Cytogenetic Profile and Phenotypical and Reproductive Complaints in 39 Patients with Turner Syndrome: A Single Center Experience

Turner Sendromlu 39 Hastada Sitogenetik Profil, Fenotipik ve Reprodüktif Şikayetler: Tek Merkez Deneyimi

Ferah Kazancı[1], Zerrin Çelik[2]

[1]Department of Gynecologic Oncology, Faculty of Medicine, Gazi University, Ankara, Turkey
[2]Department of Medical Gnetics, Faculty of Medicine, Baskent University, Ankara, Turkey

ABSTRACT

Background/Aim: Turner syndrome (TS) is a genetic failure that influence phenotypic girls who have full or incomplete monosomy of X chromosome with a variety of clinical signs. The purpose of this study was to estimate TS cases based on their cytogenetic findings and clinical implications.
Material and methods: Thirty-nine cases diagnosed with TS were retrospectively analyzed between November 2006 and December 2019. These patients were identified among 505 people who had their karyotypes analyzed for different reasons, including primary amenorrhea (PA), premature ovarian insufficiency (POI), TS phenotype, and uterine agenesis (UA). Karyotype analysis was carried out using Giemsa staining in accordance with the standard method on peripheral blood and fluorescence in situ hybridization (FISH) was used when necessary.
Results: The median age of TS cases were 15 years (ranging from 4 to 32). The distribution of reasons for admission was as follows: 61.5% TS phenotype, 25.6% PA, 10.3% POI, and 2.6% UA with horseshoe kidney. The frequency of cytogenetic finding was 38.5% pure monosomy X and 61.5 % mosaic [30.7% monosomy X with structural rearrangements, 18% with X chromosomal structural abnormalities, 7.7% with X aneuploidy and 5.1% with Y chromosomal structural abnormalities]. The most accepted reason for both pure and mosaic TS group was TS phenotype.
Conclusion: TS develops when one sex chromosome is wholly or incompletely removed as well as structurally altered. Phenotype, fertility, and life quality may differ according to the variability of cytogenetic findings. Comprehensive cytogenetic analysis is required for the patients for medical follow-up and genetic counselling.

Keywords: Turner syndrome, cytogenetic findings, phenotypical symptoms, primary amenorrhea, premature ovarian insufficiency.

Received: 01.02.2021 **Accepted:** 01.19.2022

ÖZET

Amaç: Turner sendromu (TS), X kromozomunun tam veya kısmı monozomisi sonucu oluşan, çeşitli klinik belirtilerle seyreden, fenotipik olarak kızları etkileyen genetik bir hastalıkdır. Bu çalışmanın amacı, TS vakalarını sitogenetik bulguları ve klinik sonuçlarıyla birlikte değerlendirmektir.
Yöntem: Kasım 2006 ile Aralık 2019 arasında TS tanısı alan 39 vaka retrospektif olarak incelendi. Bu hastalar, primer amenore (PA), prematüre over yetmezliği (POI), TS fenotipi ve uterus agenezisi (UA) dahil olmak üzere farklı nedenlerle karyotipleri analiz edilen 505 kişi arasından belirlendi. Karyotip analizi, periferik kan üzerinde standart yönteme uygun olarak Giemsa boyaması kullanılarak yapıldı ve gerektiğinde floresans in situ hibridizasyon (FISH) yöntemi ile inceleme yapıldı.
Bulgular: TS vakalarının median yaşı 15'tir (4 ile 32 arasında değişmektedir). Başvuru nedenlerinin dağılımı %61,5 TS fenotip, %25,6 PA, %10,3 POI ve %2,6 at nalı böbrekli UA idi. Sitogenetik bulgu sıklığı %38.5 saf monozomi X ve %61.5 mozaik [yapısal yeniden düzenlemelerle birlikte monozomi X %30.7, X kromozomal yapısal anormallikler ile %18, X anöploidisi ile %7.7 ve Y kromozomal yapısal anormallikler ile %5.1] idi. Hem saf hem de mozaik TS grubu için en çok başvuru nedeni TS fenotipiydi.
Sonuç: TS, bir cinsiyet kromozomunun tamamen veya kısmi olarak eksilmesinin yanı sıra yapısal olarak değiştirilmesiyle de gelişir. Fenotipik bulgular, fertilite durumu ve yaşam kalitesi, sitogenetik bulgulara göre farklılık gösterebilir. Tıbbi takip ve genetik danışmanlık için hastalarda kapsamlı sitogenetik analiz gereklidir.

