

Long-term Outcome in Patients with Turner Syndrome – Retrospective Study

Codruta Diana Petchesi^{1,2}, Alin Remus Iuhas^{3,4}, Ramona Hodisan^{1*}, Dana Carmen Zaha^{1,3}, Alexandru Daniel Jurca¹

¹Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania. ²Regional Center for Medical Genetics Bihor (part of ERN THACA), Emergency Clinical County Hospital Bihor, Oradea, Romania. ³Emergency Clinical County Hospital Bihor, Oradea, Romania. ⁴Department of Medical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania.

Abstract

Turner syndrome is one of the most frequent chromosomal disorders and has an increased associated morbidity. The clinical picture of Turner syndrome reveals itself gradually, not every patient exhibits the full clinical picture, but gonadal dysgenesis and short stature are invariably present. We describe the long-term outcomes in a cohort of 41 patients with Turner syndrome followed at the Regional Center for Medical Genetics Bihor. A retrospective study was performed using the medical records; epidemiological, clinical, laboratory, cytogenetic, and imaging data were analyzed. The frequency of congenital heart abnormalities and intellectual disability was increased in the study group, necessitating a more effective screening technique in our country, to identify all the cases with TS. Early diagnosis and hormonal treatment are critical for a patient's favorable prognosis in stature, bone metabolism, cardiovascular system, and quality of life. Patients with TS have higher rates of related morbidity, especially skeletal, kidney, ophthalmological, and dermatological and a multidisciplinary team is essential for the management of TS cases.

Keywords: Turner syndrome, Short stature, Growth hormone, Long-term outcome

INTRODUCTION

Turner syndrome (TS) is one of the most frequent chromosomal disorders, with a birth incidence of 1 in 2000 live-born girls [1, 2]. Incidence at birth is much higher, about 98% of pregnancies with Turner syndrome are lost as miscarriages and stillbirths [3]. In half of the cases, it is caused by the absence of a sexual chromosome due to meiotic nondisjunction [4]. Mosaic Turner syndrome occurs due to mitotic nondisjunction, and the patient exhibits different combinations of monosomy cell lines with normal cell lines or other abnormal cell lines. Mosaicism has been reported frequently in aneuploidies and it seems to influence the survival rate [5, 6]. Rarely, it is caused by partial deletions which include pseudoautosomal regions 1 and 2 (PAR1, PAR2), or structural anomalies like isochromosome Xq and ring chromosome X [7]. The clinical picture of Turner syndrome reveals itself gradually: at birth borderline small for gestational age, broad chest with widely spaced nipples, congenital lymphedema, and congenital heart defects (coarctation of the aorta, bicuspid aortic valve); in infancy short stature, recurrent ear infections and sometimes hearing loss; in adolescence absent or incomplete puberty, specific learning difficulties, and immune disorders; in adulthood fertility problems, aortic dilatation, hypertension and many more [2]. Not every patient exhibits the full clinical picture, but gonadal dysgenesis and short stature are invariably present. Traditional treatment aims to treat the complications, and the modern approach includes also

medical treatment with growth hormone and estrogen-progesterone substitution [8, 9]. The study aims to evaluate the long-term outcome in a cohort of 41 patients with Turner syndrome registered between 1983 and 2023.

MATERIALS AND METHODS

Subjects

We have conducted a retrospective study involving the medical records of 41 patients registered with the Regional Center for Medical Genetics Bihor, part of the Emergency Clinical County Hospital Bihor, Oradea, Romania. In the study, we included patients with a cytogenetically confirmed diagnosis of TS and were reevaluated regularly.

Address for correspondence: Ramona Hodisan, Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania. ramona.hodisan@didactic.uoradea.ro

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non commercially, as long as the author is credited and the new creations are licensed under the identical terms.

