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ARTICLE

# Features of Turner syndrome in patients managed at the adult endocrinology clinic, Steve Biko Academic Hospital

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**Background:** Turner syndrome is a multisystem disease with varied clinical features influenced by genetic composition and possibly ethnicity.
**Objective:** To review local data and identify the clinical features more common in our population.
**Methods:** A retrospective review of the clinical, biochemical features and karyotype of all patients with a confirmed diagnosis of Turner syndrome receiving treatment at the adult endocrinology clinic, Steve Biko Academic Hospital, was performed. Seventeen patients with complete data sets were identified.
**Conclusion:** Our population group had a higher percentage of mosaic Turner syndrome than that described in the literature. The clinical features also differed significantly from the classic features described, with the exception of the universal presence of short stature and hypogonadism. This may explain the delayed age of diagnosis. Screening programmes are necessary, and the consistent finding of short stature can be used as a screening tool in early childhood to identify more patients who will benefit from referral.

**Keywords:** Turner syndrome, short stature, primary amenorrhea, primary infertility, diabetes, thyroiditis, osteoporosis, webbed neck, auto-immune diseases, hearing loss, scoliosis

## Introduction

Turner syndrome was first described nearly a century ago in the 1930s by three independent clinicians, Seresevskij, Ullrich and Turner.[1] Turner syndrome is one of the most common chromosomal abnormalities and prevalence was estimated to be 1 in 2 500 live births. A recent study in Denmark showed that the prevalence is higher at 59 cases per 100 000, or 1 in 1 695 newborn females.[2] This may reflect a true change in prevalence or an improvement in diagnostic techniques leading to increased detection.

Turner syndrome is a complex clinical syndrome associated with partial or complete monosomy of the X-chromosome. The karyotypic composition of the Turner syndrome population is changing and it is thought that the clinical presentation is too. This may lead to late or even non-diagnosis with potentially devastating long-term effects. If not diagnosed in infancy, relevant medical care (screening and intervention) may be delayed or not instituted at all. This will have negative medical and socioeconomic consequences. Diagnosis after the age of 13 years has been linked to lower levels of education as well as lower levels of employment and earning.[3] This all culminates in impaired health-related quality of life.[4]

## Methods

The study was a retrospective, descriptive analysis of all the known patients with Turner syndrome seen in the adult endocrinology clinic at Steve Biko Academic Hospital from January 2021–June 30, 2022. After institutional ethical approval, the case records were reviewed retrospectively.

Clinical examination included recording basic biometrics like height and weight and documenting typical features of Turner syndrome. A webbed neck is defined as an additional skin fold going from the neck to the shoulder, but this has no objective measurement for diagnosis. It was identified based on the clinical judgement of two independent clinicians. Systemic examination of all patients was done to identify other systemic conditions associated with Turner syndrome. Patients who did not have DEXA scans, echocardiography, renal ultrasound and audiometry in the last three years were referred for the relevant testing according to standard screening protocols in Turner syndrome patients. HbA1C, AST, ALT and thyroid function tests were done as part of routine care.

## Results

Seventeen patients who had complete data sets were included. The patient characteristics are summarised in Table 1. On genetic testing, 6 patients (35.3%) had the classic 45,X0 karyotype with 11 patients (64.7%) having mosaicism. The commonest mosaicism identified was 46.Xi (Xq) with 5 cases (29.4%). All our patients had short stature and, initially, absent secondary sexual characteristics complicated by primary infertility.