Anahtar Sözcükler: Turner sendromu, sitogenetik bulgular, fenotipik semptomlar, primer amenore, prematüre over yetmezliği.

Geliş Tarihi: 02.01.2021 **Kabul Tarihi:** 19.01.2022

ORCID IDs: F.K.0000-0002-3910-0821,Z.Ç.Y.0000-0001-9158-220X

Address for Correspondence / Yazışma Adresi Ferah Kazancı, Department of Gynecologic Oncology, Faculty of Medicine, Gazi University, Besevler, 06500, Ankara, Turkey
E-mail: ferahkazanci@hotmail.com

doi:http://dx.doi.org/10.12996/gmj.2023.6

INTRODUCTION

Turner syndrome (TS) is a common sex chromosome abnormality and is generally produced by a sporadic chromosomal nondisjunction (1). TS consists of many different phenotypes related to a whole or fractional monosomy of the X chromosome (1). Approximately 45-50 percent of TS cases have 45,X monosomy karyotype, and the remainder have multiple chromosomal abnormalities, such as structural chromosome abnormality or mosaicism (2). TS is observed nearly one in 2500 live birth females (3). Short stature, swollen hands or feet, nuchal folds, low hairline, low set ears, small mandible, typical facial appearance, and webbed neck are all physical phenotypes associated with TS (4). Clinicians deal with growth retardation, endocrine, cardiovascular psychosocial and reproductive issues in addition to a challenging array of genetic problems in this disease. The existence of specific visible characteristics in phenotypic females, as well as the whole or fractional lack of the second sex chromosome, together or separately cell line mosaicism, are required for the diagnosis of TS (5).

Although cases with mosaic karyotype has usually a mild severity in Turner syndrome, establishing phenotype–karyotype correlations is difficult. Because of unknown proportion of chromosomal mosaicism is difficult to assess the relative contribution of each cell line to each organ system of patients with Turner syndrome (6). Pregnancies are mostly occur in Turner's syndrome women with mosaic karyotype (7). Those are known to be at increased risk of miscarriage, still birth and having an offspring with congenital malformation or aneuploidy. Therefore, in all cases genetic counseling and karyotype analysis should be considered (8).

The goal of this study is to assess the TS cases in terms of cytogenetic, phenotypical and clinical features and compare the findings to those of other investigations.

MATERIAL and METHODS

In this retrospective study, the data of thirty-nine TS patients between November 2006 and December 2019 at the Department of Medical Genetics, Baskent University School of Medicine were analyzed.

Patients

Thirty-nine TS cytogenetic abnormality cases selected among 505 patients who applied to our clinic for reasons such as primary amenorrhea (PA), premature ovarian insufficiency(POI), TS phenotype, uterine agenesis were analyzed in terms of clinical features and cytogenetic findings**.** The defect to attain menarche is known as PA. Primary amenorrhea is determined as the lack of menstrual bleeding at 15 years age in combination with secondary sexual characteristics, or at 13 years age in without the existence of secondary sexual characteristics (9). Premature ovarian insufficiency is characterized by a lack of menses, a premature decrease in the number of ovarian follicles, or the cessation of folliculogenesis before the natural menopause, which occurs around the age of 40. Premature ovarian insufficiency has a high hereditary constituent, with X chromosomal abnormalities being the most common cause, particularly in cases of ovarian dysgenesis (9). Short stature, small mandibula, nuchal folds, low hair line and set ears, nail hypoplasia, high palate, wide thoracic cage are all phenotypic characteristics of TS (10). Except for the TS phenotype and reproductive complaints, those who applied for cardiovascular, renal and skeletal anomalies, etc. reasons were excluded from the study.

