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ORIGINAL ARTICLE

# Clinical characterization of girls with Turner syndrome

## Caracterización de una cohorte de pacientes pediátricas con Síndrome de Turner

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**What do we know about the subject matter of this study?**

Turner syndrome is a genetic disorder whose main clinical manifestations are short stature, ovarian insufficiency, and congenital heart defects. It is characterized by a wide spectrum in the phenotype which makes its early diagnosis difficult in some cases. In our sphere, there are few studies describing this syndrome.

**What does this study contribute to what is already known?**

We describe the clinical and paraclinical characteristics, karyotypes, and comorbidities of 97 patients with Turner syndrome. Short stature, lipid disorders, cardiovascular malformations, and hearing and neuropsychiatric disorders were frequent. Late diagnosis (median age: 8.5 years) was observed. 51% had karyotype 45,X, with more typical physical examination features.

## Abstract

Turner syndrome is a genetic disorder that occurs in women with partial or complete absence of an X chromosome. **Objective**: To describe the clinical, laboratory, and genotypic characteristics of patients with Turner syndrome, treated at three health institutions in Medellin. **Patients and Method**: A retrospective study was carried out. A total of 97 patients with Turner syndrome (< 18 years) confirmed by karyotype between 2011 and 2018 were included. Patients whose karyotype did not meet the specification of the American College of Medical Genetics were excluded. Data on sociodemographic details, nutritional variables, phenotypic characteristics, and laboratory tests were collected. A descriptive analysis was performed in SPSS software version 20. **Results**: Median age at diagnosis was 8.5 years (IQR 4-12). The main clinical characteristic was short stature (90%). Additionally, they

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presented cardiovascular malformations (35%), renal alterations (26%), hearing disorders, mainly hypoacusis (33%), and neuropsychiatric disorders (44%). The most frequent karyotype was 45,X (51%) followed by 45,X/46,XX (14%). The patients with 45,X karyotype had the most classic clinical characteristics. Patients > 5 years old had a higher proportion of weight excess than the general population. Dyslipidemia was found in 62% and hypothyroidism in 22%. 70% of patients > 11 years received pubertal induction; 23% presented spontaneous puberty and 44% of them required hormonal maintenance. 86% received somatropin. **Conclusion**: The patients with Turner syndrome in our study presented a high frequency of short stature and cardiovascular, renal, hearing, endocrine, and neuropsychiatric comorbidities. The diagnosis was delayed due to the lack of clinical suspicion given its variable presentation.

## Introduction

Turner syndrome is a chromosomal disorder with partial or complete absence of an X chromosome, characterized by manifestations that may include typical facies, short stature, ovarian insufficiency, sensorineural and/or conductive hearing loss, congenital cardiovascular defects, renal and skeletal anomalies, among others. It is associated with a group of endocrine, autoimmune, visual, and neuropsychiatric diseases, which require specialized follow-up by a multidisciplinary team[1–4].

Its incidence is 1:1700 to 1:2500 live newborns, with a generally late diagnosis[5–7]. It is described that 20% of cases are diagnosed at birth due to the presence of classic clinical features, 20% in infancy due to short stature, 50% late in adolescence due to the presence of delayed puberty or primary amenorrhea, and the remaining 10% are diagnosed in adulthood due to secondary amenorrhea and infertility[7,8].

Early diagnosis of this entity helps in the adequate management of comorbidities, in addition to achieving a height closer to normal with the use of growth hormone and the timely initiation of pubertal induction[7,9,10]. The high risk of complications may be related to late diagnosis which, at the same time, is influenced by the variability in the clinical expression of these patients and the difficulties for general practitioners and pediatricians in its recognition. In our sphere, there are few studies on Turner syndrome and, in general, they do not integrate clinical diversity with genetics [11–13]. The objective of this study was to describe the clinical and paraclinical characteristics, comorbidities, and most frequent endocrinological disorders of patients with Turner syndrome, specifically of each genotype, seen at three healthcare institutions in Medellin, Colombia.

