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RESEARCH ARTICLE

Turner syndrome: experience with a select group from the Mexican population

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ABSTRACT

Background. Turner syndrome (TS) is a condition that presents in females with partial or total absence of the X chromosome. The aim of this article is to describe, in a select group of patients with Turner syndrome, comorbidity associated with this entity, diagnostic difficulties and some aspects related to the social environment of these patients. Analyzed data were obtained from members of the Turner Syndrome Association of Mexico AC.

Methods. A questionnaire was administered and anthropometric measurements and laboratory studies were performed to explore comorbidities as well as diagnostic and social problems presented in these patients.

Results. There was a delayed diagnosis and inadequate follow-up of these patients with poor detection of comorbidities and a probable lack of social integration of those females born with this syndrome.

Conclusions. We need to continuously educate the medical community in regard to early detection and referral of these patients, both in the primary care setting as well as in the community, and also to implement strategies to improve social performance of those with Turner syndrome.

Key words: Turner syndrome, comorbidities, diagnosis, monitoring, medical treatment.

INTRODUCTION

Turner syndrome (TS) is a condition that presents itself in women with total or partial absence of the X chromosome. It is estimated that it occurs in 1/2,500-3,000 live newborn females. However, 99% of the cases of TS with karyotype (45,X0) result in spontaneous abortion.[1-3]

TS is a genetic disorder that may be accompanied by comorbidities such as cardiovascular malformations, which have been reported with a frequency of 17-45% without a clear correlation of the phenotype-genotype. The bicuspid aortic valve and coarctation of the aorta are the most common disorders. Patients with any of these alterations have a greater risk of presenting progressive dilatation of the aortic root.[3-10] A higher incidence of other comorbidities also exists that, if not detected in time, decrease the quality of life of girls with TS and their families. Among these are obesity (30%), arterial hypertension (50%), glucose intolerance (15-50%), type 2 diabetes mellitus (10%), autoimmune diseases such as hypothyroidism (15-30%), alopecia (5%), vitiligo (5%), psoriasis (<5%) and juvenile rheumatoid arthritis (<5%). Other conditions include recurrent otitis media (90%), renal malformations (40%), neurosensorial deafness (27%), strabismus (18%), ptosis (13%), scoliosis (10%), celiac disease (2-10%), gonadoblastoma (7%) when there are sequences of the Y chromosome (can be avoided with prophylactic gonadectomy). The risk of developing colon cancer is unknown,

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although a greater incidence of cases has been reported in patients with TS. Also, it has been reported that 50-80% of these patients will have osteopenia, osteoporosis and fractures at early ages. Fortunately, hormone replacement therapy and treatment with recombinant growth hormone improve the bone mass density.[3-5,8,11-20]

In the psychosocial realm, persons with TS have normal intelligence (IQ 90). However, they have psychomotor and social difficulties in reading, spatial perception, visual motor integration, math and memory. They may also have hyperactivity, immaturity, anxiety and depression.[21]

The diagnosis is difficult to establish because the physician does not always recognize the clinical picture at early ages, and when it is detected the associated comorbidities are not always intentionally sought. The objective of this article is to determine in a selected group of patients with TS the associated comorbidities, diagnostic difficulties and some aspects related with the social environment of the girls.

SUBJECTS AND METHODS

Population

We included patients with TS who were affiliated with the Turner Syndrome Association of Mexico AC and who agreed to participate in the study. Excluded were patients who did not have a complete questionnaire and anthropometry or laboratory studies planned for this project. This study was carried out during November 2011 by the staff of the National Center for the Health of Children and Adolescents (CeNSIA).

The sample of patients was intentional. A call to the 300 members of the Turner Syndrome Association of Mexico was made to participate in the study. Of these members, 45 girls and women aged between 2 and 42 years from nine states of the central Mexico agreed to participate. The guardians of the girls <18 years and of the women with TS >18 years signed an informed consent letter before participation in the study.

Study Design

A cross-sectional and descriptive study was performed consisting of a survey, anthropometric measurements and laboratory tests. Two previously trained physicians applied an exploratory questionnaire with closed questions regarding sociodemographic and psychosocial areas: history of education, age at diagnosis of TS, features that led to the diagnosis, associated comorbidities previously diagnosed by specialist physicians during follow-up of the condition and medical treatment established.