## Discussion

Turner syndrome affects individuals at multi-organ level. The extent of organ involvement varies widely, but seems to be more severe in pure 45,X variants than with mosaicism.[5] Increased morbidity and mortality have been reported compared with age-matched controls. The increase in mortality was almost fourfold.[2]

Patients may present with different karyotypes, all lacking X-chromosome material. It can be divided into two major groups: total or partial absence of the p-arm of the second X-

**Table 1:** Patient characteristics

| Physical finding | | Classic karyotype percentage (*n*) | Mosaic karyotype percentage (*n*) | Total percentage affected (n) |
|---|---|---|---|---|
| Karyotype | | 35.3 (6) | 64.7 (11) | 100 (17) |
| Mean weight (kg) | | 55.4 | 43.6 | 47.79 ± 13.86 |
| Mean height (cm) | | 140.2 | 137.17 | 138.26 ± 5.91 |
| Mean BMI (kg/m$^2$) | | 27.5 | 23.2 | 24.72 ± 6.24 |
| Obese/overweight | | 5 (29.4) | 4 (23.5) | 9 (52.9) |
| Age at diagnosis (years) $n = 17$ | | 17.08 | 18.8 | 18.2 |
| Ethnicity | Black | 23.5 (4) | 64.7 (11) | 88.2 (15) |
| | White | 11.8 (2) | 0 | 11.8 (2) |
| Skeletal | Short stature | 35.3 (6) | 64.7 (11) | 100 (17) |
| | Short neck | 17.6 (3) | 17.6 (3) | 35.3 (6) |
| | Increased upper:lower body ratio | 23.5 (4) | 47.0 (8) | 75 (12) |
| | Cubitus valgus | 35.3 (6) | 47.0 (8) | 82.4 (14) |
| | Short metacarpal | 35.3 (6) | 35.3 (6) | 29.4 (12) |
| | Scoliosis | 0% (0) | 5.9 (1) | 5.9 (1) |
| | Kyphosis | 5.9 (1) | 23.5 (4) | 29.4 (5) |
| | Madelung deformity | 5.9 (1) | 5.9 (1) | 11.8 (2) |
| | High-arched palate | 11.8 (2) | 11.8 (2) | 23.5 (4) |
| | Osteoporosis | 23.5 (4) | 47.0 (8) | 70.5 (12) |
| Lymphatic obstruction | Low posterior hairline | 11.9 (2) | 17.6 (3) | 29.4 (5) |
| | Webbed neck | 23.5 (4) | 11.8 (2) | 35.3 (6) |
| | Oedema of hands or feet | 17.6 (3) | 23.5 (4) | 41.2 (7) |
| Other | Strabismus | 0 | 0 | 0 |
| | Ptosis | 5.9 (1) | 0 | 5.9 (1) |
| | Widely spaced nipples, broad chest | 23.5 (4) | 11.8 (2) | 35.3 (6) |
| Cardiovascular | Bicuspid aortic valve | 5.9 (1) | 5.9 (1) | 11.8 (2) |
| | Aortic coarctation | 0 | 0 | 0 |
| | Ventricular septal defect | 0 | 5.9 (1) | 5.9 (1) |
| | Atrial septal defect | 5.9 (1) | 5.9 (1) | 11.8 (2) |
| Renal anomaly | Horseshoe kidney | 0 | 5.9 (1) | 5.9 (1) |
| | Hydronephrosis | 5.9 (1) | 0 (0) | 5.9 (1) |
| | Unilateral agenesis | (0) | 5.9 (1) | 5.9 (1) |
| Liver | Abnormal liver function tests (AST, ALT elevation) | 17.6 (3) | 23.5 (4) | 41.2 (7) |
| | Fatty liver disease based on ultrasound evaluation | 17.6 (3) | 17.6 (3) | 35.3 (6) |
| Hypertension | | 0 | 5.9 (1) | 5.9 (1) |
| Diabetes type 2 | | 5.9 (1) | 5.9 (1) | 11.8 (2) |
| Hashimoto thyroiditis | | 5.9 (1) | 17.6 (3) | 23.5 (4) |
| Ear | Recurrent otitis media | 11.8 (2) | 0 | 11.8 (2) |
| | Conductive hearing loss | 5.9 (1) | 5.9 (1) | 11.8 (2) |
| | Sensorineural hearing loss | 5.9 (1) | 0 (0) | 5.9 (1) |
| | Earlobe abnormalities | 5.9 (1) | 5.9 (1) | 11.8 (2) |
| Skin and nails | Vitiligo | 11.8 (2) | 11.8 (2) | 23.5 (4) |
| | Alopecia | 0 | 11.8 (2) | 11.8 (2) |
| | Nail dysplasia | 5.9 (1) | 23.5 (4) | 29.4 (5) |
| | Multiple pigmented nevi | 17.6 (3) | 35.3 (6) | 52.9 (9) |
| Fertility | Biological children | 0 | 0 | 0 |
| | Gonadoblastoma | 0 | 0 | 0 |

