Variables associated with diagnostic delay in Turner syndrome

Fatores associados a atraso no diagnóstico da síndrome de Turner

Investigación de factores asociados a retraso en el diagnóstico del síndrome de Turner

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ABSTRACT

Objective: To investigate the possible reasons for diagnostic delay in Turner syndrome (TS), i.e., a diagnosis made after the age when pubertal delay may be established.

Methods: Cross-sectional study with data obtained from the records of 29 TS patients aged more than two years who were diagnosed between 2004 and 2007. Data on personal and family history and physical examination from patients diagnosed before 13 years old (age limit from which pubertal delay may be characterized in girls) were compared to those of girls diagnosed after 13 years by Fisher exact test and Student's t-test.

Results: No significant differences were noted regarding mothers' and patients' stature, personal history of TS-associated diseases (considered individually), parental schooling, familial recurrence of short stature, presence of each dysmorphic feature considered separately, and total number of dysmorphic features. The two groups differed regarding the presence of at least one TS-associated disease (which was associated to early diagnosis) and number of siblings (which was higher among patients with delayed diagnosis and associated with lower maternal schooling).

Conclusions: Early diagnosis was more associated with the presence of a TS-associated disease (which may have required referral to secondary or tertiary health care services) than with the presence of dysmorphic signs. The results indicate that less evident growth deficit, physicians' inability to recognize abnormalities associated with TS and socioeconomic aspects may contribute to diagnostic delay. Pediatric training should emphasize recognition of the clinical spectrum of TS and public genetic services should be expanded.

Key-words: Turner syndrome; chromosome aberrations; early diagnosis; congenital abnormalities.

RESUMO

Objetivo: Investigar as possíveis razões do atraso no diagnóstico da síndrome de Turner (ST), ou seja, aquele realizado após a idade em que se pode estabelecer o atraso puberal.

Métodos: Estudo transversal com obtenção de dados dos prontuários de 29 pacientes com ST diagnosticadas com mais de dois anos, entre 2004 e 2007. Foram comparados antecedentes pessoais e familiares e dados de exame físico das pacientes diagnosticadas com menos de 13 anos (limite a partir do qual se pode caracterizar atraso puberal em meninas) com os daquelas diagnosticadas após os 13 anos por meio dos testes *t* de Student e exato de Fisher.

Resultados: Não houve diferenças significativas quanto à estatura materna e da própria paciente, história de afecções associadas (consideradas individualmente), escolaridade dos pais, recorrência familiar de baixa estatura, presença de cada sinal dismórfico isoladamente e total de sinais observados. Os

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dois grupos diferiram quanto à presença de ao menos uma afecção sugestiva dessa síndrome (associada ao diagnóstico mais precoce) e ao número de irmãos (maior no diagnóstico tardio e associado à menor escolaridade materna).

Conclusões: O diagnóstico precoce relacionou-se mais à presença de alguma das afecções associadas à ST (possivelmente determinando-se encaminhamento a serviços de maior complexidade) do que a sinais dismórficos. Há indicações de que déficit de crescimento menos evidente, dificuldade dos médicos em reconhecer anomalias sugestivas dessa síndrome e determinantes socioeconômicos contribuam para o atraso no diagnóstico. É necessário enfatizar na formação pediátrica o reconhecimento do espectro clínico dessa síndrome e ampliar os serviços públicos de genética.

Palavras-chave: síndrome de Turner; aberrações cromossômicas; diagnóstico precoce; anormalidades congênitas.

RESUMEN

Objetivo: Investigar las posibles razones del retraso en el diagnóstico del síndrome de Turner (ST), es decir, aquél realizado después de la edad en que se puede establecer retraso puberal.

Métodos: Estudio transversal con obtención de datos de los prontuarios de 29 pacientes diagnosticadas con ST mayores de 2 años de edad entre 2004 y 2007. Se compararon antecedentes personales y familiares y datos de examen físico de las pacientes diagnosticadas a una edad menor de 13 años (límite a partir del cual se puede caracterizar retraso puberal en niñas) con los de aquellas diagnosticadas después de los 13 años mediante las pruebas t y chi-cuadrado.

Resultados: No hubo diferencias significativas respecto a la estatura materna y de la paciente misma, historial de afecciones asociadas (consideradas individualmente), escolaridad de los padres; recurrencia familiar de baja estatura, presencia de cada señal dismórfica aislada y total de señales observadas. Los dos grupos difirieron respecto a la presencia de al menos una afección sugestiva de ese síndrome (asociada al diagnóstico más temprano) y al número de hermanos (mayor en el diagnóstico tardío y asociado a la menor escolaridad materna).