A trained physician carried out anthropometric measurements for each participant. Weight was measured in kilograms with the patient standing in the center of a scale with light clothing and no shoes. Height was measured with the patient standing and with her back to a stadiometer independent of the scale. For girls with height <1 m, height was measured in centimeters with an infantometer with the subject lying on a firm, flat surface. Waist circumference (WC) was measured standing and with arms raised in a horizontal position, half the distance between the inferior border of the last rib and the superior border of the iliac crest, during exhalation. According to gender and age, percentiles were calculated with NHANES III tables.[22] BMI was calculated with the Quetelet (kg/m^2) formula.[23]

Laboratory studies were done after fasting for 12 h. Glucose, insulin levels, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol fraction, and triglycerides were determined using a semi-automated peroxidase method (Dimension, Siemens), as well as thyroid function tests using the chemiluminescence method.

Operational Definitions. To classify overweight and obesity with the BMI, Centers for Disease Control (CDC) tables were used according to age and gender.[24] For girls 2-18 years of age, overweight was defined as BMI $\geq 85^{th}$ percentile and obesity as BMI $\geq 95^{th}$ percentile. For the group >18 years of age, overweight was defined as BMI ≥ 25 and obesity as BMI ≥ 30 according to the WHO criteria.[25] In the group <18 years of age, metabolic syndrome was defined as the presence of three of the following criteria: WC $\geq$ 90 percentile, fasting glucose $\geq$ 100 mg/dl, blood pressure $\geq 90^{th}$ percentile according to height, HDL cholesterol $\leq 5^{th}$ percentile according to the NHANES III tables and TG $\geq 90^{th}$ percentile according to the NHANES III tables.[26,27] For the group >18 years of age, the criteria of the International Federation of Diabetes (IFD) were used that define metabolic syndrome when waist circumference is $\geq$ 80 cm plus two of the following criteria: triglycerides $\geq$ 150 mg/dl, HDL cholesterol $\leq$ 50 mg/dl, blood pressure $\geq$ 130/85 mmHg, fasting

glucose ≥ 100 mg/dl.[28] Estimation of insulin sensitivity was carried out with the HOMA-IR model, which used the following formula

HOMA = [Insulin (mU/ml) x glucose (mmol/l)]/ 22.5

A value of HOMA-IR ≥ 2. 53 in children and adolescents, and a value ≥ 2. 64 for the adult population was considered to be insulin resistant.[26]

Statistical Analysis. For purposes of analysis, the total number of participants was divided into two groups: <18 years (n = 26) and >18 years (n = 19). We used descriptive statistics for frequencies, means, minimum, maximum, median and ranges.

RESULTS

There were 45 patients included in the study from 2-42 years of age who were distributed according to age ranges (Table 1). The majority of the study participants came from the central-south region of the country, specifically the Federal District (DF) 48.9% (23/47), State of Mexico 31.9% (15/47), Puebla, 6.4% (3/47), and one each from the states mentioned as follows: Campeche, Coahuila, Guerrero, Hidalgo, Tlaxcala and Tamaulipas.

For analysis, results were divided into two parts. The first is the personal history, which was referred to as self-assessment (reported by the relatives of the participants and the patients themselves in the applied questionnaire). The second part was referred to as observational and was related to anthropometric measurements and laboratory results.

SELF EVALUATION

Sociodemographic Area. Of the participants >6 years of age, 3/43 (7%) had no studies done. In the group 13-17 years of age, none failed a school year, but 3/16 (18.7%) had to take remedial classes. Within the group >18 years of age, 5/19 (26.3%) failed a school year and 6/19 (31.57%) had to take remedial classes. It was interesting to note that 5/12 (41.6%) of the females >25 years completed a bachelor's degree.

From 6 years of age, school and work absenteeism was reported in 22/43 (51.1%) participants in the 3 months prior to completion of the questionnaire. The median number of times they were absent was four (range: 1-24 times). The most common reason for the absenteeism reported was the need for medical attention in 46.7%.

Psychosocial Sphere. One hundred percent (n =19) of the population >18 years of age were single. Moreover, only 4/27 women >14 years reported having a boyfriend and only 2/12 of the participants >20 years of age were sexually active. The majority of the participants [26/45 (57.8%)] reported having been bullied by coworkers, at school or by family members; 7/45 (15.5%) reported being dissatisfied with their lives. Despite this, 60% (27/45) did not seek support through a support group.