chromosome. Most females with Turner syndrome (50%) are missing an entire sex chromosome, 20% have a mosaic karyotype (most commonly 45,X/46,XX) and 25% have a partial deletion of one X-chromosome.[6] This differed from our population, in which the majority (64.7%) had a mosaic karyotype. In 75–80% of cases, the loss or partial loss of the X-chromosome is from the male gamete.[5] In addition to these karyotypes, 0–61.1% of women have varying amounts of Y-chromosome material, 3% of these women being 45,X/46,XY. Karyotype analysis is essential in risk stratification as the

presence of Y-chromosome material has been shown to increase the risk of gonadal malignancies.[1,7] None of the patients enrolled in the study had any Y-chromosome material.

In the clinical practice guidelines for the care of girls and women with Turner syndrome, it was suggested that Turner syndrome diagnosis be considered when a phenotypical female presents with one or more typical clinical manifestations of Turner syndrome accompanied by a karyotype containing one X chromosome and complete or partial absence of the second sex chromosome.[8] The consequence of the loss/partial loss of the X-chromosome is highly variable. The phenotype is unpredictable, and the signs of Turner syndrome are often overlooked, leading to a delay in diagnosis or not diagnosing it at all. In our population, the average age of diagnosis was 18.2 years, which is very late. In a recent article by Tuke *et al*.[9] it was found that using single-nucleotide polymorphism array data on blood from the UK Biobank study ($n = 245{,}000$) in Great Britain identified many undiagnosed mosaic Turner syndrome patients as well as 30 non-diagnosed 45,X patients. This study reported a combined Turner syndrome prevalence of 88 per 100 000 females, confirming that this condition is not as rare as thought.

Short stature (defined as –2 standard deviations for chronological age), the most common presenting symptom of Turner syndrome, is due to the SHOX gene escaping X-inactivation. This study revealed the mean height for classic Turner syndrome patients to be 140.2 cm, and 137.17 cm in the patients with mosaicism. This was unexpected, as classic Turner syndrome patients are typically described as being shorter than patients with mosaic Turner syndrome. This may possibly be due to chance since the number of patients in our classic group was quite small. In addition to short stature, the SHOX haploinsufficiency is also associated with scoliosis, micrognathia, high-arched palate, Madelung deformity, increased carrying angle and reduced leg length.[1] Our population had less micrognathia, high-arched palate and Madelung deformity but a similar incidence of increased carrying angle.

Cardiovascular disease is a major cause of morbidity and mortality in Turner syndrome patients. It has been shown to reduce their life expectancy by approximately 10 years. The prevalence of cardiac malformations was 23%, and as high as 56% in some studies. The karyotype most involved is 45,X.[10,11] The congenital abnormalities described are mostly left heart obstructive lesions. The most common lesions identified were bicuspid aortic valve (12.5–30%), coarctation of the aorta (6.9–11%) and aortic valve disease (3.2%). Frequently acquired cardiac conditions of the left side of the heart include atherosclerotic heart disease, hypertension, left ventricle hypertrophy, left atria hypertrophy and aortic aneurysm with or without aortic rupture.[10–12] Aortic dissection may occur at any age. The incidence is increased 100-fold in patients with Turner syndrome. Bicuspid aortic valve is an independent risk factor for aortic aneurysm and rupture.[13] Our population had an incidence of cardiovascular disease similar to that reported in other studies with equal distribution between classic Turner syndrome and mosaic Turner syndrome.

