complex medical disorder involving multiple organs and impacts the patient's physical and psychological problems. In 1938, an American endocrinologist, Dr. Henry Turner reported seven women with short stature, webbing neck, cubitus valgus and dysgenesis gonad and named the condition turner syndrome (TS).<sup>1,2</sup> He was the first to initiate estrogen replacement therapy.<sup>1</sup> Normally, one body cell has 46-chromosomes or 23 pairs of chromosomes, where male has X dan Y sex chromosomes (46, XY) and the female has two X sex chromosomes (46, XX). However, TS is the chromosomal anomaly in girls caused by a partial or complete absence of one X chromosome (45X) in some or all cells of the body.<sup>3</sup> The prevalence of TS is approximately 1 in 2500 live female birth.<sup>2,4</sup> Some patients may have only one or two of the mild characteristics of turner syndrome and are often difficult to identify, called mosaic turner syndrome.<sup>5</sup> Meanwhile, girls who have several characteristics at once and are easily recognized are referred to as classic turner syndrome.<sup>5</sup>

The clinical characteristics of turner syndrome differ according to the age at diagnosis.<sup>1,6</sup> In the prenatal period, gestational ultrasound examination revealed a cystic hygroma, hydrops fetalis or cardiac defects in the fetus.<sup>1,6</sup> In the neonate period, there were complaints of congenital lymphedema of hands and feet and dysmorphic features.<sup>1,6</sup> Late diagnosis occurs in late adolescence or early adulthood with the most complaints of primary amenorrhea, underdeveloped secondary sexual development and stature being shorter than their peers.<sup>1,6</sup> About 50% of the excess mortality in Turner syndrome is attributable to cardiovascular disorders, while the remaining excess mortality is due to a host of different conditions, including endocrine, gastrointestinal, respiratory (mainly pneumonia), neurological, urogenital and musculoskeletal disorders.<sup>7,15</sup>

The definitive diagnosis of turner syndrome is chromosomal analysis examination with the standard 30-cell karyotype which can detect up to 10% mosaicism with 95% confidence.<sup>1,6</sup> Approximately 40-50% of individuals with TS have a monosomy (45,X) karyotype, meaning that all cells only have one X chromosome; 15-25% have 45,X/46,XX mosaicism and another 10-12% have 45,X/46,XY mosaicism, meaning that some cells only have one X chromosome, whereas others have two X chromosomes or X and Y chromosomes.<sup>8</sup>

Although the intelligence of children with Turner syndrome is normal, some have the risk of impairments in the cognitive, behavioral and social domains. These include learning disabilities, particularly in spatial perception, visual-motor integration, mathematics, memory, the ability to formulate goals and plan action sequences to attain them, and attention span.<sup>9,10</sup> Most TS female are infertile because of ovarian failure and uterus hypoplasia so are unable to carry conception. They have normal female external genitalia with gonadal dysgenesis.<sup>11</sup>

This report highlights that late diagnosis in late adolescence is an important issue because it affects the final height, sexual health and psychological development of the patient.

### Case

A 16-years and 4-months old female adolescent came to the endocrinology outpatient clinic in Wahidin Sudirohusodo hospital with a complaint that she had never had a menstrual period since 14-years old. She also complained of the absence of secondary sex growth and posture short stature compared to her peers. There was no history of using contraception pills and endocrine disease. There was no history of menstrual disorder in her family. Her mother's menarche was at 14 years old. On physical examination we found an epicanthic fold, low set ears, low hairline at the back of the neck, webbed neck, broad chest with widely spaced nipples, and cubitus valgus. An anthropometric examination revealed body weight was 33 kg, height 137,5 cm, HFA 84,3% (stunted). Assessment of maturation in secondary sexual development based on tanner's stage was stage 1 (undeveloped breast glands and areola) for breast development and also stage 1 (no hair) for pubic hair.



Fig 1. The Patient

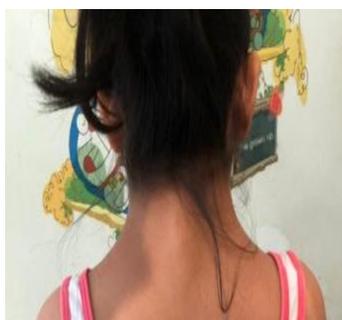


Fig 2. Webbed Neck and Low Hairline



Fig 3. Broad chest with widely spaced nipples

Laboratory examination showed Hb 11,7 gr/dl, leukocytes 7800/m<sup>3</sup>, platelets 376.000/m<sup>3</sup>, calcium 8,5 mg/dl, magnesium 0,24 mg/dl, FT4 1,33, TSHs 3,16, IGF-1 158 and vitamin D 25-OH total 24,3. The chromosome analysis results were 45 with one X chromosome (monosomy X) indicating Turner Syndrome.