Clinical Data. The most frequent age at which the diagnosis was made was between 6 and 12 years of age (Table 2). It is important to mention that only 50% of the population was diagnosed during the first 5 years of life. It was concerning to discover that one participant was not diagnosed until the age of 21. In >80% of the cases, the physician who made the diagnosis was a specialist. Short stature was the sign that most frequently motivated seeking medical care and guided the diagnosis. In 8/45 of the participants the diagnosis was done due to suspicion by the treating physician because the parents were unaware of any signs of the disease. It was interesting that 12 participants had lymphedema, but only in seven cases did this sign lead to the diagnosis.

Comorbidities. The most common heart diseases seen were aortic coarctation in 7/45 (15.6%) patients and bicuspid aorta in 4/45 (8.9%). At the time of the evaluation, all participants denied having high blood pressure and 3/45 participants reported having dyslipidemia, with an average appearance at 9 years of age. Of the endocrine diseases, 4/45 women reported hypothyroidism and 3/45 hyperthyroidism; the mean age at the time of diagnosis of these diseases was 12 and 11 years, respectively. Other comorbidities were reported (Table 3). It was notable that

Table 1. Distribution of the population according to age range

Age range (years)	n = 45	%
≤ 2	2	4.4
6-12	8	17.8
13-17	16	35.6
≥ 18	19	42.2

a high percentage of the patients reported problems with attention deficit and mood disorders.

Medical Management and Follow-up. Regarding follow-up, it was found that 22/45 (48.9%) participants were beneficiaries of some type of health institution and the remainder were cared for by other agencies. Two patients abandoned their follow-up (Table 4). In the total population, an average monthly expenditure for medications related with their care was reported to be $1,241.67 MXN (without including the cost of growth hormone).

Follow-up of these girls and women by a multidisciplinary team is important. In their respective institutions they have been evaluated, at least in 85% of the cases, for endocrinology, genetics and cardiology services; in >50% by the service of dentistry, orthopedics, dermatology, ophthalmology, psychology and nutrition; and less than half of the patients have been evaluated by psychiatry, otolaryngology, audiology and speech therapy.

The majority of the participants [33/45 (73.3%)] received growth hormone therapy at some point in their lives. The median age of treatment initiation was 8 years and the average duration was 1 year 8 months. The effect that the growth hormone had on the patient's stature was not known because this information was not explored in the study. In the group >14 years of age, 19/27 women (70.3%) received hormone replacement therapy with estrogen beginning at an average age of 14 years. Less than half of the participants [19/45 (42.2%)] mentioned having received calcium supplement and only 7/45 (15.6%) received vitamin D.

OBSERVATIONAL

Anthropometry. The median height observed in the patients >18 years of age (n = 19) was 142 cm, ranking between the 5th and 10th percentiles in the height graphs for TS (range: 129-153 cm). In the group 6-12 years of age (n = 8), the median height was the 25th percentile of the graphs for height in TS; of the age group 13-17 years (n = 16) between the 25th and 50th percentiles of the same graphs. Surprisingly, there were no differences found between the median of the percentile of height for those who received hormone replacement for at least 2 years (n = 19) and those who did not receive hormone replacement (n = 13) (median in the 25th percentile for the height graph for TS for both groups, raw data not presented.)

When analyzing all the study groups <18 years of age, it was found that 8/26 (30.7%) of the participants present-

Table 2. Diagnostic data of the participants

Age at diagnosis	*n*	%
Neonate	8	17.8
1 month-2 years	9	20.0
3-5 years	5	11.1
6-12 years	16	35.6
13-18 years	6	13.3
>18 years	1	2.2
Medical personnel who made the diagnosis		
Pediatrician	7	15.6
General physician	1	2.2
Endocrinologist	17	37.8
Geneticist	19	42.2
Orthodpedist	1	2.2
Signs detected by the parents*		
Short stature	25	55.6
Lack of sexual development	2	4.4
Growth delay	1	2.2
Lymphedema	7	15.6
Cardiac affectation	2	4.4

*Does not total 45 because in eight cases diagnostic suspicion was done by a physician.