How to cite this article: Petchesi CD, Iuhas AR, Hodisan R, Zaha DC, Jurca AD. Long-term Outcome in Patients with Turner Syndrome – Retrospective Study. Arch Pharm Pract. 2024;15(3):54-7. <https://doi.org/xxxxxxxxxxxxxxxxxxx>
<https://doi.org/10.51847/dfg57HvhDj>

Data

Epidemiological, clinical, laboratory, cytogenetic, and imaging data from the medical records were analyzed.

Cytogenetics

All the patients had been genetically investigated by peripheral blood karyotype using standard cytogenetic methods (lymphocyte cell culture and G-banding karyotype analysis). Fluorescence in situ hybridization (FISH) tests using CytoCell Y chromosome-specific probes were performed in selected patients.

RESULTS AND DISCUSSION

The Regional Center for Medical Genetics Bihor has 52 patients with TS registered between 1983 and 2023. From this lot, 11 patients (21%) have been lost during the transition to adulthood and only 41 patients had followed periodic reevaluations. Some of the patients have been followed for over 30 years, the distribution of patients by age is presented in **Table 1**.

Table 1. Distribution of patients by present age

Present age	Number of cases	%
Under the age of 10	5	14%
Between 11-30 years	13	32%
Between 31-60 years	23	54%
Total	41	100%

Note. %= Percentage

The diagnosis was established at birth, in about a third of the patients, the rest being diagnosed at puberty or in adulthood (**Figure 1**). None of the cases benefitted from prenatal diagnosis. Compared to other studies [10, 11] the diagnosis was late and was driven by short stature in childhood, respectively short stature and delayed puberty later.

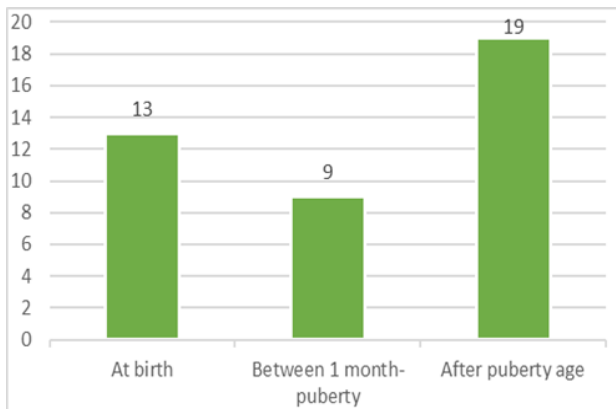


Figure 1. Distribution of patients by age at diagnosis

Regarding the age of the mother at conception we noticed that in more than half of the cases, the age of the mother was over 30 years, with the presence of the maternal age effect, as described in other aneuploidies [12, 13] (**Table 2**).

Table 2. Distribution of patients by maternal age at conception

Maternal age	Number of cases	%
18-30 years	18	44%
31-40 years	19	46,3%
41-50 years	3	7,3%
Over 50 years	1	2,4%
Total	41	100%

Note. %= Percentage

Clinical features at birth described in the literature were present in our lot as follows: prenatal growth deficiency (14 cases, 34%), congenital lymphedema (4 cases, 9,7%), and congenital heart anomalies (40 cases, 97%). Compared to other studies in the literature, the incidence of congenital heart anomalies is very increased [14]. We suspect that only the severe cases of TS have been registered with the genetic department, while the mild cases, without heart anomalies, are underdiagnosed.

The karyotype revealed monosomy X in more than half of the cases (51%). In a third of the cases (13 cases), mosaicism was detected as follows: 45, X/46, XY (1 case), 45, X/46, Xi(Xq) (1 case), and 45, X/46, XX (11 cases). Structural anomalies such as ring chromosome X or isochromosome Xq were found in 17% of the cases (**Figure 2**).