Karyotype analysis

Chromosome studies on lymphocyte cultures were carried out in 39 patients. The karyotype analysis was carried out with respect to the classic procedure on peripheral blood using Giemsa staining. At least 30 metaphases were counted for each sample before reporting. The results were presented in accordance with International System for Human Cytogenetic Nomenclature (11). FISH analysis was applied at the very least of 200 interphase cells via using LSI SRY/CEPX Probe Kit (Abbott molecular, IL). FISH analysis was performed on only patients with the presence of the Y chromosome in karyotype analysis, so this result was confirmed.

Statistical methods

SPSS software version 22.0 was used for the statistical analysis of the investigation data. We used descriptive statistics as categorical and continuous variables. The categorical variables were represented by number and percentage, and continuous variables were offered as mean ± standard deviation for normal distributed data and median (minimum-maximum value) for non-normal distributed data.

The confirmation of ethics committee was received by the ethics committee of Baskent University Faculty of Medicine on Semptember 8,2020. (Project code: KA20/341).Informed Consent: Written informed consent was obtained from patients who participated in this study.

RESULTS

In our clinic, karyotype analysis was performed on 505 patients who were admitted with reproductive complaints and TS phenotype. TS karyotypes were detected in 39 cases out of these 505 patients. The distribution of the karyotype analysis results of these 505 female patients according to the application indications was as follows: 91% normal karyotype, 5.5% pure TS, 2.1% mosaic TS, and 1.4% 46,XY.

The median age of TS cases was 15 years (range 4 to 32). The frequency of cytogenetic finding was as 38.5% monosomy X, 30.7% monosomy X with structural abnormalities, 18% mosaic TS with X chromosomal structural abnormalities, 7.7% mosaic TS with aneuploidy, and 5.1% mosaic TS with Y chromosome. The cytogenetic analysis results of cases with Turner Syndrome is demonstrated in Table 1.

The distribution of reasons for admission is 61.5% TS phenotype, 25.6% PA, 10.3% POI, and 2.6% UA with horseshoe kidney. The distribution of patients' indications among TS karyotypes is demonstrated in Figure1. The median age at diagnosis was similar in both pure and mosaic TS groups (respectively 14.50 years and 15 years) (Mann-Whitney U test; p=0.975). However, considering the application complaints of TS patients, it was observed that the age at diagnosis was significantly older for reproductive problems than the TS phenotypes (Mann-Whitney U test, p<0.00). The distribution of the ages of the patients according to cytogenetic results are shown in Figure 2. When the symptoms at presentation, such as reproductive complaints and turner phenotype, were examined, the results of karyotype analysis were similar in pure and mosaic groups (Fisher's Exact test; p=0.718). When the distribution of cytogenetic findings among the patients diagnosed with reproductive indications was analyzed, it was observed that structural anomalies such as deletion, duplication, derivation, and isochromosome were more than pure and mosaic TS karyotype, respectively (73.7%, 26,7).

In our series, mosaic TS with Y chromosome was observed only in two cases (5.2%) and this result was confirmed by FISH analysis. Karyotype analysis was performed for one of them due to the Turner phenotype and the other for POI.

