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THE CLINICAL PATTERN OF TURNER SYNDROME

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ABSTRACT

Background: Turner syndrome (TS) is defined as a multisystem chromosomopathy syndrome, affecting approximately 1 in every 2000 live‑born females. Many patients can present without the other classic dysmorphic features of the syndrome including edema of extremities, cardiac anomalies, nuchal folds, and small mandible. So our object in this retrospective study is to clarify the clinical feature of Turner syndrome and focus on short stature as the only marker to do karyotype in the female patient. **Methods:** This study was conducted at the endocrinology clinic from 2016 to 2021. Thirteen female patients were evaluated for short stature in the endocrine clinic. All patients underwent complete blood account, kidney and liver function test, bone age by left wrist x-ray, thyroid function test, celiac disease, insulin-like growth factor-1, and karyotype. **Results:** Thirteen female patients evaluated for short stature were ascertained with a final diagnosis of turner syndrome. The age of the patient range from 8 to 13 years. Six girls (46.2%) were diagnosed with classical monosomy 45, X, and seven girls (53.8) with other X chromosome abnormalities. Five girls (38.5%) were started on hormonal replacement therapy. **Conclusion:** Many female patients with TS may live with silent syndrome until the parents notice here child is short stature or they complained of primary amenorrhea. So the turner syndrome may be asymptomatic but they will develop short stature approximately 100% for this reason any female patient with short stature should do karyotype to exclude turners syndrome.

KEYWORDS: Turner syndrome, chromosomal, short stature, karyotype, growth hormone treatment, hormone replacement therapy.

INTRODUCTION

Turner's syndrome (TS) is defined as a multisystem chromosomopathy syndrome, affecting approximately 1 in every 2000-1/2500 female infants.[1] TS occurs due to partial or total deficiency of the X chromosome.[2] The clinical picture of TS consists of short stature, facial and skeletal dysmorphism, anomalies of some internal organs, and gonadal dysgenesis.

Short stature is present in 95%-100% of affected patients.[3] The main cause of short stature is not known but a primary defect is considered among causative factors. Bone and haploinsufficiency of the SHOX gene (short stature homeobox) located on the short arm of the X (Xp22) and Y (YpL1) chromosome which causes impaired skeletal development with reduced sensitivity to the action of the endogenous growth hormone (GH).[4] Gonadal dysgenesis is frequent, only 5-10% of patients spontaneously developed puberty and an even smaller proportion of subjects have spontaneous menstruation, which however persists for a limited period.

Approximately 25-30% of TS patients have congenital heart disease (CHD), compared to 2-3% in the general population.[5] CHD is responsible for early mortality in TS. The etiological factors responsible for CHD in TS are not yet fully known. CHD mainly affects the coarctation of the aorta, bicuspid aortic valve, pulmonary and systemic venous return abnormalities.[6]

Urinary tract malformations are present in approximately 25–40% of patients with TS.[7] The most frequently encountered anomalies are the horseshoe-shaped kidney, anomalies of the collecting ducts, malformation, and other position anomalies.[8] These malformations carry a greater risk of hypertension, urinary tract infections, and hydronephrosis. So the renal ultrasound is recommended in all patients at the diagnosis of TS.

TS increases the risk of autoimmune diseases such as Hashimoto's disease, celiac disease (CD), type 1 diabetes mellitus, alopecia, juvenile rheumatoid arthritis, uveitis, and chronic inflammatory bowel disease.[9] The incidence

of developing one or more of these conditions increases with age and, therefore, TS patients of all ages must have a regular follow-up, screening, and periodic review of symptoms.

Hearing loss may occur in 15-20% of TS patients due to anatomical-function factors, such as craniofacial morphological anomalies with the malfunction of the Eustachian tube.[10] Conductive hearing loss in childhood occurs due to chronic severe otitis media, also sensorineural hearing loss may occur at adult age.