Conclusiones: El diagnóstico temprano se relacionó más a la presencia de alguna de las afecciones asociadas al ST (posiblemente determinando encaminamiento a servicios de mayor complejidad) que a señales dismórficas. Hay indicaciones de que déficit de crecimiento menos evidente, dificultades de los médicos en reconocer anomalías sugestivas de ese síndrome y factores socioeconómicos contribuyan para el retraso en el diagnóstico. Es necesario enfatizar en la formación pediátrica el reconocimiento del espectro clínico de ese síndrome y ampliar los servicios públicos de genética.

Palabras-clave: Síndrome de Turner; aberraciones cromosómicas; diagnóstico temprano; anomalías congénitas.

Introduction

Turner syndrome (TS) is determined by the presence of one X chromosome and the total or partial absence of the second sex chromosome (X or Y), which affects the expression orregulation of genes located on this second chromosome. In X chromosome , the critical region for the appearance of the signs of TS is in the short arm (Xp11.2 - p22.1)[1]. It affects approximately 1:2500 live-born females[2], but among girls with proportionate short stature and good psychomotor development receiving care at the pediatric service of a teaching hospital, this frequency increases to 12.5%[3].

The main clinical signs of TS are short stature and gonadal dysgenesis. Various dysmorphic features can also be observed, such as low posterior hairline, strabismus, drooping eyelids, high-arched palate, micrognathia, short neck, webbed neck, lymphedema of the hands and/or feet, shortened metacarpals, Madelung deformity, *cubitus valgus*, *genu valgum*, scoliosis and multiple pigmented nevi; congenital anomalies, particularly cardiovascular and renal; acquired conditions, as thyroid disorders, hearing impairment, hypertension, osteoporosis and obesity, as well as psychosocial problems[4-7]. There is great phenotypic variability, from patients with highly dysmorphic appearance to those who are hardly distinguishable from the general population.

The relevance of an early TS diagnosis lies on also allowing the early diagnosis of congenital and acquired conditions and the establishment of the proper therapeutic measures. An early diagnosis also allows for the detection of cases with Y chromosome in the karyotype, in which the appearance of gonadal neoplasias can be prevented by prophylactic gonadectomy; and allows for growth promotion treatments and sex hormone replacement to be carried out at the proper age, thus avoiding additional damage to the health of patients[5].

However, in many cases, the diagnosis is only obtained after the beginning of adolescence, when pubertal delay is characterized – in our service, the mean age of diagnosis is 12 years old, with a standard deviation of 7.1 years[8]. In some

patients, delayed diagnosis could be due to phenotypical variability, causing patients without evident dysmorphisms to be diagnosed later. Additionally, clinical experience shows that many mothers, when seeking medical care for their daughters complaining of growth deficiency, mention that the symptom was at first attributed to the family history of short stature, particularly maternal.

On the other hand, the finding of a more severe growth deficit, the presence of conditions frequently associated with TS, such as auto-immune thyroid disease and anomalies of the heart, kidney, and/or urine-collecting system, and comparison with the growth of normal siblings could call the pediatrician's attention to the pathological character of growth deficit. In addition to that, higher educational level of the parents could also drive them to seek medical care.

Given the importance of an early diagnosis of TS and the various hypotheses to explain the wide age variation in the diagnosis of these patients, this study aims to investigate the possible reasons for delayed diagnosis, which is herein defined as that which was obtained after the age in which pubertal delay can be established.

Method

The study analyzed 35 patients aged zero to 32.6 years old (mean 11.8 years old) diagnosed from 2004 to 2007 at the Interdisciplinary Group of Study of Sex Determination and Differentiation (GIEDDS) Outpatient Clinic of the Clinical Hospital of the State University of Campinas (UNICAMP). Among these, the study included 29 patients over two years old, once nursing infants tend to have a different clinical manifestation from the remaining patients, with a predominance of signs such as lymphedema of the hands and feet, excess skin on the neck and more severe cardiopathies, whereas other dysmorphic signs are less evident in this age group. From the 29 patients, seven had a 45,X karyotype, four had 45,X/46,XX mosaicism and the remaining presented structural abnormalities of sex chromosomes, with or without mosaicism with a 45,X cell line.

