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Turner syndrome: a pediatric diagnosis frequently made by non-pediatricians

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Abstract

Objective: To analyze the clinical features of patients with suspected diagnosis of Turner syndrome (TS) in a reference service.

Methods: Retrospective analysis of 425 patients: data pertaining to age, height and pubertal stage at diagnosis, as well as the specialty of the physician who referred the patient were collected. Patients with and without TS were compared, as well as those with TS according to specialty of the physician; the correlation between age and height at diagnosis was analyzed.

Results: TS diagnosis was made in 36.9% of the cases with a mean age of 12.0 years, and height z score = 3.09; pubertal delay was found in 71.4% of the 63 patients aged more than 13 years. When compared to the other patients, girls with TS had a higher height deficit and higher frequency of pubertal delay. TS patients referred by pediatricians were significantly younger (9.3 years vs. 15.4 years), but their height and frequency of pubertal delay were similar to those referred by non-pediatricians. There was a significant negative linear correlation between age and height in the total amount of patients with TS, but not among those referred by non-pediatricians.

Conclusions: Mean age at TS diagnosis is still higher than that observed in developed countries, and the presence of spontaneous pubertal signs and/or less pronounced growth deficit in some cases may contribute to delayed clinical suspicion of TS. Information required for early TS diagnosis must be spread among pediatricians and non-pediatricians.

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Introduction

Turner syndrome (TS), characterized by the presence of an X chromosome and total or partial loss of the second sex chromosome, has an extremely variable phenotype: from girls with pictures considered to be typical to those almost indistinguishable from the general population. The signs that usually lead to clinical suspicion depend on the age group: in newborns and infants, excess of skin in the neck, hands and feet lymphedema, and lower than expected height; from

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2 years old to the beginning of adolescence, short stature (SS); in addition to that symptom, most of the cases present pubertal delay due to gonadal dysgenesis.[1-3]

Physicians of various specialties may face female patients whose main complaints is related to characteristics knowingly typical of TS and that are less frequent in the general population: endocrinologists (hypogonadism, SS, thyroid dysfunction); gynecologists (hypogonadism); cardiologists (aortic coarctation, bicuspid aortic valve); nephrologists (renal and urinary anomalies); plastic surgeons (neck webbing); and otorhinolaryngologists (repetition otitis, hypoacusia). Nevertheless, it is the pediatrician who is in a privileged position for formulating the TS hypothesis, not only for having routine growth evaluation among their attributions,[4] but also because they centralize the information pertaining to the presence of other alterations in other systems.

The performance of karyotype in girls with low height is not, however, a general agreement in literature. While some authors recommend doing karyotype in all the girls with low height with unknown origin,[1,5] others disagree with this position.[6,7]

In addition to providing an answer to the families' distress, the early karyotype for TS permits the onset of sex hormone replacement and growth hormone (hGH) therapeutics in the proper age. It also provides early detection of associated anomalies and, when necessary, the institution of adequate treatment. Finally, if there is a higher risk for malignant tumors in dysgenetic gonads (which occurs in cases as Y chromosome in chromosome constitution), the prophylactic gonadectomy may be done.[8]

The objective of this study was to analyze the clinical characteristics of patients with TS suspicion when they are directed to a reference service.

Methods

A retrospective study with data collected from medical records of 425 patients attended due to suspicion of TS in the ambulatory of the Interdisciplinary Study Group on Sex Determination and Differentiation (Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo, GIEDDS) between January, 1989, and October, 2006, with karyotypes done in the Medical Genetics Department of the School of Medical Sciences of the Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil. The study was approved by the Research Ethics Committee of the School of Medical Sciences of the UNICAMP, 439/2008.

The following data were obtained from the patients' medical records: age, height, and pubertal stage at the first consultation, when the material is routinely collected for karyotype, and the specialty of the physician who referred the patient to the hospital.

Data obtained were processed using the software SPSS, version 11.0 (SPSS Inc., Chicago, USA). The comparison between the proportions was made through chi square test, and in comparison between the averages of two independent samples the *t* test was used. The correlation of the age and the height at TS diagnosis was evaluated, using the Pearson's correlation coefficient. For decision making, the level of significance of 5% was adopted. The Odds Ratio (OR) calculation was done using the software Epi-Info, version 6.04d (CDC/OMS, 2001).