Table 3. Comorbidities presented in patients with Turner syndrome

Comorbidity	*n*	%
Multiple nevi	22	48.9
Lymphedema	12	26.7
Congenital cardiopathies	11	24.4
Scoliosis	11	24.4
Renal malformations	8	17.8
Hair loss	7	15.6
Hypothyroidism	4	8.9
Keloid scars	4	8.9
Seborrheic dermatitis	4	8.9
Micrognathia	4	8.9
Hyperthyroidism	3	6.6
Dyslipidemia	3	6.6
Ptosis	2	4.4
Atopic dermatitis	2	4.4
Renal tubular acidosis	1	2.2
Arterial hypertension	0	0
Psychosocial alterations		
Attention deficit and hyperactivity	18	40.0
Memory alterations	15	33.3
Anxiety	11	24.4
Depression	9	20.0
Alterations of motor coordination	7	15.6

ed overweight and obesity, whereas for those >18 years of age the proportion was greater [12/19 (63.15%)] (Table 5).

Comorbidities. Of the comorbidities detected in this group of patients, it is notable that more than a third of the participants <18 years of age had insulin resistance. To a lesser extent, this comorbidity was also substantial in the adult population. Dyslipidemia is presented in a high proportion of these patients (Table 6).

The four persons previously diagnosed with hypothyroidism were found to have good thyroid function control; however, it is important to mention that nine additional subjects were identified with subclinical hypothyroidism, 2/26 of the group <18 years of age and 7/19 of the group >18 years of age. This represents 20% of the total population studied.

DISCUSSION

TS is one of the most frequent chromosomal abnormalities seen in clinical practice. This disorder has a high index of morbidity in all age groups. It requires multidisciplinary follow-up and is fundamental to offer an integrated approach in referral centers so as to improve the quality of life of the patients and to prevent mortality.

The exact prevalence of TS and the frequency of the accompanying comorbidities are unknown in Mexico. There are only isolated reports related to this topic. For this reason, data reported in this study are important because information is gathered from a select group of girls and women with TS. In this group who are affiliated with the Turner Syndrome Association of Mexico, AC, associated comorbidities with this syndrome and diagnostic-related aspects were analyzed. Also explored were some components of the patient's social environment.

According to the questionnaire applied, it was found that 100% of the population >18 years of age were single. This contrasted with 34.6% reported in the general population and housing census 2000 in Mexico.[29] Moreover, only 10.5% of the population >18 years reported being sexually active, and the majority of the participants were bullied by others. This problem may lead to depression and other emotional disorders.[2] It is difficult to determine the origin of this problem, but it is important to carefully analyze it and to generate strategies to integrate these women into a full social and sexual life.

It is documented that girls with TS have learning problems.[2,21] In this study, 1/4 women in the population >18 years of age had one failed school cycle. According to the report by the Public Education Department in 2004, the percentage of high school failure was 31.9%, whereas at the professional level 21/100 women failed.[29] Girls and women with TS have a normal intelligence quotient; however, they may have learning problems in mathematics, spatial perception (for example, difficulty in reading a map) and visual motor coordination. These difficulties can lead to failure in school[4] as well as a high percentage of school and work absenteeism, which can have a negative influence in academic work and could explain the findings. However, despite this, the percentage of school failure was less than in the general population in Mexico according to the 2004 reports. Similarly, observa-

Table 4. Affiliations where follow-up was done of participants

Affiliation where follow-up was done (n = 45)	*n*	%
Instituto Mexicano del Seguro Social (IMSS)	19	42.2
Hospital General de México (HGM)	8	17.8
Hospital Infantil de México Federico Gómez (HIM)	7	15.6
Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE)	3	6.7
Instituto Nacional de Pediatría (INP)	3	6.7
Private	3	6.7
None	2	4.4

Table 5. Distribution of BMI according to age

	BMI classification					
Age group (years)	Normal (*n*)	%	Overweight (*n*)	%	Obesity (*n*)	%
2 (n = 2)	2	100.00	0	0	0	0
6-12 (n = 8)	4	50.00	3	37.5	1	12.5
13-17 (n = 16)	11	68.75	1	6.25	4	25.00
≥18 (n = 19)	7	36.84	6	31.57	6	31.57

BMI, body mass index.

tions about the level of education reached are surprising because 41.6% of the group >25 years of age completed a bachelor's degree. This is in contrast to the 12.8% reported nationally in the female population. These differences could be attributed to the intentional support sought by the family of those with TS in order to integrate them to a social and academic life, especially those who belong to the Turner Syndrome Association of México AC.[29]

As mentioned previously, the median age at which diagnosis of TS was done in this study was 6 years, although in one patient the diagnosis was not done until 21 years of age. This indicates the serious failure of recognition of the characteristics of TS on the part of health personnel and the family. According to what has been reported in North America, the average age at the time of diagnosis of this syndrome is 7.7 years, whereas Gravholt et al. indicated that in Denmark the average age at the time of diagnosis was 15 years.[30,31] This suggests that the lack of diagnostic suspicion is universal. The primary care physician should recognize the main manifestations of this syndrome in order to diagnose it and carry out a timely referral in order to prevent additional complications.