Table 1: The cytogenetic analysis of patients with Turner Syndrome

Cytogenetic abnormality	Karyotype	N (%)
Monosomy X	45,X	15(38.5)
Structural abnormalities		
Deletion	46,X,del(X)(p11.4) 46,Xdel(X)(p11.2p22.3) 46,X,del(X)(q13) 46,X,del(X)(q21) 46,X,del(X)(q22) 46,X,del(X)(q21q24) 46,X,del(X)(q13)	6(15.4)
Isochromosome	46,X,i(X)(q10)	2(5.1)
Duplication	46,X,dup(X)(p11.3p21) 46,X,dup(X)(q22.2q26)	2(5.1)
Reciprocal translocation	46,X,t(X;8)(q25;p23) 46,X,t(X;19)(q22;p13)	2(5.1)
Pure TS (total)		**27(69.2)**
Mosaic TS with aneuploidy	45,X/46,XX 45,X/47,XXX /46,XX	1(2.6) 2(5.1)
Mosaic TS with X chr. structural abnormality		
Isochromosome	45,X/46,X,i(X)(q10)	3(7.7)
Ring chromosome	45,X/46,X,r(X)	2(5.1)
Derivated chromosome	45,X/46,der(X)t(X;X)(q23;q21.1)	1(2.6)
Deletion	45,X/46,X,del(X)(p11)	1(2.6)
Mosaic TS with Y chromosome		
	47,XYY. ish(Y)(SRYx1),(Y)(SRYx1)/ 45,X. ish(X)(DXZ1x1,SRYx0)/ 46,XY. ish(Y)(SRYx1)	1(2.6)
	45,X/46,XY.ish(Y)(SRYx1)	1(2.6)
Mosaic TS (total)		**12(30,8)**
Total		**39(100)**

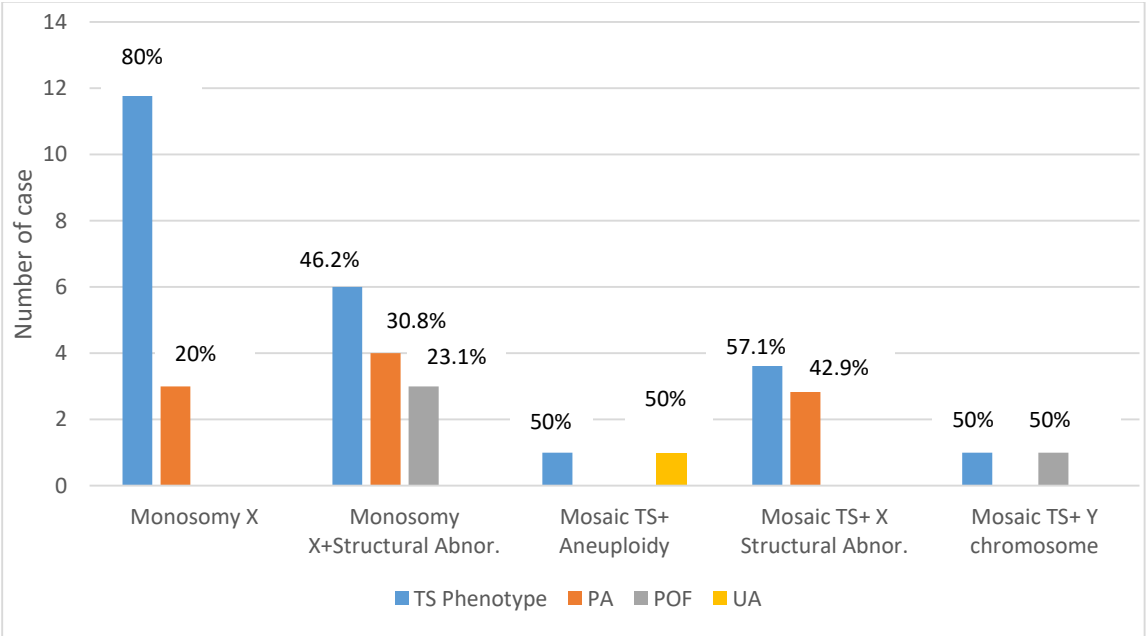

Figure1: The distribution of patients' indications among TS karyotype cases

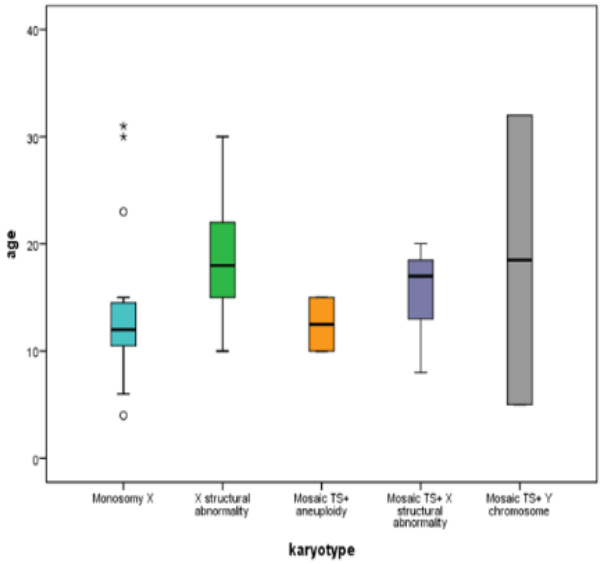

Figure2: Distribution of the ages of the patients according to cytogenetic results.