Results

TS was diagnosed in 157 out of the 425 patients (36.9%). The mean age of the patients referred was 11.6±6.8 years, those who received the TS diagnosis were 12.0±7.1 years old, with no significant difference from the group without TS (11.4±6.6 years) ($p = 0.36$). From the TS cases with ages between 0 to 18 years ($n = 138$), 14 (10.1%) were diagnosed between 0 and 1 year, 67 (48.6%) between 1 and 12 years (most between 7 and 12 years) and 57 (41.3%) between 12 and 18 years.

Height at diagnosis, turned into z score, was obtained in 423 cases. Among 155 patients with TS its average was -3.09, lower than that of those without TS ($n = 268$), whose average was -2.53 ($p < 0.001$). The patients' distribution according to age group and the height z score are found in Table 1.

It was possible to obtain data on the pubertal development in 143 out of 152 patients over 13 years old, among which 63 had TS and 80 had not. Among the TS cases, 45 (71.4%) presented pubertal delay at diagnosis, in comparison to the other 28 (35%) ($p < 0.001$; OR = 4.64; $2.15 < OR < 10.14$).

There was information about the specialty of the physician who had referred the patient in 360 cases. Out of the 129 TS cases, 79 (61.2%) had been referred by pediatricians – generalists or specialists – and the rest by other medical specialties, predominantly by endocrinologists (23.3%), geneticists from other services (7.0%), and gynecologists (6.2%). From the 231 cases in which TS was not verified, 186 (80.5%) had been referred by pediatricians. Therefore, in TS cases the frequency of patients referred by other specialties was higher than by pediatricians ($p < 0.001$; OR = 2.62; $1.57 < OR < 4.36$).

There was no significant difference in relation to the height of the patients with confirmed TS diagnosis taking into consideration the specialty of the physician who had referred (pediatrician or non-pediatrician) (height z score = -3.13±1.21 *versus* -3.15±1.46. respectively; $p = 0.938$). Nevertheless, they differed in age, given that those referred by pediatricians were significantly younger (9.31±4.80 years *versus* 15.44±7.30 years; $p < 0.001$).

Table 1 - Patients with and without TS distribution according to age group and height (in z score) at diagnosis

Patients	TS, n (%)	NTS, n (%)	Total, n (%)
Age group (years)			
0-2	17 (10.8)	13 (4.9)	30 (7.1)
0-1	14	8	22
1-2	3	5	8
2-12	64 (40.8)	148 (55.2)	212 (49.9)
2-7	17	45	62
7-12	47	103	150
12-18	57 (36.3)	81 (30.2)	138 (32.5)
> 18	19 (12.1)	26 (9.7)	45 (10.6)
Total	157 (100.0)	268 (100.0)	425 (100.0)
Z score			
≥ -2.00	30 (19.4)	69 (25.7)	99 (23.4)
-3.00 to -2.01	48 (31.0)	116 (43.3)	164 (38.8)
-4.00 to -3.01	38 (24.5)	54 (20.1)	92 (21.7)
< -4.00	39 (25.2)	29 (10.8)	68 (16.1)
Total	155 (100.0)	268 (100.0)	423 (100.0)

NTS = patients without Turner syndrome; TS = Turner syndrome.

When the frequency of pubertal delay was compared according to the specialty, datum obtained in a total of 48 cases, it was observed that this delay was present in 12/34 patients (35.3%) referred by pediatricians and in 5/14 (35.7%) from other specialists (p = 0.978).

There was a significant negative linear correlation between the age at diagnosis and the height of 155 out of the 157 TS patients (r = -0.274; p = 0.001) (Figure 1A), but 10/76 cases diagnosed after 12 years old had height within the normality range (≥ -2.00 standard deviations). When the TS patients were analyzed separately according to referring (n = 129), in those referred by pediatricians (n = 79), the correlation was even higher (r = -0.599; p < 0.001) (Figure 1B); in cases referred by non-pediatricians (n = 50) there was no significant correlation (r = -0.073; p = 0.615) (Figure 1C). Among the patients referred after 12 years old by pediatricians and non-pediatricians, those who had height within normality were 1/26 and 5/35, respectively.