When the signs that orient towards the diagnosis are identified, short stature was the pivotal sign in the majority of the cases. Because of this, the possibility of the diagnosis of TS should be contemplated with this finding, as well as to look for other specific signs. The average height in the adult population was 142 cm, similar to what has been reported in various studies that in general report averages varying between 143 and 146 cm.[1,2,21] In this study the fact that almost half of the cases (5/12) presented lymphedema was alarming, and although this is a classic sign, it was not considered to be diagnostic of TS. According to U.S. and European reports, during school age the diagnosis is made according to the presence in lymphedema in 97% of the cases and by short stature in 82%.[31] For this reason it is important to train resident physicians on the detection of short stature, how to approach it and how to perform the differential diagnosis and to recognize lymphedema as an important piece of information that orients towards the diagnosis of TS. Table 7 shows the clinical disorders found in patients with TS according to the American Academy of Pediatrics. Clinical data and comorbidities of Mexican girls in this study, in general, coincide with what has previously been reported.

With regard to morbidity, the frequency of overweight and obesity in the population studied was 50% in school-age children, 31.25% in adolescents and 30% in adults. When data are compared at the national level, in the National Health and Nutrition Survey 2012 it is notable that 34.4% of children 5-11 years of age were overweight and obese. In this study, the figure was almost double in the same age group.[32] This leads to contemplate the need to increase campaigns to support a change in the exercise and nutritional habits in these patients.

In this study, arterial hypertension was found in 21% of the women >18 years of age. This is similar to what has been reported in various studies, with figures that range from 24-40% of the adult women with TS.[8,12] It was concerning to observe that this problem had not been previously detected and highlights the importance of disseminating among the population the need to routinely measure blood pressure. The cause of high blood pressure in subjects with TS is in the majority essential hypertension. However, alterations have been identified that can cause this comorbidity such as cardiac, renal,

Table 6. Comorbidities observed in patients with Turner syndrome

	< 18 years (*n* = 26)		≥ 18 years (*n* = 19)		Total population (*n* = 45)	
Comorbidities	*n*	%	*n*	%	*n*	%
SBP >90th percentile	0	0	3	15.7	3	6.6
DBP >90th percentile	1	3.8	2	10.5	3	6.6
IR	9	34.6	4	21.0	13	28.8
TC >90th percentile or >200 mg/dl	6	23.0	11	57.8	17	37.7
Alterations in fasting glucose	0	0	3	15.7	3	6.6
HDL <5th percentile or <50 mg/dl	2	7.6	7	36.8	9	20.0
Metabolic syndrome	1	3.8	2	10.5	3	6.6

SBP, systolic blood pressure; DBP, diastolic blood pressure; IR, insulin resistance; HDL, high-density lipoprotein cholesterol; TC, total cholesterol.

malformations, obesity and autonomic nervous system disorders.[2]

Among the main morbidities that this group of patients can develop is cardiovascular disease. Gravholt et al. indicated that women with TS have twice the risk of developing ischemic disease compared to the general population.[11] In the study population >20 years of age, 50% (6/12) had at least two risk factors for developing cardiovascular diseases such as hypertension, insulin resistance or hyperlipidemia. It was alarming that more than 1/3 girls <18 years of age had insulin resistance demonstrated biochemically. In the future this may be associated with a greater incidence of chronic degenerative diseases and highlights the importance of recognizing and intentionally searching for characteristic signs in order to decrease cardiovascular risk (Table 8).

It was concerning to note that there nine women were detected (20%) with hypothyroidism who were not aware of having this disorder. In total, it was identified that 28% of the studied population had hypothyroidism, data that agree with what has been reported in various series where it is mentioned that hypothyroidism is present in 15-39% of the women with TS.[3,17,18] According to some investigators, the origin of thyroid disease in TS is autoimmune and appears during the first three decades of life.[21] For this reason, it is important to carry out a periodic search for endocrine and autoimmune diseases as the guidelines of The Endocrine Society[2] highlight, where it is suggested to perform annual thyroid function tests from the age of 4 years (Table 9).