Renal abnormalities occur in 30–40% of patients with Turner syndrome, with the most common abnormalities related to the collecting system.[1] Other abnormalities include horseshoe kidneys. Only three of the patients in this study had renal anomalies, with two of them being in the mosaic Turner syndrome group.

Otological disease is part of the widely variable phenotype in Turner syndrome patients. It varies from external morphologic abnormalities to recurrent middle ear infections as well as sensorineural or conductive hearing loss. Hearing loss is a common feature of Turner syndrome with a prevalence ranging from 36% to 84%. The auditory phenotype in Turner syndrome is complex and seems to be dynamic, with conductive hearing loss due to middle ear disease at an early age and sensorineural hearing loss later in life. Importantly, the presence of the mid-frequency dip is prognostic for the development of further progression of sensorineural hearing loss. In our population, hearing loss was detected in only three patients (17.6%), much lower than the prevalence described in the literature. Two patients had chronic otitis media, complicated by hearing loss.

The prevalence of auricular abnormalities ranges from 22% to 68%. Typical findings are low-set or cupped ears.[14–16] In this study, the incidence of auricular abnormalities was only 11.8%. The majority of otological involvement was present in the group with classic Turner syndrome.

Spontaneous fertility is rare among patients with Turner syndrome, and this was confirmed in our study population. None of them experienced any pregnancies or had any biological children. Their ovaries undergo premature apoptosis even in utero. They have an accelerated decline in ovarian reserve and have shorter reproductive lifespans. However, spontaneous menarche and fertility have been reported in patients with mosaic karyotype or very distal Xp deletions; 38% can have healthy babies with an uncomplicated antenatal course. None of our patients had spontaneous menarche. Others have poor potential for fertility and include Xq deletions, 45XO, ring X chromosome, and mosaicism including 46XY. Anti-Mullerian hormone and inhibin A are probable screening tests for assessing ovarian reserve, even in prepubertal girls with Turner syndrome. Elevated gonadotropins and hypoplastic ovaries or uterus indicate poor potential for fertility. Follicle retrieval performed at age 12–13 years has been recommended.[6, 17] This is not possible if the diagnosis is made late, as is the case in this study where the average age of diagnosis was 18.2 years.

There is an increased incidence of autoimmune diseases in patients with Turner syndrome. The most common autoimmune diseases in this group of patients are coeliac disease, Hashimoto's thyroiditis, Addison's disease, type 1 diabetes and inflammatory bowel disease. The relative risk varied between 8.2 and 14.0 in some studies.[18] In our study, the incidence of Hashimoto's thyroiditis was 23.5% and none of the patients had type 1 diabetes. Other autoimmune diseases like pernicious anaemia had an increased incidence in the literature but were still rare. Excess autoimmune antibodies are presumed to be due to defects in the major histocompatibility complex locus located on the defective X-chromosome.[18]

In addition to autoimmune-based type 1 diabetes, more than half of patients with Turner syndrome have abnormal glucose homeostasis. This may vary from insulin resistance and impaired glucose tolerance to type 2 diabetes.[19] Metabolic syndrome is more frequent in patients with Turner syndrome. Coupled with this, their physical fitness levels are lower compared with controls. BMI is not a good predictor of metabolic risk. Determination of visceral fat mass is a better predictor of metabolic risk in Turner syndrome patients.[20] The dyslipidaemia and type 2 diabetes add to the risk of atherosclerotic heart disease;

coronary artery disease is common amongst patients with Turner syndrome.[12] In our population, some of the components of metabolic syndrome that were evaluated and present included: type 2 diabetes: 2 patients (11.8%); hypertension: 1 patient (5.9%); overweight or obesity: 9 patients (53.9%). We did not routinely evaluate the lipid profiles, and we were not able to assess visceral fat mass. Waist circumferences were measured but not reported as no validated reference ranges for metabolic syndrome were available for patients with Turner syndrome.