Discussion

The studied sample represents an expressive number of patients referred to a reference service due to TS suspicion (425), with 157 having the diagnosis confirmed by karyotype. TS frequency (36.9% or a little more than 1/3) was higher than in other studies: 12.5% among girls with proportioned SS and good neuropsychomotor development[5] and 18.91% among patients investigated due to SS.[9] This study, however, did not evaluate only patients with low height, but also those with TS suspicion due to other causes, such as dysmorphic signs and/or pubertal delay.

In comparison with patients who had not had TS diagnosis cytogenetically confirmed, a higher frequency of infants among TS cases was observed – usually they are referred due to signs classically associated with the syndrome, as hands and feet lymphedema, dysmorphic signs, and or aortic coarctation[1] – and girls over 12 years old, when the pubertal delay is associated with SS in most of the cases.

Mean age at TS diagnosis (12.01±7.06 years) was lower than the one found in the same service between 1970 and 1980, before the introduction of banding techniques in routine chromosome analysis (15, 13 years), and between 1981 and 1988 (13.01 years),[10] although more elevated than the one found in European studies: 7.7 in Sweden[1] and 6.6 in Belgium.[11]

The lowering of the age at which girls with TS are diagnosed in developed countries must reflect, initially, a wider dissemination, among physicians in general and pediatricians in particular, of knowledge about the broad phenotypic spectrum associated with TS, highlighting the importance of evaluating girls with SS regardless of the presence of 'typical' dysmorphic picture and pubertal delay. It must come, also, from the wider access to the karyotype exam. These two factors – late formulation of the clinical suspicion and difficulty in obtaining the karyotype – must be in the roots of the late diagnosis of patients observed in this study.

In a study conducted in Sweden with 72 TS patients between 0 to 18 years old at diagnosis, 33 were diagnosed in the first year of life (45.9%), 24 between 1 and 12 years old (33.3%), and 15 between 12 and 18 years old (20.8%).[1] When compared to this work, it is observed that most patients in our milieu does not enjoy the benefits of early diagnosis.