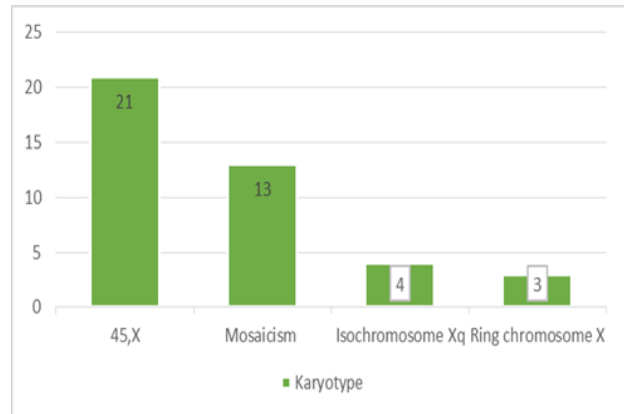


Figure 2. Distribution of patients by karyotype

Genotype-Phenotype Correlations

Isochromosome Xq usually is associated with an increased risk of autoimmunity, particularly thyroiditis, and deafness, and the risk increases with age [4]. Women with the ring X chromosome are more likely to have psychological sequelae but are less likely to have structural congenital abnormalities, and spontaneous menses occur in about a third. Mosaicism 45X/46, XY is associated with an increased risk of developing gonadoblastoma, and a minority of these women are masculinized [4].

In our study group, there were no significant variations between the clinical pictures of patients with monosomy 45,

and X and those with structural anomalies. A milder clinical picture was seen in cases of mosaicism with normal cell lines 45, X/46, and XX. Morbidity was increased, but the severity of accompanying problems was usually mild, and no patients died.

Phenotype-Treatment Correlations

Short stature with more than minus 3 standard deviations (-3SD) was present in all the cases. The safety and efficacy of growth hormone (GH) therapy were demonstrated in several studies [15-20]. 27% of the patients have followed GH treatment and have exhibited better growth (average of +1DS) compared to patients who did not follow GH treatment. The best outcome was a 30 cm growth in 5 years, and the final stature of the patient was 158 cm (-1 SD). Early diagnosis and treatment are essential for the good prognosis of a patient with a TS [21].

Gonadal dysgenesis with primary amenorrhea was observed in all the cases. Estrogen deficiency causes three specific problems: short stature, cardiovascular disease, and developmental differences in the brain [18]. Long-term estrogen replacement therapy is necessary in TS cases after puberty and completion of growth as it reduces osteoporosis and atherosclerosis. Recently, it has been shown that estrogen replacement may improve aspects of cognitive function in women with TS [22-25]. Estrogenic therapy was provided in 17 cases (41%). A combination of growth hormone and estrogen is recommended as it increases bone mineralization in girls with TS [9].

Other Features

Intellectual disability (ID) is not a mandatory feature in TS. Most patients have normal intelligence but may exhibit learning difficulties, and up to 10% can present ID. In our study lot, intellectual disability was noticed in 10 cases (24%), mostly mild ID (12%) (Table 3).

Aside from ID, behavioral issues and social isolation were reported in 17 cases (41%), primarily in patients who did not receive any hormonal treatment.

Table 3. Distribution of patients by intellectual development

Intellect	Number of cases	%
Normal	31	76%
Mild intellectual disability	5	12%
Moderate intellectual disability	3	7%
Severe intellectual disability	2	5%
Total	41	100%

Note. %= Percentage

All the patients had at least one skeletal anomaly such as anomalies of the chest, scoliosis, genu valgum club foot, congenital hip dysplasia, and polydactyly or syndactyly. Other features observed in our study lot were: kidney

disorders like polycystic kidney and renal microadenomas (13 cases, 32%); ophthalmological disorders such as strabismus, astigmatism, myopia, and congenital cataract (33 cases, 80%); and dermatological features like melanocytic naevus and hemangiomas (13 cases, 32%), webbed neck (7 cases, 17%), seizures (1 case, 9,7%), and schizophrenia (1 case, 9,7%). Type 2 diabetes mellitus is 2-4 times more frequent in TS cases and the onset age is at a young age [23, 26]. None of the cases we studied were associated with diabetes.