Osteoporosis and low bone density with earlier onset than the general population were found in more than 45% of patients with TS.[11] The increased bone fragility affects in particular the cortical bone while there is a normal density of the trabecular bone. Furthermore, these patients are at risk of fractures mainly in childhood and after the age of 45 years. So it is recommended to evaluate the calcium-phosphorus metabolism (calcium, phosphorus, alkaline phosphate, 1-25 OH vitamins D, and parathyroid hormone) and bone mineralization (DEXA) annually if there are bone problems, otherwise every two years.

Ophthalmic disorders are common in patients with TS. The most common include epicanthus, ptosis, and Nearsightedness, Strabismus.[12] Indeed, the International Turner Syndrome Meeting recommends the first pediatric ophthalmologist evaluation at diagnosis and followed every three years at pediatric age.

The diagnosis of TS is based on the execution of the karyotype.[13] In addition to karyotype, there are other techniques such as in situ hybridization with immunofluorescence (FISH) or molecular biology methods. The standard karyotype is performed on a peripheral blood sample, but in the case of a normal karyotype with a strongly suggestive clinical of TS, it can be extended to other tissue (skin biopsy).

Treatment of TS focused mainly on short stature (growth hormone replacement), induction of secondary sexual characteristics (very low doses of estrogen therapy around the age of 11-12 years), and in addition to other associated disorders (autoimmune disease, congenital heart problem, renal malformation, high blood pressure, and low vitamin D).[14]

METHODS

Over five years, thirteen female patients were referred to the endocrinology clinic of Queen Rania for Children Hospital in Amman, Jordan for evaluation of short stature.

Short stature can be defined as height below 2 SD for age and gender within the population, or height > 2 SD below the mid parental target height.

We collected data on the patients' medical history, age at diagnosis, birth weight, past medical history, nutritional history, and mid-parental height (MPH) was calculated by the method of MPH, the average of the mother's and father's height -6.5 cm(female gender). Anthropometric measures at diagnosis (weight, height, and body mass index (BMI), growth velocity, pubertal status, and any abnormal findings.

All patients underwent the first line of investigation for short stature including complete blood account, kidney, and liver function test, Estimated Sedimentation Rate (ESR), bone age by left wrist x-ray, thyroid function test, celiac disease, insulin-like growth factor-1, and karyotype.

Evaluation of TS patients was done by renal and ovary ultrasound (u/s), echocardiography, blood pressure in all four limbs, hearing assessment, free T4, TSH, antithyroid antibodies (ATA), anti-peroxide antibodies (TPO), transglutaminase antibodies, FSH, LH, estradiol evaluation for the puberty, hemoglobin A1c (HBA1C), oral glucose tolerance test (OGTT), calcium, phosphorus, alkaline phosphate, 25-OH vitamin D, parathyroid hormone, spinal x-ray, also pediatric dental and ophthalmologist consultation.

Informed consent was taken from the parents of the child in question for publication of the case details. The study protocol was approved by the ethics committee of royal medical services. For statistical evaluation, we used the Microsoft Excel 2010 software and SPSS version 18.

RESULT

Thirteen female patients were evaluated for short stature in the endocrinology clinic of Queen Rania for Children Hospital in Amman, Jordan during the study period between 2016 and 2021.

The patient age range between 8-13 years, with a mean age of diagnosis, was 10.5 ± 1.7 years. Six girls (46.2%) were diagnosed with classical monosomy 45, X, and seven girls (53.8) with other X chromosome abnormalities (Mosaic).

In our study most common phenotype clinical feature of TS was short stature 100% so according to an indication of growth hormone treatment all TS patients start on growth hormone (GH) at the dose of 0.3 mg/kg/week administered as daily subcutaneous injections. In addition to short stature, Common dysmorphic features included: Low hairline, multiple nevi, Webbing of the neck, Cubitus valgus, Pectus excavatum, delay of puberty, Short Neck, and Spine deformity.

Clinical features of TS in the patients are presented in Table 1.

In this study, the most common malformation syndrome in TS was skeletal deformity (Cubitus valgus, Pectus

excavatum, Spine deformity) then renal malformation found in 4 patients (30.8%) (horseshoe-shaped kidney, anomalies of the collecting ducts), and then cardiac malformation found in 3 patients (23.1%) (Bicuspid, aortic valve disease), and two female patients who were diagnosed with cardiac malformation were also diagnosed with hypertension.