The following data were obtained, retrospectively, through the analysis of medical records: personal history (cardiovascular diseases; hypothyroidism; recurrent urinary tract infections and/or kidney anomalies); family data (parents' educational level, which was classified as ≤8 or >8 years

Table 1 – Presence of morbid history among patients with Turner syndrome diagnosed at age two to 13 years old and ≥ 13 years old.

Morbid history	Present	Absent	Total	p
Cardiovascular disease				0,26
2 to 13 years old	3*	15	18	
≥ 13 years old	0	11	11	
Total	3	26	29	
Primary hypothyroidism				0,26
2 to 13 years old	4	14	18	
≥ 13 years old	0	11	11	
Total	4	25	29	
Recurrent Urinary Tract Infection				0,11
2 to 13 years old	7	11	18	
≥ 13 years old	1	10	11	
Total	8	21	29	
Urine-collecting system malformation				1,00
2 to 13 years old	1#	17	18	
≥ 13 years old	0	11	11	
Total	1	28	29	
Any of the history above				0,006
2 to 13 years old	12	6	18	
≥ 13 years old	1	10	11	
Total	13	16	29	

* Coarctation of the aorta and/or bicuspid aortic valve; #horseshoe-shaped kidney

Table 2 – Comparison of the physical examination findings between patients with Turner syndrome diagnosed at age two to 13 years old and ≥ 13 years old.

Dysmorphic signs	Absent	Present	Total	p
Droopy eyelids				0,37
2 to 13 years old	13	5	18	
≥ 13 years old	9	1	10	
Total	22	6	28	
Strabismus				N/A
2 to 13 years old	18	0	18	
≥ 13 years old	10	0	10	
Total	28	0	28	
Epicanthal folds				
2 to 13 years old	16	2	18	1,00
≥ 13 years old	9	1	10	
Total	25	3	28	
Webbed neck				0,60
2 to 13 years old	16	2	18	
≥ 13 years old	8	2	10	
Total	24	4	28	
Pectus excavatum				0,06
2 to 13 years old	12	6	18	
≥ 13 years old	10	0	10	
Total	22	6	28	
Residual lymphedema				1,00
2 to 13 years old	17	1	18	
≥ 13 years old	10	0	10	
Total	27	1	28	
Cubitus valgus				1,00
2 to 13 years old	4	14	18	
≥ 13 years old	2	8	10	
Total	6	22	28	
Pigmented nevi				0,24
2 to 13 years old	7	11	18	
≥ 13 years old	7	3	10	
Total	14	14	28	
Total signs	**0-2**	**3-4**	**Total**	**p**
2 to 13 years old	14	4	18	
≥ 13 years old	9	1	10	0,19
Total	23	5	28	

N/A = Not applicable.

of schooling, maternal stature expressed in z score, recurrence of short stature in the family, and number of siblings classified in 0-2 and >3); physical examination of patient (patient stature in z score; and dysmorphic signs selected among the most evident in the clinical examination and/or more characteristic of TS, such as drooping eyelids, strabismus, epicanthal folds, webbed neck, pectus excavatum, residual lymphedema over the dorsum of the fingers/toes, cubitus valgus and pigmented nevi).

Data of the patients diagnosed at two to 13 years old (13 being the age after which pubertal delay is established for females)[9,10] (n=18), were compared to those of patients aged 13 or more (n=11) through Fischer's exact test and *t* test for comparison of mean values, with a significance level of 5%. The present study was approved by the Research Ethics Committee of the Faculty of Medical Sciences of UNICAMP.

Results

There was no significant difference between the two groups regarding maternal stature; the mean z score among the 18 mothers of patients diagnosed before 13 years old was -0.39 (standard deviation - SD= 1.13) and the mean z score among the mothers of patients who were diagnosed later (n=5) was -0.62 (SD = 0.98) (p=0.69). Regarding the stature of patients themselves, the growth deficit was greater in the 18 patients diagnosed before 13 years of age (mean -3.29; SD=1.51), when compared to the 11 others (mean -2.90; SD=1.36), but the difference was not statistically significant either (p=0.49). There was also no association between the time of diagnosis and the presence of morbid history considered individually (Table 1), the educational level of mothers (p=0.19) and of fathers (p=0.39), the family recurrence of short stature (p=1.00) and the presence of dysmorphic signs (both when considered individually and in the total) (Table 2).