Various treatments were explored such as the administration of growth hormone, estrogen replacement therapy, calcium and vitamin D administration. The percentage of those who received the last two treatments was low. Given the higher risk of patients with TS to develop osteoporosis, this measure should be implemented in all TS patients. There was a high proportion of patients with growth hormone treatment. This may have been due to the fact that the majority of the population studied was insured under some type of health institution. It is notable that there was no significant difference found in the stature of those who used growth hormone and those who did not, possibly due to a lack of consistency in the application of the medication or due to another reason not explored in this study. Also, the sample size evaluated was small, which makes analysis even more complex. The use of hormone replacement therapy, in general, was initiated at 14 years of age, similar to the average age reported in studies published in the U.S. and Europe. Use of these drugs allows for improvement in bone health and the appearance of secondary sexual characteristics, among other benefits that improve quality of life.[2] In the future it would be interesting to investigate the effect of growth hormone and replacement therapy in a larger number of participants, evaluating dosage and treatment compliance.

Follow-up of subjects with TS is multidisciplinary and should be directed at identifying and treating in a timely fashion the wide range of comorbidities that may be presented by the patients. The guidelines of The Endocrine Society 2007 are suggested for the care of girls and women with TS (Tables 8 and 9).[2]

Table 7. Clinical alterations in patients with Turner syndrome

Very frequent (> 50%)
• Growth delay
• Gonadal dysgenesis
• Lymphedema of hands and feet
• Hyperconvex nails
• Ears with rotation and unusual shape
• Dental alterations
• Micrognathia
• Low hairline at the back of the head
• Broad chest with widely spaced or hypoplastic nipples
• *Cubitus valgus*
• Shortening of the 4th metacarpal
• Tibial exostosis
• Tendency toward obesity
• Recurrent otitis media
Frequency (< 50%)
• Hearing loss
• Pigmented nevi
• Webbed neck
• Renal abnormalities
• Cardiovascular abnormalities
• Hypertension
• Hypothyroidism
• Glucose intolerance
• Dyslipidemia
Occasional (< 5%)
• Scoliosis, kyphosis
• Osteoporosis
• Gonadoblastoma
• Intestinal inflammatory disease
• Colon cancer
• Neuroblastoma
• Liver disease
• Juvenile rheumatoid arthritis

Table 8. Diagnostic observation of Turner syndrome in girls and adult women

All patients
- Cardiovascular evaluation by a specialist and echocardiogram
- Renal ultrasound
- Hearing evaluation by audiologist
- Evaluation of scoliosis/kyphosis
- Evaluation of the recognition of Turner syndrome and referral to support groups
- Evaluation of growth and pubertal development

0-4 years of age
- Evaluation of hip dislocation
- Eye examination by pediatric ophthalmologist (if >1 year of age)

4-10 years of age
- Thyroid function tests (T4, TSH) and celiac disease panel (anti-transglutaminase antibodies)
- Educational and psychosocial evaluation
- Orthodontic evaluation (if >7 years of age)

>10 years of age
- Thyroid function tests (T4, TSH) and panel for celiac disease (anti-transglutaminase antibodies)
- Educational and psychosocial evaluation
- Orthodontic evaluation
- Evaluation of ovarian function/estrogen replacement
- Magnetic resonance imaging of chest searching for aortic dilatation
- Liver function tests, fasting glucose, lipids, blood cytometry, creatinine, BUN (blood urea nitrogen)
- Bone densitometry (if >18 years of age)

Table 9. Follow-up of patients with Turner syndrome

All ages
- Arterial pressure, every year
- Cardiologic evaluation, each 5-10 years
- Otorhinolaryngology and audiology, every 1-5 years

Girls <5 years
- Social skills at 4-5 years

School age
- Annual liver function and thyroid tests
- Observation for celiac disease, every 2-5 years
- Social and educational progress, each year
- Dental and orthodontic evaluation according to needs

Adolescents and adults
- Fasting glucose and lipids, annually
- Liver and thyroid function tests annually
- Check for celiac disease, every 2-5 years
- Evaluation of pubertal development in accordance with age and psychosexual adjustment

Girls with TS presented a wide range of complex comorbidities. This indicates the need to establish an integrated treatment in order to prevent, detect and appropriately treat these comorbid conditions as well as to avoid complications. Lack of training for the early recognition of patients with TS and associated comorbidities is obvious, as well as identification of missed opportunities. Strategies to improve its detection and diagnosis must be implemented for the integration of these girls and women into society and to improve their quality of life.

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