Five female patients (38.5%) who presented with an age range from 11 years to 13 years, do not enter puberty spontaneously (Tanner stage 1), and pelvic ultrasound showed a hypoplastic uterus in four female patients, and one of them with a rudimentary uterus. Ovaries could not be visualized in 2 patients, two patients had bilateral streak ovaries and one case had a unilateral streak ovary with non-visualization of the ovary on the other side. So these five female patients started him on a very low dose of estrogen replacement therapy for induction of secondary sexual characteristics.

According to autoimmune disease, four female patients (30.8%) were diagnosed with autoimmune hypothyroidism and treated with thyroxine and one female patient (7.7%) was diagnosed with celiac disease and started on a gluten-free diet.

Regarding hyperglycemia, prediabetes was found in three (23.1%) female patients by HbA1c (5.8%-6.4%) and oral glucose tolerance test (OGTT), of whom almost all were diagnosed after the age of 10 years.

Seven female patients (53.8%) were diagnosed with asymptomatic vitamin D deficiency with mild elevation of alkaline phosphatase (ALP), normal calcium, and phosphorus and treated with vitamin D.

Table 1: Clinical features of the Turner syndrome patients.

Clinical feature	Total (n=13)
None of the secondary sexual characteristics	5 (38%)
Short stature	13 (100%)
Short neck	3 (23.1%)
Webbing of neck	6 (46.2%)
Multiple nevi	7 (53.8%)
Low hairline	8 (61.5%)
Micrognathia	2 (15.4%)
Cubitus valgus	7 (53.8)
Pectus excavatum	4 (30.8%)
Spine deformity	2 (15.4%)
Hypertension	2 (15.4%)
Prediabetes	3 (23.1%)
Cardiac abnormalities	3 (23.1%)
Renal abnormalities	4 (30.8%)

DISCUSSION

The presentation of Turner syndrome varies throughout a patient's life and may be difficult to recognize clinically because the characteristic facial features can be subtle and this leads to a delay in diagnosis of turner syndrome. In our study, the patient age range was between 8-13 years, with a mean age of diagnosis, which was 10.5 ± 1.7 years. In a study from eastern India, the mean age at diagnosis was 11.7 ± 5.2 years with a range of 2–23 years.[15] This late age of diagnosis, as in our study, precludes feasibility interventions to improve growth potential such as growth hormone therapy.

In our study, short stature (100%) was the most common clinical feature of TS, and this is due to the haploinsufficiency SHOX gene which is located on the short arm of the X (Xp22) and Y (YpL1) chromosome and causes impaired skeletal development with reduced sensitivity to the action of the endogenous growth hormone in TS patients.[16] This result is similar to Gravholt et al.[17] Who recommended initiating growth hormone (GH) treatment early in TS with short stature (below 2 SD for age and gender within the population or >2 SD below mid parental height). So all patients in our study started on growth hormone but due to growth hormone resistance in TS, the effective dose of growth hormone is twice that needed in growth hormone-deficient children to achieve a similar increase in growth velocity.[18]

Other clinical features of TS in addition to the short stature in this study, sequentially: Low hairline (61.5%), multiple nevi (53.8%), Cubitus valgus (53.8), Webbing of the neck (46.2%), Pectus excavatum (30.8%), delay of puberty (38%), Short Neck (23.1%), and Spine deformity (15.4%) and Micrognathia (15.4%) Similar clinical feature were seen by other studies.[19,20]

Regarding delay puberty in TS, we found five girls 38.5% who presented with an age range from 11 years to 13 years, do not enter puberty spontaneously (Tanner stage 1) and we started them on a very low dose of estrogen replacement therapy for induction of secondary sexual characters. also, in the patients with TS who started on the low dose of estrogen early (12 years) the overall growth to adult height tended to be greater than in the group in which estradiol treatment began late which was confirmed also by Rosenfield et al.[21]