## Patients and Method

### Study design

Descriptive observational study, with retrospective collection of information through electronic medical records of a sample of patients with Turner syndrome who attended pediatric endocrinology consultation in three institutions in Medellin (*Hospital Universitario San Vicente Fundación*, *Hospital Alma Máter de Antioquia*, and *Fundación Clínica Noel*), between 2011 and 2018.

### Population

Patients under 18 years of age with a diagnosis of Turner syndrome confirmed by karyotype test were included. Patients whose karyotype test did not meet the specification of the American College of Medical Genetics (minimum 20 metaphases)[1], those who did not have a medical history available, or those who were not evaluated by pediatric endocrinology were excluded. The patients were identified through the ICD-10 diagnosis for Turner syndrome (Q960-Q964, Q968, and Q969).

### Data and variable handling

The variables' information was collected at the first consultation with the pediatric endocrinologist. Sociodemographic data, nutritional status, and dysmorphic features characteristic of the syndrome were recorded, in addition to laboratory tests and other diagnostic evaluations to assess comorbidities. Lipid profile reports were classified according to the cut-off points published in the 2011 Expert Panel Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents[14] and by the 2018 AHA/ACC blood cholesterol management guideline considering the age of girls as follows: 0-9 years, total cholesterol ≥ 200 mg/dl; low HDL cholesterol < 40 mg/dl, LDL cholesterol ≥ 130 mg/dl, and triglycerides ≥ 100 mg/dl, and for girls aged 10 to 18 years the same values were considered except triglycerides, being high ≥ 130 mg/dl [15]; it was classified as mixed dyslipidemia when the patient had elevated total cholesterol with high LDL cholesterol and high triglycerides.

Vitamin D levels were classified according to the

Endocrine Society's Global Consensus Recommendations on Prevention and Management of Nutritional Rickets as follows: deficiency (< 12 ng/ml), insufficiency (12-20 ng/ml), and sufficiency (> 20 ng/ml)[16].

To assess the height and nutritional status of the patients, the values of the measurements were compared with the WHO growth standards for children[17,18].

**Statistical analysis**

For qualitative variables, frequencies and proportions were calculated; for quantitative variables, normality was assessed with the Shapiro-Wilk test, reported as median and interquartile range (IQR) or mean and standard deviation (SD). The SPSS software version 20 was used.

**Ethical considerations**

The study was approved by the Research Ethics Committee of the *Hospital Universitario de San Vicente Fundación* (No.22-2018-27 of 2018), the Technical Research Committee of the *Hospital Alma Máter de Antioquia* (No.101-17 of 2018), and the Ethics Committee of the *Fundación Clínica Noel* (12/09/2018).

## Results

193 medical records were reviewed, including in the study 97 patients who met the inclusion criteria. 96 patients were excluded as follows: 18 without karyotype test reports, 21 with normal karyotype results, and 57 without evaluation by pediatric endocrinology.

The median age at diagnosis was 8.5 years (IQR 4-12 years) with a minimum age of 1 month and a maximum of 16.5 years. This information was available in 78/97 patients (80%), the remaining patients had been diagnosed in other institutions. The area of origin was rural in 18/89 patients (20%). Table 1 shows the characteristics at birth.

The most frequent dysmorphic features on physical examination were short neck (78%), followed by a high-arched palate (67%), low-set ears and pinna abnormalities (64%), and low posterior hairline (63%) (Table 2). The endocrinologists recorded Turner facies in 72% of the patients to encompass facial features and normal facies were reported in 25%.

**Tabla 1. Características al nacimiento**

| Característica | n | |
|---|---|---|
| Edad gestacional en semanas, mediana (RIC) | 61 | 38 (37-39) |
| Prematuridad, n (%) | 61 | 13 (21) |
| Peso al nacer en kilos, media (DE) | 61 | 2,54 ± 0,604 |
| Talla al nacer en centímetros, mediana (RIC) | 54 | 47 (44-49) |
| Linfedema al nacer, n (%) | 70 | 17 (24) |

n: pacientes en los que fue posible conseguir la información. RIC: rango intercuartílico, DE: desviación estándar.