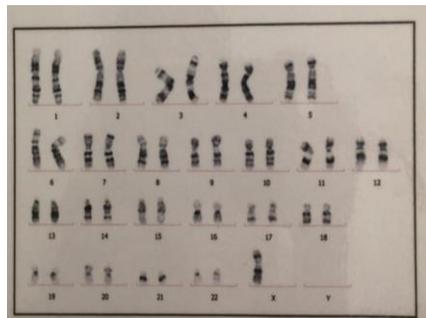


Fig 4. Chromosome analysis of the patient

On X-ray manus Sinistra with impression estimated bone age according to 12 years old, echocardiography examination revealed the dimensions of the cardiac chambers were within normal limits. On ultrasonography examination revealed a streaky uterus and MRI pelvic revealed a bilateral streaky uterus and ovarian.

The patient has been diagnosed with turner syndrome based on anamnesis, physical examination, laboratory examination and chromosomal analysis. The treatment for turner syndrome was growth hormone therapy and vitamin D supplement. The administration of estrogen replacement therapy will be given after the patient has reached maximum height. During treatment, the patient is regular follow-up every 3 months to monitor growth rate, a complication of the disease, and side effects of therapy at the endocrinology outpatient clinic of the Wahidin Sudirohusodo Hospital Makassar. The prognosis of the patient is Bonam for Quo ad vitam (survival) and dubia for Quo ad sanationam (cured) and functionam (functional).

## Discussion

We reported a case of turner syndrome in a 16-years and 4-months old female adolescent based on the clinical features and chromosomal analysis examination. The late age of presentation is caused by the lack of knowledge and awareness about TS. The complexity in the diagnosis of TS is influenced by its varied clinical features and affects many other systems and tissues.<sup>2,12</sup> The most common clinical features are short stature, primary amenorrhea and characteristic dysmorphic features.<sup>2,12</sup> In this patient, the typical manifestations are primary amenorrhea, absence of secondary sex growth and posture short stature. The characteristic dysmorphic features are epicanthic fold, low set ears, low hairline at the back of the neck, webbed neck, broad chest with widely spaced nipples, and cubitus valgus.<sup>6,7</sup> On USG examination, the patient has a streaky uterus due to deficient gonadal hormone stimulus. She does not undergo puberty and is unable to conceive. The chromosome analysis results were 45,X chromosome

(monosomy X). Based on this, the patient suffers from classic Turner Syndrome.

The etiology of TS is a structural abnormality of the X chromosome that occurs after conception and is responsible for causing the clinical features.<sup>5,7</sup> Structural abnormalities of the X chromosome such as ring chromosomes (shape like a ring), isochromosomes (X chromosome with two long arms instead of a long arm and a short arm) and deletions (part of the chromosome is missing).<sup>5,10</sup> The cause of the missing or abnormal X chromosome in TS is not known. Turner syndrome is not a hereditary disease and there are no contributing risk factors for maternal age, and environment.<sup>13</sup>

Patients with TS are at increased risk of psoriasis, juvenile idiopathic arthritis, type 1 diabetes, adrenocortical insufficiency, osteoporosis, and inflammatory bowel disease. The overall mortality rate for patients with TS is higher than that for normal individuals because of the higher incidence of cardiovascular disease and autoimmune disease.<sup>1</sup>

There are many aspects of the medical care of a woman with TS that may need attention. The administration of growth hormone therapy was needed for bone development and to increase the adult height of the patient.<sup>1</sup> The patient had a vitamin D insufficiency so vitamin D supplement was given to strengthen the bones and prevent osteoporosis.<sup>1</sup> Estrogen replacement therapy can help to begin developing secondary sexual characteristics and uterus health.<sup>1</sup> Management of TS requires long-term follow-ups and should focus on the patient's mental, reproductive, and physical growth to minimize complications associated with TS.

## **Conclusion**

Timely diagnosis can help initiation of therapy with comprehensive care and reduce morbidity. The physicians should focus on early recognition of turner syndrome if you find a girl with short stature, amenorrhea, and dysmorphic features. Patients with suspected turner syndrome should be referred to a pediatric endocrinologist.

## **Declaration**

### *Ethics Approval and Consent to Participate*

DR Wahidin Sudirohusodo Hospital's ethics committee and review board has approved this study.

### *Consent for Publication*

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### *Authors' contributions*

ANF, NMP and HA were responsible for the management of our patient; ANF, NMP, and HA participated in the study design, and coordination and helped draft the manuscript. All authors read and approved the final manuscript.

### **Conflict of Interests**

There is no conflict of interest in this research

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