Abnormal liver function tests are a common finding in patients with Turner syndrome. For years this was assumed to be due to obesity, another common finding in patients with Turner syndrome. A recent study by Rohani *et al*. showed that most cases were related to long-term hormone replacement. The same study showed that 14% of cases of abnormal liver function tests were due to autoimmunity. Only in 7% was it due to obesity.[21] This study showed a high incidence of abnormal liver function tests (41.2%) with an almost equal distribution between mosaic and classic Turner syndrome. Six patients (35.3%) had features of fatty liver disease detected on ultrasonography. We do not have enough information to comment on the underlying aetiology.

Up to 80% of patients with Turner syndrome will develop osteoporosis, and they have a 25% increased fracture risk when compared with controls.[22] Osteoporosis is thought to be multifactorial in aetiology.[23] It is mainly the result of the oestrogen-deficient state related to primary ovarian failure. High FSH levels also contribute, with FSH binding directly to the FSH receptor on the osteoclast and activating the bone-resorbing osteoclast. Haploinsufficiency of the SHOX gene, responsible for the short stature, also contributes to altered microarchitecture of bone.[24] In our population, the prevalence of osteoporosis was high at 70.5%; it was slightly higher in the mosaic Turner syndrome group than in the classic group (72.7% versus 66.7%).

Except for short stature and primary ovarian failure, we find in practice that our patients, especially the black African population, differ significantly from the classic features described in textbooks. This contributes to delayed diagnosis and referral. The classic descriptions stem from research done in white Caucasian populations.

Our population included 88.2% black adults, and 64.7% had a mosaic Turner syndrome karyotype. Our retrospective analysis of clinical features showed a higher percentage of patients with cubitus valgus, oedema of hands or feet, multiple pigmented nevi and nail dysplasia compared with that reported in a recent study by Steiner and Saenger.[25] Our population also had less strabismus, ptosis and high-arched palates. Because our patients are mainly from a lower socioeconomic background, this can introduce potential bias when evaluating cognitive function due to limited access to education. Considering this potential bias, we opted not to evaluate or report on cognitive function.

Our study once again confirms the variable phenotype present in Turner syndrome. In our study population, those patients with the classic 45,X had more of the typical features associated with Turner syndrome, as expected. The disconnect often seen between phenotype and genotype and, as described in the literature, is not explained by current knowledge and needs further research. Recent studies suggest that the genotype–phenotype relationship is more complex than a classic gene-dosage theory. Theories include second-hit insult and more genetic modifications that affect the phenotype.[26]

Policies should be implemented for early identification of patients with Turner syndrome. Implementing a short stature screening programme in early childhood at community level or primary care level can improve the detection and appropriate referral of patients for tertiary-level care by a multidisciplinary team. These screening programmes can be cost-effective as they do not need highly skilled staff or expensive equipment.

The study was limited by the small number of patients included. There was also incomplete data related to visceral fat percentage/waist circumference, and metabolic syndrome components such as lipograms. As a result of these factors, some of the findings may still be due to chance. Larger studies are necessary to confirm our findings, especially the differences as compared with the current literature on Turner syndrome.

## Conclusions

Turner syndrome is a multisystem disease, affecting patients throughout their lives. It is associated with increased morbidity and mortality. Our population group had a higher percentage of mosaic Turner syndrome than described in the literature. The clinical features also differed significantly from the classic features described, except for the universal presence of short stature and hypogonadism. This may explain the delayed age of diagnosis.

Raising awareness of the varied phenotype of Turner syndrome, the varied expression of the clinical signs in mosaicism and improving the laboratory techniques used in genetic screening may lead to earlier diagnosis.

Screening programmes are necessary, and the one consistent finding of short stature can be used as a screening tool in early childhood to identify more patients who will benefit from treatment. Such screening programmes can be implemented at the primary care level with minimum training required and low costs associated with them.

Effective treatment from a multidisciplinary team, guided by international consensus guidelines, will ensure cost-effective treatment alongside improved outcomes.

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