**Growth**

The mean height at diagnosis was -2.84 ± 1.1 SD. 90% of the patients had short stature at the first consultation. 33% of the girls under 5 years of age had a weight/height ratio between -1 and -2 SD. In patients older than 5 years, 8% were obese and 21% were overweight. A total of 74/86 patients (86%) received somatropin, with a mean age at the onset of 8.9 years ± 4.1, with a minimum age of 2 years and a maximum of 16 years (n = 41 patients with complete data). Information on somatropin treatment was not available in 11 patients. The median dose was 0.045 mg/kg/d (0.04-0.05) and treatment duration was 27 months (IQR 13-61.5).

**Puberty**

23% of the patients had spontaneous puberty, which was defined as the presence of breast growth in Tanner stage II reported by the endocrinologist without the initiation of hormone replacement therapy. Of these patients, 44% required hormone replacement therapy to continue puberty.

Patients older or equal to 11 years of age (n = 58) presented elevated gonadotropins (LH 18.1 mIU/mL ± 12.3) and FSH (72.3 mIU/mL ± 47.4), confirming the presence of hypergonadotropic hypogonadism. Of these, 70% received pubertal induction with a median age of 14 years (12-15). The most frequently used method was oral conjugated estrogens (84%), followed by transdermal estrogens (16%).

Two patients had spontaneous menarche at normal age (12 and 14 years), with mosaic karyotypes: 45,X/46,XX and 45,X/47,XXX, respectively.

**Comorbidities**

Among the comorbidities observed, hearing impairment was the most frequent (61%), followed by lipid disorders (59%), and neuropsychiatric disorders (44%). Cardiovascular malformations were present in 35% of patients (Table 3).

**Karyotypes and their correlation with phenotype and comorbidities**

The most frequent karyotype was 45,X (51%), followed by 45,X/46,XX mosaicism (15%) (Table 4). Patients with karyotype 45,X presented a higher proportion of cardiovascular, hearing, and visual comorbidities, more classic phenotype, a higher proportion of webbed neck, short neck, cubitus valgus, low posterior hairline, and skeletal thorax deformities. Among the patients with karyotype with structural anomalies,

the most frequently found was the Xq isochromosome; these patients have the lowest median height and clinical characteristics in similar proportions to the 45,X karyotype, with skeletal malformations standing out. Patients with karyotype 45,X/46,XX mosaicism had a lower proportion of phenotype characteristics and associated comorbidities (Table 5).

Patients with karyotypes 45,X/46,XY and 45,X/46,XX, showed the highest proportion of neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD), depression, and conduct disorders. When grouping patients with karyotypes with structural abnormalities, 55% presented psychiatric disorders (Table 5). When the 6 patients with a ring chromosome karyotype were analyzed in isolation, 2/6 patients (33%) had behavioral disorders and reported no other disorders.

## Discussion

In our study, we report the characteristics of 97 patients with Turner syndrome in Medellin, finding that the age at diagnosis was late with a median of 8.5 years. The most important clinical features were short neck, high-arched palate, low-set ears and pinna abnormalities, and low posterior hairline. The most frequent comorbidities were auditory (61%) and cardiovascular (35%). 51% had karyotype 45,X, with more typical features on physical examination.

The age at diagnosis was late (8.5 years), compared with other studies in Mexico (6 years)[19] and the United States (3 years)[20] and early compared with the study in

**Tabla 2. Características clínicas al examen físico**

| Características clínicas | n | Frecuencia | % |
|---|---|---|---|
| Cuello corto | 91 | 71 | 78 |
| Paladar alto arqueado | 84 | 56 | 67 |
| Pabellones auriculares bajos | 88 | 56 | 64 |
| Implantación tridente del cabello | 87 | 55 | 63 |
| Cubitus valgus | 89 | 52 | 58 |
| Aumento en la distancia entre los pezones | 90 | 42 | 47 |
| Uñas hiperconvexas/displásicas | 78 | 24 | 31 |
| Epicanto | 90 | 27 | 30 |
| Implantación baja del cabello | 88 | 26 | 30 |
| *Pterigium colli* | 88 | 22 | 25 |
| Pabellones rotados atrás | 87 | 20 | 23 |
| Múltiples nevus | 89 | 19 | 21 |
| Dientes apiñados | 60 | 12 | 20 |
| Acortamiento cuarto metacarpiano | 84 | 15 | 18 |
| Pectus excavatum | 88 | 13 | 15 |
| Tórax en escudo | 89 | 7 | 8 |
| Escoliosis | 87 | 7 | 8 |
| Ptosis palpebral | 46 | 3 | 7 |
| Genu valgo | 84 | 5 | 6 |
| Luxación de cadera | 88 | 4 | 5 |
| Deformidad de Madelung | 87 | 1 | 1 |

