

Trends in age at diagnosis of Turner syndrome

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ABSTRACT

The age at diagnosis of 242 girls with Turner syndrome (TS) treated in Belgium with growth hormone between 1991 and 2002 was evaluated. The median (range) age at diagnosis was 6.6 (0-18.3) years. Patients with 45,X karyotype were diagnosed earlier than patients with other karyotypes. Compared to a previous survey, performed on 100 patients 12 years earlier, more patients were diagnosed during infancy and childhood, and less during adolescence. However, in 22% of the girls the diagnosis was made after the age of 12 years; these girls showed the largest height deficit. As early diagnosis has several potential advantages we recommend that a cytogenetic analysis should be considered in all girls with unexplained short stature with height below -2 SD of the mean for age or below the parent specific lower limit of height.

Growth retardation and short stature are the main characteristics of Turner syndrome (TS), a chromosomal disorder with a large spectrum of manifestations.

Treatment of TS girls with recombinant human growth hormone (GH) increases adult height.¹⁻³ Although it is not clear whether early initiation of GH treatment will result in a taller final height, if started at a relatively young age height can be normalised during childhood, allowing an age appropriate start of oestrogen therapy for puberty induction.^{1 2} Timely initiation of GH treatment requires early diagnosis, but the diagnosis of TS, however, is often late.^{4 5}

In the present study we tested the hypothesis that the availability of growth promoting treatment has increased the watchfulness for the diagnosis of TS in short girls, resulting in an earlier diagnosis. For this purpose we evaluated the age at diagnosis of all TS girls who started GH treatment between 1991 and 2002, and we compared the results with those of our previous survey published in 1991.⁴

SUBJECTS AND METHODS

From the database of the Belgian Study group for Paediatric Endocrinology, containing the data of approximately 95% of all children treated with GH in Belgium since 1987, we retrieved all TS patients who started GH treatment between 1991 (the first year after the registration of GH therapy for TS in Belgium) and 2002. Two hundred and forty two girls with TS were included: 113 patients (47%) had the 45,X karyotype, the remainder had various mosaicisms or structural anomalies of one X chromosome. The age at which the diagnostically cytogenetic examination was performed was considered as the age at diagnosis. In patients aged 1 year or older, height at diagnosis was expressed as standard deviation score (SDS) using the Tanner 1965 references.^{6 7} Results are expressed as absolute numbers (percentages), median (range), or mean (SD) values. The results for patients with the 45,X karyotype were compared with those with other karyotypes. The obtained results were also compared with those of our previous survey on 100 TS patients, not treated with GH, referred to the Division of Paediatric Endocrinology of the University of Leuven, Belgium, between 1972 and 1988.⁴ Observed numbers were compared by the χ^2 test. Comparisons between groups were done with the Mann- Witney U test.

RESULTS

Table 1 shows the results in comparison to our previous survey. For the whole group, the median age at diagnosis was 6.6 years, and ranged from prenatal life to 18.3 years. Patients with the 45,X karyotype were diagnosed earlier than patients with other karyotypes (1.2 v 9.6 years; $p < 0.001$). Seventy three (30%) of the patients were diagnosed before the age of 1 year, of whom four were diagnosed prenatally, 115 (48%) were detected in childhood (1-12 years), and 54 (22%) in adolescence (>12 years). Patients with the 45,X karyotype were more frequently diagnosed before the age of 1 year, often due to the presence of oedema, dysmorphic features, or a cardiopathy. In the patients diagnosed after the age of 1 year, the median age at diagnosis was 10.1 years; there was no difference between the patients with the 45,X karyotype or the other karyotypes.

Compared to our previous analysis, the median age at diagnosis was significantly younger for the whole group of patients, as well as for the patients diagnosed beyond the age of 1 year. More patients were diagnosed in infancy and childhood, and less during adolescence, illustrating a significant age shift to earlier diagnosis (χ^2 19.8; $p < 0.0001$).