DISCUSSION

Turner syndrome is a chromosomal failure that is seen in phenotypic females who have a single X chromosome and a whole or incomplete lack of the second sex chromosome with many different clinical signs (12). In this study, the cytogenetic and clinical features of 39 patients diagnosed among 550 patients admitted with the suspicion of Turner Syndrome were evaluated by retrospective analysis.

Patients had a variety of clinical features, including abnormal growth and body proportions, gonadal dysgenesis ultimately led sexual infantilism, primary amenorrhea, premature ovarian insufficiency, infertility, cardiovascular, renal and skeletal anomalies, and the existence of some disorders, such as Hashimoto thyroiditis with hypothyroidism, diabetes mellitus type 2, osteoporosis, and hypertension (5).

The incidence of TS is about 1 in 2500 liveborn females. More than 99% of pregnancies with 45,X karyotype result in spontan miscarriage before 28 weeks. It has been estimated that among 45,X peoples who have survived birth, there is undetected mosaicism for a normal cell line anywhere; however, this has yet to be verified (13).

Gonadal dysgenesis with streak gonads, short stature, and lymphoedema in utero and at parturition are the hallmarks of TS patients. Twenty percent of TS patients were determined at birth due to the detection of characteristic sign or somatic disorders and two-thirds of them were associated with 45,X monosomy karyotype (14).

The late-onset signs of TS, such as small stature, pubertas tarda, primary or secondary amenorrhea, and premature ovarian insufficiency, were detected in other remaining TS cases throughout adolescence or later (14). According to Kammoun et al., the presenting complaint was statural retardation or dysmorphic features in pediatric patients, it was reproductive abnormalities in adult patients. In their study, the age of the cases differed from two days to 51 years, and most of them were adults (48%) (15). The median age at diagnosis was 15 years (range 4-35 years) due to late onset symptoms like the others in our series (16). In our study, we detected no significance in terms of age at diagnosis between pure or mosaic TS groups. When the patients were analyzed within subgroups in terms of age during the diagnosis, the median age was 14 among monosomy X karyotype cases, which is similar to the other reports (3). However, the median age except for the monosomy X group was 16 years old at diagnosis, and this ratio was higher than the monosomy X group as in the literature (3,16). It is not surprising that cases with different karyotypes than 45,X present longer delays as they typically exhibited the fewer stigmata. The clinical features were observed mildly in the patients with pure and mosaic monosomy X with structural abnormalities (17). Most of these females have suffered from primary amenorrhea or very premature ovarian insufficiency, and the delay in diagnosis was therefore quite striking (18).

In our series, the median age at diagnosis was significantly higher in patients who were admitted due to reproductive complaints (19 years old) than TS phenotype (12 years old)(Mann-Whitney U test, p<0.000). The low-level mosaicism in the 45,X may occur due to age-related loss. That is why, the age of the girls should be considered when analyzing the cells (19).

Elkarhat et al. reported their 21 year experience regarding the cytogenetic findings of patients with PA and TS phenotype (20). They identified 110 (19.78%) patients with TS diagnosis of 556 patients with different clinical TS spectrum and 17 (10.56%) TS cases among the patients who were admitted due to 161 PA cases (20). In our study, the ratio of TS was 7.8%, 6.1%, 8.7%, respectively, among the PA, POI and TS phenotype patients.