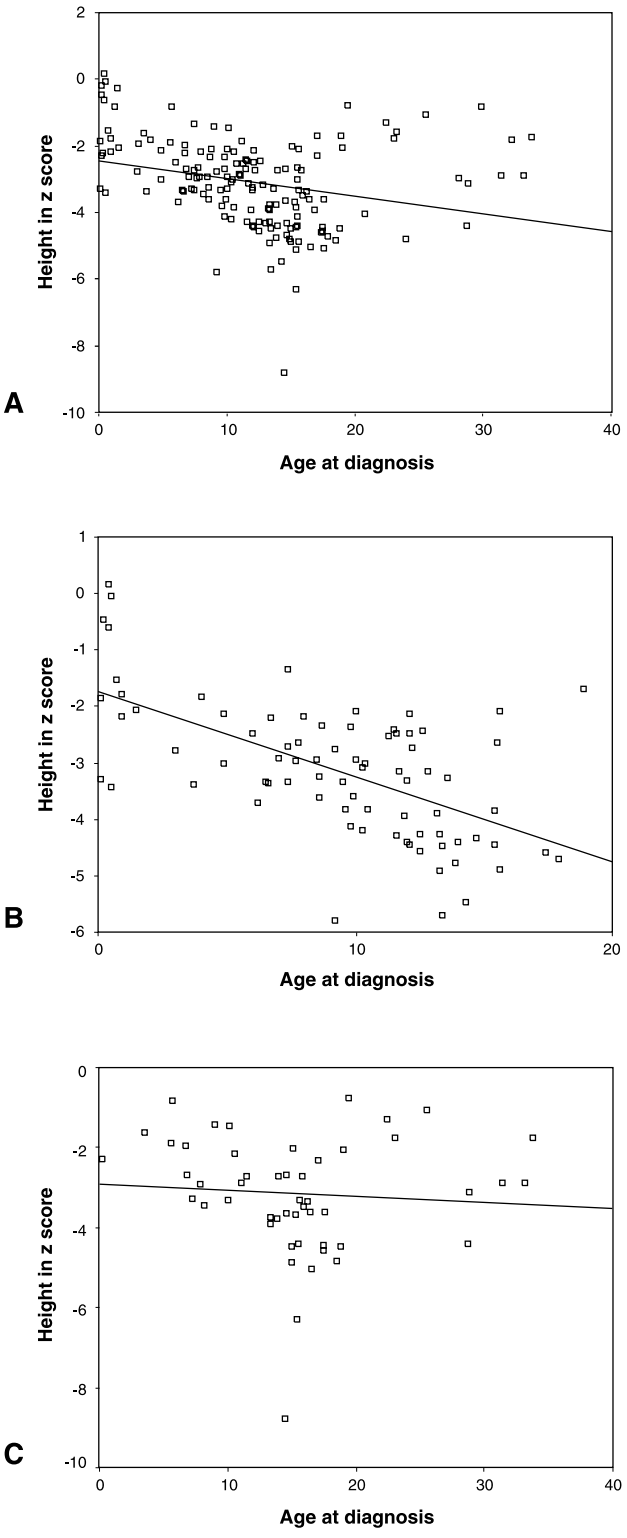

Figure 1 - Regression lines obtained from age and height (in z score) data at diagnosis from: **A**) 155 patients with TS; **B**) 79 referred by pediatricians; **C**) 50 referred by non-pediatricians

Height in TS cases was significantly lower than in the non-TS group, as observed by other authors.[12] Among the TS patients, practically 50% had z score for height lower than -3.00, compared to the 31% of those who had no TS. Besides that, around 25% of the TS patients had a z score lower than -4.00 compared to only 11% of those without TS. Therefore, the higher the height deficit is, higher is the probability of the patient being indeed a TS sufferer.

Height in z score of TS patients at diagnosis (-3.09±1.34) was similar to the one observed by other authors (-3.51±1.7).[12] It is worth noticing, though, that almost 50% of the cases diagnosed over 18 years old had the height within normality, corroborating the observation, in clinical practice, that the lower height impairment tends to determine a later diagnosis, possibly by hindering the early suspicion by pediatricians.

As expected, in most of the TS cases (71.4%) pubertal delay was present; this condition was also observed in 28/73 non-TS patients (35%), which may be due to the presence, in this group, of constitutional growth delay, XX pure gonadal dysgenesis, and GH deficiency patients. The presence of spontaneous pubertal signs must not, therefore, displace the TS hypothesis in girls with SS or characteristic dysmorphyc picture, since in up to 41% of the cases residual gonadal function might exist.[13]

Similarly to what was observed by other authors,[14] in this study a negative linear correlation between TS patients' age and height was observed. This occurs due to the progressive decrease in growth velocity, resulting in the older patients having a higher height deviation in relation to the mean population. It was expectable, thus, that TS patients referred by non-pediatricians, with a mean age of 15.44 years, had an average higher height deviation than those referred by pediatricians, diagnosed at around 9.3 years old.

This did not happen, however, and the separate analysis of the correlation between age and height in cases referred by pediatricians and non-pediatricians showed an even higher correlation in the first case and next to zero in the second. This suggests that the non-pediatrician physician would have attended mainly patients with a lower growth deficit, making previous clinical suspicion difficult for the pediatrician, or even with dysmorphic signs less evident, but it was not evaluated in this study.

A possible bias of this work would be the possibility that various patients were referred first by their pediatricians to endocrinologists, who would have referred them to specialized service. However, the significantly higher age of the patients referred by non-pediatricians suggests that

this had not occurred in a large enough number of cases so as to interfere in the results.

As in a significant part of the cases in our milieu TS diagnosis is still being made from adolescence on, these patients end up not enjoying the benefits of an early investigation on the presence of Y chromosome and associated diseases (cardiovascular, renal, urinary anomalies and thyroid diseases, among others). Early diagnosis would permit, yet, that they be submitted to hGH therapy for increasing final height – in our service, the mean spontaneous final height was recently estimated in 144.8cm.[15] Besides that, it would be possible to initiate sex hormones replacement in the proper age, preventing osteopenia emergence[16] and the worsening of psychosocial problems.[17]

However, although pediatricians must have a crucial role in early diagnosis formulation, the frequency with which it has been occurring in our milieu is lower than the one observed in world literature. For this situation, there might be, also, the contribution of the fact that they are less alert to other TS indicative signs other than SS. Therefore, it is important that there be a wider exposition in the pediatric milieu on the necessity of making TS hypothesis in girls with SS of undefined etiology, particularly when associated with low growth velocity, as well as in the pubertal delay cases and when there are characteristics typically associated with this syndrome, as neck webbing, lymphedema, and aortic coarctation or bicuspid aortic valve.[1]

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