In the present survey the mean (SD) height at diagnosis was -2.40 (0.93) SDS, which is less short than in our previous survey (-2.90 (1.00) SDS; $p < 0.001$). The height deficit was more important in the adolescent girls. Below the age of 6 years 47% of the patients were shorter than -2 SDS, while in the adolescent girls 87% were smaller than -2 SDS. There were no differences between the patients with the 45,X karyotype and the others.

DISCUSSION

In our present survey the median age at diagnosis of TS was 6.6 years, which is significantly earlier than the age of diagnosis a decade ago.⁴ More patients were diagnosed during infancy and childhood, which is a favourable trend. This may be due to an increased awareness for the diagnosis of TS in short girls since the availability of growth promoting treatment and the many related publications. Moreover, advances in prenatal diagnostics and genetics may also contribute to this trend.

However, our data also show that in this cohort, about 20% of the girls with TS are diagnosed beyond the age of 12 years, most of them with a serious height deficit. These patients have missed the opportunity of early GH treatment, enabling normalisation of height during childhood and age appropriate induction of puberty.¹ As our present survey is based on TS patients treated with GH, and as GH treatment in girls with TS in Belgium is usually started after the age of 6 years,¹ patients not yet treated with GH are not included in the present survey and probably more patients are currently diagnosed at an earlier age. On the other hand, studies have shown that a significant number of TS patients are diagnosed in adulthood⁸ and these patients are also missed in this paediatric survey.

Besides the initiation of GH treatment, early diagnosis has other potential advantages: the prevention of comorbidities (for example, hypertension), which may enhance the quality of life in these girls.⁹ Recurrent otitis media, resulting in chronic otitis media and progressive hearing loss needs an early and aggressive management.¹⁰ A history of middle ear disease in a girl with short stature should make the clinician aware of the possibility of Turner syndrome. Hence, we reconfirm our and others' recommendation^{4 5} that a cytogenetic analysis is indicated in girls with unexplained short stature with their height more than 2 SD below the mean for age or below the parent specific lower limit of height.¹¹

Table 1. Age and height at diagnosis in Belgian girls with Turner syndrome

	2003 survey			1991 survey		
	All	45,X	Others	All	45,X	Others
Age at diagnosis (median (range))						
All ages	6.6‡ (0.0-18.3)	1.2†† (0.0–17.5)	9.6* (0.0-18.3)	11.2 (0.0-17.4)	6.71 (0.0-17.0)	11.7 (0-17.4)
Diagnosis >1 y	10.1† (1.1–18.3)	9.7* (1.1-17.5)	10.5* (1.4-18.3)	12.3 (1.6-17.4)	12.8 (1.6-17.0)	11.9 (3.9-17.4)
Number (%) of patients per age category at diagnosis						
All ages	242 (100)	113 (47)	129 (53)	100 (100)	44 (44)	56 (56)
<1 y	73 (30)	54 (22)	19(8)	15 (15)	13 (13)	2(2)
1-12 y	115(48)	42(17)	73 (30)	40 (40)	13 (13)	27 (27)
> 12 y	54(22)	17(7)	37 (15)	45 (45)	18 (18)	27 (27)
Height SDS at diagnosis (mean (SD)) in patients aged 1 year or older at diagnosis						
<1 y	22.40 (0.93)‡	22.26 (0.78)†	22.47 (0.99)*	22.90 (1.00)	23.04 (0.93)	22.82 (0.89)
1-12 y	22.15(0.76)	22.10(0.74)	22.18 (0.76)	22.41 (0.86)	22.38 (1.00)	22.43 (0.79)
> 12 y**	22.92(1.05)*	22.67(0.71)†	23.04 (1.15)	23.34 (0.99)	23.57 (0.99)	23.21 (0.82)

*p<0.05; †p<0.01; ‡p<0.001: 2003 v1991 survey.

§p<0.05; ¶p<0.001: 45,X v other karyotypes.

**All groups at p<0.01 level different from same group of 1-12 years.

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