According to ACMG (American Collage of Medical Genetics) guidelines and other studies in literature, the kind and frequency rate of chromosome abnormalities in TS are as follows: 45,X (40-50%), mosaicism (15-25%), pure mosaicism (7-16%), isochromosome with pure TS or mosaicism TS (15-18%), ring or marker chromosome with pure TS or mosaicism TS (7-16%), deletion with pure TS or mosaicism TS (2-5%), mosaicism with triple X(3%), Y chromosome structural abnormalities with mosaicism TS (6-12%), and others (2-8%) (1,3,20). In this study, the distribution of karyotype in TS patients is almost similar to the literature (TableI) (2,5,17,20).

The relationship between the karyotypes and phenotypes in TS is not clear. The association with karyotypes and phenotypes has been compared in studies with larger samples, but the results were confusing due to the variation in patients age, differences in description of the clinical characteristics, and common confusion about the proportion of mosaicism in several tissues (6,21). Clinical characteristics are exceptionally changeable; individuals with a 45,X karyotype is disposed to have more clinical hallmarks than those with a mosaic with together a normal cell line (45,X/46,XX or 45,X/ 46,XY) (22,23,24). The deletion of the long arm of the X (Xq-) is probably far better related to having a natural height and with PA and POI (9,25). Kammoun et al. detected that short stature and primary amenorrhea were associated with the complete deletion of one chromosome X or instability gene dose because of constructional X anomalies while infertility, habitual abortions and secondary amenorrhea were related to mosaic karyotype (15).

The most of genes responsible for the physical characteristic are located on Xp (Xp11.2-p22) while the genes related to ovarian function are located on Xq (Xq24) in TS (26,27). X chromosomal deletions of smaller size result in unique features. Deletion in the X chromosome on the long(q) arm at the 24th locus (Xq24) causes primary and secondary amenorrhea without a short stature or other TS hallmarks and women should admit having POI (9,10,28). In our series, the deletions in the X chromosome both on the short (p) arm at 11 and 22 locus and on the q at 24, 22, 13 locus were observed in 3 and 4 cases among the all patients, respectively. The ratio of reproductive disorders such as, PA, POI, UA was determined higher in pure TS with X structural abnormalities (12 cases, 80%) than pure TS patients (3 cases, 20%) in this study.

The frequency of mosaicism for a cell line with a normal or defective Y chromosome ranges from 6% to 11% in patients with TS. If a 30-cell analysis disclose an evidently non-mosaic 45,X karyotype, more research is needed. FISH analysis, which uses X and Y probes, can determine low level sex chromosome mosaicism (29). In our study, this ratio was 5.2%, and in all of them, SRY (male sex-determining gene) gene was observed, and they were detected by using FISH or polymerase chain reaction (PCR). The presence of Y chromosome ingredient among women with TS is significant due to an increased risk of gonadoblastoma (2). Although gonadoblastoma has a good prognosis, it can transfrom into dysgerminoma with metastaic potential. It has been suggested that the location responsible for gonadoblastoma is on the pericentric locus of the Y chromosome. No relationship between progressing gonadoblastoma and SRY gene is observed (2). The detection ratio of concealed Y chromosome mosaicism can differ by using different techniques. Utilizing molecular techniques such as PCR, 5 percent of patients had Y chromosome mosaicism, whereas the ratio was 0-4% using interphase fluorescent in situ hybridization (FISH) with a probe for the Y centromer (30,31).

Ring chromosomes usually consist of the breaking of both terminal parts on chromosome on either side of centromere, followed by the fusing of the broken ends. The size of the ring chromosome and the breaking of short and long arms have a significant impact on the phenotypic. Ring chromosomes are seen in about 6% of TS patients, particularly in those with mosaicism for the 45, X cell line, similar to our cases (26,32).

CONCLUSION

The greatest part of females with TS have a 45,X karyotype; however, several karyotype variations such as, short or long arm deletion, ring chromosome, isochromosome, derivations, inversions, and mosaicism are observed. Patients with TS have different clinical features according to the variability of structure on karyotype. Reproductive disorders depending on gonadal dsygenesis are a feature in almost all patients with TS. Multiple organs are affected in TS patients at all stages of life since it requires a multidisciplinary care strategy. Knowledge about genetic rearrangements related to phenotype and clinical findings of TS patients can be elucidated using different cytogenetic and molecular methods.