Long-term complications included high blood pressure (21 cases, 51%) and arthritis which required physiotherapy (17 cases, 41%).

CONCLUSION

Besides short stature and gonadal failure, patients with TS have higher rates of related morbidity, especially skeletal, kidney, ophthalmological, and dermatological and a multidisciplinary team is essential for their management. The frequency of congenital heart abnormalities and intellectual disability was increased in the study group, necessitating a more effective screening technique in our country, to identify all the cases with TS. Early diagnosis and hormonal treatment are critical for a patient's favorable prognosis in stature, bone metabolism, cardiovascular system, and quality of life.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: The study was conducted under the Declaration of Helsinki and approved by the Institutional Ethics Committee of Emergency Clinical County Hospital Bihor (protocol code 23395/06.07.2023).

REFERENCES

- Cui X, Cui Y, Shi L, Luan J, Zhou X, Han J. A basic understanding of turner syndrome: Incidence, complications, diagnosis, and treatment. *Intractable Rare Dis Res.* 2018;7(4):223-8. doi:10.1097/GIM.0b013e3181c684b2
- Medial Home Portal. [Internet]. Turner Syndrome. 2019 [updated 2019 August; cited 2024 Apr 25]. Available from: <https://www.medicalhomeportal.org/diagnoses-and-conditions/turner-syndrome#SectionPracticeGuidelines>
- Morgan T. Turner syndrome: Diagnosis and management. *Am Fam Physician.* 2007;76(3):405-17.
- Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al. Clinical practice guidelines for the care of girls and women with turner syndrome: Proceedings from the 2016 cincinnati international turner syndrome meeting. *Eur J Endocrinol.* 2017;177(3):G1-70. doi:10.1530/EJE-17-0430
- Jurcă MC, Bembea M, Iuhas OA, Kozma K, Petchesi CD, Jurcă AD, et al. Double autosomal trisomy with mosaicism 47, XY (+ 8)/47, XY (+ 21). Morphological and genetic changes of a rare case. *Rom J Morphol Embryol.* 2018;59(3):985-8.
- Spinella F, Fiorentino F, Biricik A, Bono S, Ruberti A, Cotroneo E, et al. Extent of chromosomal mosaicism influences the clinical outcome of in vitro fertilization treatments. *Fertil Steril.* 2018;109(1):77-83. doi:10.1016/j.fertnstert.2017.09.025