n: pacientes en los que fue posible conseguir la información.

**Tabla 3. Comorbilidades de las pacientes**

| | N | n | % |
|---|---|---|---|
| *Comorbilidades* | | | |
| Malformaciones cardiovasculares | 91 | 32 | 35 |
| Ninguna | | 59 | 65 |
| Aorta bivalva | | 14 | 15 |
| Coartación de aorta | | 5 | 6 |
| Válvula mitral mixomatosa | | 4 | 4 |
| Ductus arterioso | | 2 | 2 |
| Dilatación de aorta | | 1 | 1 |
| Otras | | 6 | 7 |
| Malformaciones renales | 86 | 22 | 26 |
| Ninguna | | 64 | 75 |
| Doble sistema colector | | 7 | 8 |
| Riñón en herradura | | 6 | 7 |
| Hidronefrosis | | 3 | 4 |
| Hipoplasia renal | | 2 | 2 |
| Reflujo vesicoureteral | | 2 | 2 |
| Otra | | 2 | 2 |

| | | | |
|---|---|---|---|
| Trastornos auditivos | 46 | 28 | 61 |
| Ninguna | | 18 | 39 |
| Otitis media recurrente | | 14 | 30 |
| Hipoacusia conductiva | | 7 | 15 |
| Hipoacusia neurosensorial | | 4 | 9 |
| Hipoacusia mixta | | 3 | 7 |
| Trastornos visuales | 46 | 15 | 33 |
| Ninguno | | 31 | 67 |
| Defecto de refracción | | 7 | 15 |
| Estrabismo | | 4 | 9 |
| Otra | | 4 | 9 |
| Trastornos neuropsiquiátricos | 63 | 28 | 44 |
| Ninguno | | 35 | 56 |
| Trastorno por déficit de atención e hiperactividad | | 15 | 24 |
| Depresión | | 3 | 5 |
| Trastornos del comportamiento | | 3 | 5 |
| Ansiedad | | 2 | 3 |
| Déficit cognitivo | | 2 | 3 |
| Trastorno del aprendizaje | | 2 | 3 |
| Trastorno del espectro autista | | 1 | 1 |
| Otras manifestaciones | 97 | | |
| Enfermedad inflamatoria intestinal | | 1 | 1 |
| Atresia de vías biliares | | 1 | 1 |
| Neurofibromatosis | | 1 | 1 |
| | | | |
| *Endocrinopatías* | | | |
| Hipotiroidismo | 94 | 21 | 22 |
| Tiroiditis | 84 | 9 | 11 |
| Metabolismo de los lípidos | | | |
| 0 a 9 años | 9 | | |
| Normal | | 1 | 11 |
| Colesterol total normal, HDL bajo | | 1 | 11 |
| Hipercolesterolemia con LDL alto | | 2 | 22 |
| Hipertrigliceridemia | | 3 | 34 |
| Dislipidemia mixta | | 2 | 22 |
| Mayores de 9 años | 21 | | |
| Normal | | 8 | 39 |
| Colesterol total normal, HDL bajo | | 4 | 19 |
| Hipercolesterolemia con LDL alto | | 3 | 14 |
| Hipercolesterolemia con hipertrigliceridemia | | 3 | 14 |
| Dislipidemia mixta | | 3 | 14 |
| Metabolismo de los carbohidratos | | | |
| Glucosa (mg/dL), media (DE) | 40 | 90,3 ± 36,4 | |
| HbA1C (%), mediana (RIC) | 41 | 5,3 (5-5,6) | |
| Diabetes mellitus tipo 1 | 97 | 2 | 2 |
| Salud ósea | 28 | | |
| 25 hidroxivitamina D (ng/mL), mediana (RIC) | | 23,2 (19,4-28,1) | |
| Insuficiencia | | 8 | 29 |
| Suficiencia | | 20 | 71 |

N: pacientes con información en la variable. n: frecuencia absoluta en la variable. %: porcentaje. RIC: rango intercuartílico, DE: desviación estándar.