Conflict of interest
No conflict of interest was declared by the authors.

REFERENCES

1. Carvalho AB, Lemos-Marini SFH, Guerra-Junior G, Maciel-Guerra AT. Clinical and cytogenetic features of 516 patients with suspected Turner syndrome-a single-center experience. J Pediatr Endocrinol Metab.2018;31(2):167-173.
2. Wolff DJ, Van Dyke DL, Powell CM. A Working Group of the ACMG Laboratory Quality Assurance Comittee.ADDENDUM . Laboratory guideline for Turner syndrome. Genet Med. 2016;18(1):107.
3. Bucerzan S, Miclea D, Popp R, Alkhzouz C, Lazea C, Victor Pop I, et al. Clinical and genetic characteristics in a group of 45 patients with Turner syndrome(monocentric study) Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. Therap Clin Risk Manag. 2017;13:613-622.
4. Dabrowski E, Jensen R, Johnson EK, Habiby RL, Brickman WJ, Finlayson C. Turner Syndrome Systematic Review:Spontaneous Thelarche and Menarche Stratified by Karyotype. Horm Res Paediatr. 2019;92(3):143-149.
5. Miguel-Neto J, Carvalho AB, Marques-de- Faria AP, Guerra-Junior G, Maciel-Guerra AT. New approach to phenotypic variability and karyotype-phenotype correlation in Turner syndrome. J Pediatr Endocrinol Metab. 2016;29(4):475–479.
6. Yeşilkaya E, Bereket A, Darendeliler F, Baş F, Poyrazoğlu Ş, Aydın BK, et al. Turner syndrome and associated problems in Turkish Children: A Multicenter Study. J Clin Res Pediatr Endocrinol 2015;7(1): 27-36.
7. Onalan G, Yılmaz Z, Durak T, Sahin FI, Zeyneloglu HB. Successful pregnancy with preimplantation genetic diagnosis in a woman with mosaic Turner syndrome. Fertil Steril 2011; 95(5):1788.e1-3. doi: 10.1016/j.fertnstert.2010.12.055.
8. Pimblett AC, La Rosa C, King FJT, Davies MC, Conway GC. The Turner syndrome life course project: Karyotype-phenotype analyses across the lifespan.
Clinical Endocrinology. 2017;87:532–538. Doi: 10.1111/cen.13394
9. Jain U, Gupta P. Aetiological analysis of primary amenorrhea: a retrospective study . Int J Reprod Contracept Obstet Gynecol. 2021;10(2):xxx-xxx www.ijrcog.org https://dx.doi.org/10.18203/2320-1770.ijrcog20210043
10. Mondal S, Bhattacharjee R, Chowdhury S, Chawdhury S, Mukhopadhyay S. Karyotype-Phenotype Correlation in Turner Syndrome at a Single Center in Eastern India. Indian Pediatr. 2021;58(1):34-37.
11. Stevens-Kroef M, Simons A, Rack K, Hastings RJ. Cytogenetic Nomenclature and Reporting. In. Wan T.(eds) Cancer Cytogenetics. Methods in Molecular Biology.2017. Humana Press, New York, NY.
12. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein OK et al. International Turner Syndrome Consensus Group. Clinical practice guidlines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinati International Turner Syndrome Meeting. Eur J Endocrinol. 2017; 177(3) G1-G70.
13. Tuke MA, Ruth KS, Wood AR, Beaumont RN, Tyrell J, Jones SE, et al. Mosaic Turner syndrome shows reduced penetrance in adult population study. Genet Med 2019;21(4):877-886.
14. Lim HH, Kil HR, Koo SH. Incidence, puberty, and fertility in 45,X/47,XXX mosaicism: Report of a patient and literatüre review. Am J Med Genet. 2017;173A:1961-1964.
15. Kammoun I, Chaabouni M, Trabelsi M, Quertani I, Karoua L, Chelly I, et al. Genetic analysis of Turner syndrome: 89 cases in Tunisia Ann Endocrinol. 2008;69(5):440-5.