However, the analysis did find differences between the two groups regarding the history of at least one morbidity that suggests TS (diagnosis was earlier in the presence of at least one of these background morbidities) (p=0.006) (Table 1) and the number of siblings. The latter was greater for delayed diagnosis, with 14 out of the 18 girls diagnosed before 13 years old having zero to two siblings and nine among the 11 who had been diagnosed after 13 years old having three or more siblings (p=0.003). The greater number of siblings was, in turn, associated with a lower educational level of the mother: among the 26 cases in which both data were obtained, seven of the 14 mothers with two or less children had more than eight years of schooling, whereas 11 of the 12 mothers with three or more children had less than eight years of education (p=0.04).

Discussion

The mean age at diagnosis of the patients that make up this sample (11.8 years old) is higher than that currently found in other countries: 7.7 years in the USA[11] and 6.6 years old in Belgium[12]. Even so, among the North-American patients it was observed that TS diagnosis was obtained, on average, 5.2 years after the stature was below the 5th percentile in the growth curve[11].

In the daily medical practice, it is common to diagnose TS patients who are already adolescent or even adult, in whom the short stature had been noticed by the family since childhood, but who are only sent for medical evaluation when pubertal delay is already evident. It is possible to assume that delayed diagnosis, i.e., diagnosis of TS only after the manifestation of pubertal delay, is at least in part caused by the characteristics of patients themselves and their families.

The lack of significant differences regarding maternal stature did not confirm the hypothesis that the short stature of the mother contributed for the delayed diagnosis of their daughters, through the assumption, by doctors and the family themselves, that the growth deficit of the child was explained by family traits. The same is suggested by the fact that there is no association of delayed diagnosis with a family history of short stature.

On the other hand, this sample was remarkable in showing no significant differences regarding the stature deviation of patients under and over 13 years old in comparison to the average. Once TS involves a progressive decrease in growth speed as patients age[13], patients who were diagnosed later in life were expected to present with significantly greater stature deficit – on the contrary, this deficit was greater in patients who were diagnosed earlier, although the significance level was not reached. This result allows us to speculate that, in patients with delayed diagnosis, short stature was not as severe during childhood.

When comparing the remaining date of patients in the sample based on the age from which pubertal delay is established, there were no significant differences observed in relation to most of the data analyzed. Regarding the recognition of certain dysmorphisms and congenital and

acquired anomalies suggesting TS, such as webbed neck, cubitus valgus and multiple pigmented nevi, cardiopathies (coarctation of the aorta, bicuspid aortic valve), kidney and urinary tract abnormalities (horseshoe-shaped kidney, double urine-collecting system) and autoimmune thyroid disease[5], these results indicate the need to enhance the medical training, especially that of pediatricians, in order to allow them to recognize these and other signs associated with this chromosome abnormality. In fact, several patients did not have an early diagnosis although they did present these signs.

It should also be considered, however, that none of the patients included presented more than four among the nine signs selected in this study as the most evident or characteristic of TS, which suggests that "typical" clinical pictures such as those described in textbooks are not routinely observed.

When the patient groups were compared regarding the history of at least one morbidity that suggested TS, a significant association was observed with earlier diagnosis. This finding suggests that the association of short stature with the presence of one or more anomalies analyzed makes it more likely for physicians to acknowledge the need for a more in-depth investigation, possibly through referring the patient to secondary or tertiary healthcare services.

Patients diagnosed after 13 years of age differed from the remaining regarding the number of siblings (which, contrary to our assumptions, was greater in the delayed diagnosis group), and it was possible to observe a significant association between the greater number of siblings and lower educational level of the mother, thus suggesting the interference of socioeconomic factors, such as low family income and restricted access to healthcare services. In these cases, it appears to be less likely to look for medical services to investigate the short stature, unlike what happens in situations related to acute and emergency health problems.

We concluded that, in this sample, the early diagnosis of TS was more often associated with the presence of any previous morbidity related to the syndrome, which is more likely to determine the referral to secondary or tertiary healthcare services than the presence of dysmorphic signs. On the other hand, there are indications that less evident growth deficit, difficulty, on the part of physicians, to recognize abnormalities that suggest the syndrome and socioeconomic determinants contribute to delayed diagnosis.

The reduction of the age of TS diagnosis in our country will depend, therefore, not only on the expansion and improvement of the basic healthcare services, but also on the improvement of medical training – particularly of pediatricians– enabling physicians to recognize the spectrum of clinical manifestations of this syndrome, including dysmorphic signs, congenital visceral anomalies and acquired conditions. It is also essential to expand the country's genetic services, so as to enable the routine chromosome analysis of short stature of unknown origin in girls, as many authors, as well as national and international consensuses, have been suggesting[5,6,11].

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