Turkey (10.2 years)[21]. In addition to this high variability in the ages at diagnosis, there was a delay between clinical suspicion and confirmation; in the USA, this delay was estimated at 7.7 years[22]. This reflects the difficulties in diagnosing this syndrome on time, regardless of the country, which can be explained by the lack of clinical suspicion at younger ages, due to the wide phenotypic spectrum and, in our sphere, probably due to the care of the newborn and the infant population predominantly by general practitioners, who require a higher level of suspicion in the face of subtle pictures. The delay in confirming the diagnosis could be explained by the difficulties in accessing karyotyping and its costs for the health system at the beginning of the period in which the study was carried out.

Short stature was the most common phenotypic characteristic, similar to the study conducted in Mexico[19], supporting the idea that every girl with short sta-

**Tabla 4. Resultado de los cariotipos de las pacientes**

| Cariotipos | Descripción | n | % |
|---|---|---|---|
| 45,X | Monosomía del X | 49 | 51 |
| 45X/46XX | Mosaicismo con monosomía del X | 14 | 15 |
| 45,X/46,X i(Xq) [a] 46,X/i(Xq) | Isocromosoma (Xq) | 11 | 11 |
| 45,X/46XY | Disgenesia gonadal mixta | 7 | 7 |
| 45,X/46,X r(X) | Cromosoma X en anillo | 6 | 6 |
| 46,XX del(q22) | Deleción Xq | 3 | 3 |
| 45,X/46,XX/47,XXX; 45,X/47,XXX | Mosaicismo con "triple X" | 3 | 3 |
| 45,X/46,Xmar | Monosomía del X con cromosoma marcador | 2 | 2 |
| 45,X/46,X, del(X)p 11-3pter | Deleción Xp | 1 | 1 |
| 45,X/ 46,X,psi idic(X)(p11) | Isodicéntrico Xp | 1 | 1 |

[a] De los 11 cariotipos, 10 fueron mosaicismos 45,X/46,X i(Xq) y 1 no estaba en mosaicismo 46,X/i(Xq).

**Tabla 5. Correlación cariotipo- fenotipo**

| Cariotipos | 45,X % n = 49 | 45,X/46,XX % n = 14 | 45,X/46,Xr (X) % n = 6 | Isocromosoma (Xq) % n = 11 | Otros % =17 |
|---|---|---|---|---|---|
| Talla/Edad [a] | -2,85 ± 1,16 | -2,74 ± 1,19 | -2,27 ± 1,26 | -3,09 ± 1,41 | -2,99 ± 0,74 |
| Malformación cardiovascular | 47 | 36 | 29 | 9 | 25 |
| Malformación Renal n (%) | 19 | 23 | 33 | 20 | 47 |
| Auditivas | 52 | 89 | 33 | 40 | 75 |
| Visuales | 41 | 17 | 66 | 60 | 30 |
| Neuropsiquiátricas | 35 | 56 | 83 | 25 | 55 |
| Epicanto | 16 | 17 | 0 | 27 | 31 |
| Cuello corto | 82 | 69 | 100 | 64 | 75 |
| *Pterigium colli* | 36 | 15 | 20 | 0 | 20 |
| Paladar alto y arqueado | 74 | 58 | 33 | 63 | 69 |
| Pabellones auriculares bajos | 80 | 42 | 33 | 55 | 53 |
| Cabello tridente | 70 | 46 | 20 | 80 | 63 |
| Cubitus valgus | 52 | 64 | 43 | 80 | 63 |
| Deformidad en el tórax | 48 | 57 | 17 | 60 | 31 |
| Aumento de distancia entre los pezones | 54 | 43 | 17 | 64 | 31 |
| Uñas hiperconvexas/displásicas | 100 | 100 | 100 | 100 | 38 |
| Escoliosis | 5 | 7 | 17 | 33 | 0 |
| Luxación de cadera | 2 | 8 | 0 | 9 | 6 |

[a] Media (DE).

ture should be evaluated with a karyotype test, regardless of the presence of other associated characteristics[1].