7. National Library of Medicine. [Internet]. Turner syndrome. 2023 [updated 2023 August 8; cited 2024 Apr 25]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554621>
8. Medscape. [Internet]. Turner syndrome [updated 2021 March 19; cited 2024 Apr 25]. Available from: https://emedicine.medscape.com/article/949681-overview?&icd=login_success_email_match_fpf
9. Ross JL, Quigley CA, Cao D, Feuillan P, Kowal K, Chipman JJ, et al. Growth hormone plus childhood low-dose estrogen in turner's syndrome. *N Engl J Med.* 2011;364(13):1230-42. doi:10.1056/NEJMoa1005669
10. Simm D, Degenhardt K, Gerdemann C, Völkl TM, Rauch A, Dörr HG. Chronological age of patients with turner syndrome at diagnosis. *Klin Padiatr.* 2007;220(1):16-20. doi:10.1055/s-2007-972569
11. Swauger S, Backeljauw P, Hornung L, Shafer J, Casnellie L, Gutmark-Little I. Age at and indication for diagnosis of turner syndrome in the pediatric population. *Am J Med Genet A.* 2021;185(11):3411-7. doi:10.1002/ajmg.a.62459
12. Chiang T, Schultz RM, Lampson MA. Meiotic origins of maternal age-related aneuploidy. *Biol Reprod.* 2012;86(1):1-7. doi:10.1095/biolreprod.111.094367
13. Mikwar M, MacFarlane AJ, Marchetti F. Mechanisms of oocyte aneuploidy associated with advanced maternal age. *Mutat Res Rev Mutat Res.* 2020;785:108320. doi:10.1016/j.mrrev.2020.108320
14. Fuchs MM, Attenhofer Jost C, Babovic-Vuksanovic D, Connolly HM, Egbe A. Long-term outcomes in patients with turner syndrome: A 68-year follow-up. *J Am Heart Assoc.* 2019;8(11):e011501. doi:10.1161/JAHA.118.011501
15. Chacko EM, Rapaport R. Short stature and its treatment in turner and Noonan syndromes. *Curr Opin Endocrinol Diabetes Obes.* 2012;19(1):40-6. doi:10.1097/MED.0b013e32834ed64e
16. Dantas NCB, Braz AF, Malaquias A, Lemos-Marini S, Arnhold IJP, Silveira ER, et al. Adult height in 299 patients with turner syndrome with or without growth hormone therapy: Results and literature review. *Horm Res Paediatr.* 2021;94(1-2):63-70. doi:10.1159/000516869
17. Gnacińska M, Magnuszewska H, Sworczak K. Metabolic consequences of recombinant human growth hormone therapy in patients with turner syndrome. *Pediatr Endocrinol Diabetes Metab.* 2023;29(1):16-21. doi:10.5114/pedm.2022.123204
18. Backeljauw P, Blair JC, Ferran JM, Kelepouris N, Miller BS, Pietropoli A, et al. Early GH treatment is effective and well tolerated in children with turner syndrome: NordiNet@ IOS and answer program. *J Clin Endocrinol Metab.* 2023;108(10):2653-65. doi:10.1210/clinem/dgad159
19. Backeljauw P, Kanumakala S, Loche S, Schwab KO, Pfäffle RW, Höybye C, et al. Safety and effectiveness of recombinant human growth hormone in children with turner syndrome: Data from the patro children study. *Horm Res Paediatr.* 2021;94(3-4):133-43. doi:10.1159/000515875
20. Aly J, Kruszka P. Novel insights in turner syndrome. *Curr Opin Pediatr.* 2022;34(4):447-60. doi:10.1097/MOP.0000000000001135
21. Iuhas A, Jurca C, Kozma K, Riza AL, Streață I, Petchesi C, et al. *PAH* pathogenic variants and clinical correlations in a group of Hyperphenylalaninemia patients from North-Western Romania. *Diagnostics (Basel).* 2023;13(8):1483. doi:10.3390/diagnostics13081483
22. Kim S, Kim H, Lee I, Choi E, Baek J, Lee J, et al. Effects of hormone replacement therapy on bone mineral density in Korean adults with turner syndrome. *J Korean Med Sci.* 2024;39(1):e9. doi:10.3346/jkms.2024.39.e9
23. Giordano R, Forno D, Lanfranco F, Manieri C, Ghizzoni L, Ghigo E. Metabolic and cardiovascular outcomes in a group of adult patients with turner's syndrome under hormonal replacement therapy. *Eur J Endocrinol.* 2011;164(5):819-26. doi:10.1530/EJE-11-0002
24. Jordan TL, Klabunde M, Green T, Hong DS, Ross JL, Jo B, et al. Longitudinal investigation of cognition, social competence, and anxiety in children and adolescents with turner syndrome. *Horm Behav.* 2023;149:105300. doi:10.1016/j.yhbeh.2022.105300
25. Klein KO, Rosenfield RL, Santen RJ, Gawlik AM, Backeljauw PF, Gravholt CH, et al. Estrogen replacement in turner syndrome: Literature review and practical considerations. *J Clin Endocrinol Metab.* 2018;103(5):1790-803.
26. Mitsch C, Alexandrou E, Norris AW, Pinnaro CT. Hyperglycemia in turner syndrome: Impact, mechanisms, and areas for future research. *Front Endocrinol (Lausanne).* 2023;14:1116889. doi:10.3389/fendo.2023.1116889