16. Kılınç S, Yıldız M, Güven A. Associated clinical abnormalities among patients with Turner syndrome. North Clinic Istanb. 2020;7(3):226-230.
17. Linhardt JM, Hagen CP, Rajpert-De ME, Kjaergaard S, Peterson BI, Skakkebaek NE, et al. 45,X/46,XY mosaicism:phenotypic characteristics, growth, and reproductive function- a retrospective longutiduinal study. J Clin Endoc Metab.2012;97(8):E1540-E1549.
18. Negreiros LP, Bolina ER, Guimaraes MM. Pubertal development profile in patients with Turner's syndrome. J Pediatr Endocrinol Metab. 2014;27(9-10):845–849
19. Russell LM, Strike P, Browne CE, Jacobs PA. X chromosome loss and ageing. Cytogenet Genome Res. 2007; 116(3):181-5.
20. Elkarhat Z, Belkady B, Charoute H, Zarouf L, Razoki L, Aboulfaraj J, et al. Cytogenetic profile of patients with clinical spectrum of ambiguous genitalia, amenorrhea,and Turner phenotype: A21-year-single-center experience.Am J Med Genet. 2019;179A:1516-1524.
21. Bernard V, Donadille B, Zenaty D, Courtillot C, Salenave S, de la Perriere AB, et al. Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome. Molecular analysis of genes on Xp controlling Turner Syndrome and Premature Ovarian Failure(POF). Hum Reprod.2016;31(4):782-788.
22. Gonzalez L, Witchel SM. The patient with Turner syndrome: Puberty and medical management concerns. Fertil Steril. 2012;98(4);780-86.
23. Doğan M, Eröz R, Bolu S, Yüce H. Evaluation of karyotype composition of our Turner Syndrome Patients with their application complaints and antropometrics. Korunalp Tıp Dergisi 2018;10(2):248-252.
24. Tangi R, Lin L, Guo Z, Hou H, Yu Q. Ovarian reserve evaluation in woman with 45,X/47,XXX mosaicism: A case report and review of literatüre. Mol Genet Genomic Med.2019;7(7):e732.
25. Paolucci DG, Bamba V. Turner Syndrome: Care of the patient: Birth to Late Adolescence. Pediatr Endocrinol Rev.2017;2(2):454-461.
26. Huang YC, Lee CT, Wu MZ, Liu SY, Tung YC, Ho HN, et al. The spectrum of 45,X/46,XY mosaicism in Taiwanese children: The experience of a single center. J Formos Med Assoc. 2019;118(1 Pt3):450-456.
27. Ibarra-Ramirez M, Martinez-de-Villarreal LE. Clinical and genetic aspects of Turner's syndrome. Medicina Universitaria.2016;18(70)42-48.
28. Lau EYC, Fung YK. 45,X/46,XY Mosaicism in an 18-year-old Girl with Primary Amenorrhea : A Case Report. J ASEAN Fed Endocr Soc. 2020;35(1):114-117.
29. Guzewicz L, Howell S, Crerand CE, Umbaugh H, Nokoff NJ, Barker J, et al. Clinical phenotype and management of individuals with mosaic monosomy X with Y chromosome material stratified by genital phenotype. Am J Med Genet A. 2021;185(5):1437-1447.
30. Gravholt CH, Viuff MH, Brun S, Stochholm K, Andersen NH. Turner syndrome: mechanisms and management. Nat Rev Endocrinol 2019;15(10):601-614.
31. Leone PE, Yumiceba V, Vergara AJ, Perez-Villa A, Armendariz-Castillo I, Garcia-Cardenas JM, et al. Cytogenetic and genomic analysis of a patient with turner syndrome and t(2;12): a case report. Mol Cytogenet. 2020:13(1);46.
https ://doi.org/10.1186/s13039-020-00515-0.
32. Semra Gürsoy, Derya Erçal Turner Syndrome and Its Variants. J Pediatr Res 2017;4(4):171-5