The earliest clinical sign that could suggest the diagnosis is the presence of lymphedema, which was present in 24% of patients, similar to that reported in other studies [1,19]. A thorough and detailed semiological evaluation in these patients could identify key minor diagnostic features such as hyperconvex fingernail and nail dysplasia, present in 31% of the patients studied in contrast to worldwide series that report between 10-13%[1,23].

Patients with Turner syndrome are at increased risk of cardiovascular and metabolic disease in early adulthood, which begins in childhood associated with the accumulation of central adiposity[24–26]. In our study, patients under 5 years of age were not overweight, but strikingly, those older than 5 years of age presented 29% of excess weight (overweight or obesity), which is slightly higher than that reported in the general Colombian population according to the 2015 National Health and Nutrition Survey (24.4%)[27]. This supports what has already been reported in the literature about the increased susceptibility to weight gain characteristic of Turner syndrome[24]. The increased prevalence of cardiometabolic risk factors such as hypertension, insulin resistance, diabetes mellitus, dyslipidemia, and central obesity contribute to morbidity and mortality in these patients. This is why the recommended cardiovascular follow-up includes physical examination, electrocardiogram, evaluation of cardiovascular disease risk factors, transesophageal echocardiogram, and heart MRI, with follow-up varying according to the initial risk classification between each year and 5 years[28,29].

Regarding pubertal development, in this study, it was found that 77% of the patients did not present spontaneous onset of pubertal development. This agrees with what has been reported in the literature where primary ovarian insufficiency is one of the most frequent manifestations in girls with Turner syndrome, requiring induction with estrogen therapy for pubertal development[1]. Additionally, it has been reported that about 20% of patients reach some degree of spontaneous puberty, 16% have menarche and 6% have regular menstrual cycles, and then evolve to oligomenorrhea, anovulatory cycles, and complete gonadal failure in up to 96% of cases[9,30]. Since our study was not designed for long-term follow-up, it is not known what proportion of patients with spontaneous puberty subsequently progressed to gonadal failure.

In our patients, the mean age of pubertal induction initiation was late (14 years, IQR 12-15), similar to another study performed in Argentina which was 15.1 years, since management guidelines recommend monitoring FSH at 11 years or even earlier, and initiating pubertal induction at this age or when FSH elevation is observed[1]. The guidelines also suggest that pubertal induction should be initiated with estrogens at low doses, preferring the transdermal route[9]. However, in our sphere, there are difficulties in the use of this route due to the unavailability of estradiol patches with low concentrations, so it is required to fractionate the patches of conventional concentrations, limiting their use.

The increased cardiovascular risk is multifactorial and related to genetics, epigenetics, hypogonadism, medical comorbidities, and lifestyle. In our study, we found 61% of dyslipidemia in girls over 9 years of age, similar to that described in the study by Valencia et al [11], confirming the high cardiovascular risk from an early age and reinforcing the importance of adequate primary prevention to avoid overweight and obesity, through strict recommendations for a healthy lifestyle in pediatric consultations, in addition to screening for lipid profile from the age of 9 years[1,32].

Autoimmune thyroiditis was present in 10% of the patients, similar to what was reported in a Turkish study (11.1%)[21] but lower than that reported in other studies, with a prevalence of 26.8% and 39.4%, respectively[24,25]. This variation could be related to the diversity in the susceptibility of each population and the relationship between chromosomal disorders and autoimmunity since the long arm of the X chromosome contains the major histocompatibility complex locus that allows immune adaptation to the exposure of different pathogens[33]. Additionally, the number of X chromosomes and the consequent X-linked dosage is critical for the maintenance or loss of immune tolerance, resulting in the activation or deactivation of certain genes, such as the DDX3 gene (DEAD-Box helicase 3), related to interferon production. Other genes related to the production of interleukins such as CD40L, and FOXP3, among many others, are also involved [34].