TS increases the risk of various autoimmune disorders of which hypothyroidism is the most common autoimmune disorder associated with TS. In our study, we found four (30.8%) girls with autoimmune hypothyroidism and this finding is a little less than previous reviews done by Mohamed et al. reported a 38.6% prevalence of autoimmune thyroid disease among the Turner Syndrome population.[22] Also, one girl (7.7%) was diagnosed by small intestine biopsy with celiac disease (CD). Many reports have indicated an association between TS and celiac disease so the available data confirm the screening of celiac disease in every patient diagnosed with TS and this is also confirmed by Al-Bluwi et al.[23] and Dias et al.[24]

According to diabetes mellitus and their relation with TS, we found three (23.1%) patients with prediabetic, one patient was HBA1C 6.2% and the other two patients were OGTT reading after 2 hours was 140-200 mg/dl. Fortunately, we don't diagnose diabetes mellitus in TS but during follow up the patient is in the endocrine clinic HBA1C, OGTT, and glucose monitor series. Ibarra-Gasparini et al demonstrate the risk of DM is markedly elevated in patients with TS and they need routine screening of DM in TS patients.[25]

In TS there is a strong association with renal anomalies. In our study, we found four patients (30.8%) with renal anomalies with normal renal function, three of them with horseshoe kidneys and one with unilateral renal duplication. Carvalho et al.[26] stated that about 29.3% of their TS patients had renal problems which is approximately similar to our result.

In addition to renal anomalies also there is cardiovascular involvement in TS patients. We found in our study three (23.1%) patients have cardiovascular anomalies two of them with coarctation of the aorta and one with a bicuspid aortic valve. The prevalence of cardiovascular anomalies in this study is much less than Yetman et al.[27] (56%). Also, cardiovascular and renal anomalies increase the risk of hypertension in TS for this reason every patient with TS should monitor blood pressure in four limbs. We diagnosed two patients with hypertension in our study.

Seven female patients (53.8%) were diagnosed with asymptomatic vitamin D deficiency with high parathyroid hormone, mild elevation of alkaline phosphatase (ALP), normal calcium, and phosphorus and treated with vitamin D. The mechanisms responsible for osteoporosis in TS have not been completely understood but some authors sustain the direct effect of estrogen deficiency and the effect of X chromosome abnormality.[28,29]

According to the ophthalmic and hearing assessment, we didn't find any defects in our patients. While the previous study confirmed the relationship between ophthalmic and auditory defects in TS patients.

CONCLUSION

In our study, the triggered factor for the diagnosis of TS in childhood and adolescence was short stature. So any female patient diagnosed with short stature must do a karyotype to exclude TS.

Also, delayed puberty or primary amenorrhea triggered factors for the diagnosis of TS in adolescence.

For this, we try to increase awareness of the clinical pattern of TS in childhood and adolescence. As we mentioned, TS is a multi-system syndrome that includes skeletal, cardiovascular, the renal systems in addition to the association with autoimmune disease (autoimmune thyroiditis and celiac disease), auditory, and ophthalmic defect. So we need multidisciplinary teams who have experience in balancing the requirements for an optimum outcome such as a screen for cardiac anomalies, screening for renal anomalies, screening for autoimmune disease, early initiation of GH therapy, initiation of hormone replacement therapy (HRT) at the time of normal puberty, and referral for developmental/ neurocognitive evaluations at the time of diagnosis.

Limitation of the study

Our study had some limitations. Firstly, we did not assess the TS patients for cardiac abnormality by cardiac MRI for this reason we think have a low prevalence of cardiac abnormality in our study. Also, auditory and ophthalmic malformation was not assessed in this study.

Competing interests

The authors declare no competing interest.

Author's contribution

Dr. Abdalrazzaq Alyassein: contributed to the initial management of a patient.
Dr. Ibrahim Sawalha and Dr. Nasser Eyadeh Bani Khaled: Conception and study design.
Dr. Hadeel Alqurine: Data collection.
Dr. Fadi Farhan ayyash: Manuscript drafting.

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