In this study, 44% of the patients had some neuropsychiatric disorder, which is similar to that reported in the study by Cardoso 2004 (52%)[35]. The frequency of neuropsychiatric disorders in our patients is likely higher since there is an evident underdiagnosis of these pathologies and there is a need for a structured screening of these disorders as recommended by the new Turner syndrome guideline[1]. Among the neuropsychiatric disorders evaluated in our study, the most frequent was ADHD (24%), similar to that published by Green et al.[36] who reported a prevalence of 24% and also described that patients with Turner syndrome are at 18-fold times risk of presenting ADHD than the general female population.

Regarding depressive disorders, in our study, we found a frequency of 5%, which is lower than that reported in the literature (25.5-41%)[35,37], and probably reflects the underdiagnosis of these psychopathologies.

On the other hand, Reimann et al. found that depressive symptoms occurred in 12.1% of patients with an early diagnosis of Turner syndrome and 40.4% of patients with a late diagnosis[37], emphasizing the importance of a timely diagnosis, both of Turner syndrome and its comorbidities, with an active assessment of neuropsychiatric disorders at each consultation[38].

Regarding the cytogenetic study, the most frequent karyotype found was 45,X (45%), followed by 45,X/46,XX (14%), and the isochromosome Xq (45,X/46,X,*i*[Xq]) (11%), similar to that reported in other series such as a multicenter study in Turkey, where karyotypes 45,X (50.7%) and 45,X/46,XX (10.8%) were predominant[21]; a Brazilian study with karyotype 45,X in 64% of cases[39] and a study in London, which described this same karyotype in 41.6%, followed in frequency by isochromosome (Xq) in 18.8% and 45,X/46,XX mosaicism in 15.7%[40].

In addition, in our study, it was also found that the most frequent structural anomaly karyotype was the isochromosome Xq (11%), compared with other structural anomalies that had frequencies lower than 7%, similar to a series previously described[21,40,41]. Patients carriers of isochromosome Xq karyotype had a high proportion of skeletal malformations and a phenotype very similar to patients with the 45,X karyotype. This may be explained by the fact that the isochromosome Xq is a mirror image of 2 copies of the long arm of the X chromosome, commonly associated with a 45,X cell line. On the short arm of the X chromosome are loci related to the classic phenotype of these patients: the SHOX gene, which is located in the pseudoautosomal region of the X chromosome (Xp22). This gene codes for a transcription factor that is implicated in short stature and skeletal abnormalities associated with Turner syndrome. Males and females have 2 copies of SHOX, which is why haploinsufficiency of the SHOX gene explains part of the phenotype of girls with Turner syndrome. Additionally, on the short arm of the X chromosome, there are gene loci associated with ovarian insufficiency, such as bone morphogenetic protein 15 (BMP15) located on Xp11.2[30].

The greatest strength of the study is the number of patients evaluated. The limitations were the convenience sampling and that since it is a retrospective study, some data were lost, generating information bias.

Considering our results, we suggest prospective studies that evaluate all dimensions involved in the outcomes of Turner syndrome, including aspects such as response to growth hormone use, pubertal induction, implementation of screening scales for the detection of neuropsychiatric problems, and monitoring and follow-up of cardiovascular and metabolic disorders.

In addition, we suggest the creation of structured protocols for the diagnosis, follow-up, and treatment of these patients based on the management recommendations of the Turner syndrome clinical practice guidelines in order to reduce their morbidity and overcome the barriers of the health system.

## Conclusion

The patients with Turner syndrome in our study had short stature and cardiovascular, renal, auditory, endocrine, and neuropsychiatric comorbidities. The diagnosis was late, so the primary care physician and the pediatrician should be trained to suspect it early in order to reduce complications and improve the quality of life of these patients.

Prospective studies are required in girls with Turner syndrome in our country that evaluate neuropsychiatric disorders, response to growth hormone treatment, and pubertal induction.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

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