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Age-Related Perception of Stature, Acceptance of Therapy, and Psychosocial Functioning in Human Growth Hormone-Treated Girls with Turner's Syndrome

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ABSTRACT

This study evaluated the perception of stature, acceptance of therapy, and psychosocial functioning in relation to age at onset and time on treatment during 2 yr of GH therapy in 31 girls with Turner's syndrome grouped by age (group A: 3.7–5.8 yr, n = 9; group B: 7.2–11.8 yr, n = 13; group C: 12.5–16.4 yr, n = 9). The growth response after 2 yr was significant in the 3 groups when calculated in terms of growth norms for untreated Turner girls (mean increase in height SD score: +1.2, +1.5, and +1.1, respectively). The effect was less marked in terms of growth norms for normal girls, particularly in group B (+0.5 SD score). Height was perceived as a problem by most patients, except in the youngest girls at the start of treatment (group A) and in the majority of the adolescents after 2 yr of GH therapy (group C), without evidence of relation to growth response during therapy. The GH injections were fairly well accepted by all patients, except those younger than 6 yr. In all patients, expected adult height was unrealistic and became more realistic with age, whereas no consistent changes were observed in relation to growth response to GH therapy. The Child Behavior Checklist revealed elevated mean scores at the behavioral subscales of attention problems (group A and B), social problems, withdrawal, and anxiety-depression (most obviously in group B). No significant changes were seen during GH therapy. In group C, an elevated mean social problem score at the Youth Self Report and a low mean social self-esteem score at the Self-Esteem Inventory were observed before therapy and showed a significant improvement during 2 yr of GH treatment. These results, however, might be biased due to an increase in social desirability during therapy. We conclude that the perception of height, acceptance of GH therapy, and psychosocial functioning in girls with Turner's syndrome show important differences between age groups, with only slight changes observed during GH therapy.

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In patients with Turner's syndrome, psychosocial difficulties, including low self-esteem and social immaturity, have been described without evidence of psychopathological symptoms (1–4). Hyperactivity, poor concentration, and learning difficulties have been reported (5–7). Some researchers found that being short may negatively affect psychosocial functioning and self-esteem, although the severity of psychosocial problems associated with short stature is variable (8–12). In Turner's syndrome, short stature alone could not explain the multiple psychosocial problems according to McCauley *et al.* and Skuse *et al.* (4, 7). Rovet *et al.*, however, reported a positive correlation between height and social competence in patients with Turner's syndrome (3).

GH therapy undoubtedly results in increased growth velocity in Turner patients (13). The impact of GH therapy on psychosocial functioning has been studied by few researchers. In 66 short children, aged 5–15 yr, a beneficial effect on attitudes to being short was found after 2 yr of GH treatment, particularly in younger children (14). In a mixed group of GH-treated short patients, including girls with Turner's syndrome, a positive attitude toward height and a high level of satisfaction and compliance with GH therapy were observed regardless of height gain (15). In contrast, a positive correlation between height velocity and improvement in psychosocial functioning was found by Rovet *et al.* in patients with Turner's syndrome after 2 yr of GH therapy (16). The discrepancy between those data as well as controversies concerning the ultimate auxological and psychosocial benefits from GH therapy (17) led us to investigate the perception of stature and GH therapy as well as psychosocial functioning in a group of 31 children and adolescents with Turner's syndrome during 2 yr of treatment using human GH (hGH). As there are important age-related changes in cognitive and affective development, we hypothesized that the perception of short stature and GH therapy as well as psychosocial functioning could be different according to age. Therefore, the patients were divided into 3 age groups.

Subjects and Methods

PATIENTS AND AUXOLOGICAL EVALUATION

Thirty-one children with Turner's syndrome who started GH therapy at ages ranging between 3.7–16.4 yr were included in the study. The exclusion criteria were chronological age below 3 yr, bone age above 13 yr, spontaneous pubertal development or previous GH or sex or anabolic steroid therapy, and associated thyroid disorders or diabetes. Written informed consent from the parents and oral consent from the patients were obtained. The patients were followed during 2 yr in the Pediatric Endocrine Units of five Belgian University hospitals. GH (Humatrope, Eli Lilly & Co., Indianapolis, IN) was given as a daily sc injection at a dose of 0.15 IU/kg. No patient received estrogen replacement therapy during the first year of GH therapy. During the second year, six patients (group C, see below) were treated using ethinyl estradiol (50 ng/kg·day) based on a decision made individually by each pediatric endocrinologist together with each patient. Four patients started estrogen therapy after 12 months, one after 18 months, and one after 21 months

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of study. At 24 months of study, all six showed stage B2 breast development according to Tanner (18).

Height was measured every 3 months using a wall-mounted stadiometer. Weight was also measured. Target height was calculated as proposed by Tanner *et al.* by adding father's height to mother's height, subtracting 13 cm, and dividing the total by two (19). SD scores of height were calculated in terms of growth norms for normal girls (20) and Turner girls (21). In each patient, a dysmorphy score was calculated using the following 17 findings, which each accounted for 1 point: short neck, webbed neck, micrognathia, low posterior hairline, palpebral ptosis, strabismus, impaired vision, dysmorphic low set ears, hearing impairment, cubitus valgus, short metacarpals, pectus excavatum, shield thorax, increased body hair, more than 20 pigmented nevi, and nail dysplasia. X-Ray films of the left hand and wrist were obtained annually, and bone age was estimated according to the method of Tanner and Whitehouse, TW2 RUS, by a single experienced pediatric radiologist (22). The patients were divided into 3 groups according to chronological age at the onset of treatment (**Table 1**). Time between diagnosis and initiation of the study was variable and, on the average, shorter in the older patients. There were no significant differences among the 3 age groups with respect to target height and dysmorphy score (**Table 1**) or pretreatment height SD score in terms of growth norms for Turner girls (**Table 2**). Although all but 1 patient in group A had the classical 45X karyotype, the majority of patients in groups B and C showed other karyotypes, listed in **Table 1**.

Table 1. Clinical data of Turner patients before starting GH therapy.

	Group A (3–6 yr)	Group B (7–12 yr)	Group C (13–16 yr)
n	9	13	9
Chronological age (yr)	4.8 ± 0.7	9.9 ± 1.4	14.2 ± 1.4
Time since diagnosis (yr)	3.4 ± 1.9	2.5 ± 3.6	0.2 ± 0.1
Target ht (cm)	165.8 ± 4.8	162.1 ± 5.9	162.4 ± 4.5
Dysmorphy score	7.4 ± 3.1	8.4 ± 3.0	6.1 ± 2.0
Karyotype			
45X	8	4	4
45X/46XX	1	1	
45X/46Xi(Xq)		3	2
46Xi(Xq)			1
45X/47XXX			1
45X/46XY/47XYY		1	
45X/46XY			1
45X/46Xt(X)/47Xt(XX)		1	
45X/46Xt(XY)		1	
45X/46X, r(X)		2	

Data are the mean ± SD.

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PSYCHOLOGICAL EVALUATION

Two psychologists (K.L. and D.X.H.), one Dutch and one French-speaking, performed the study so as to have families interviewed in their mother tongue. The psychological evaluation took place 1 month before initiating GH therapy and after 1 and 2 yr of therapy.

Standardized questionnaires were used to evaluate behavior, intellectual skills, and global psychosocial functioning. The Child Behavior Checklist (CBC), developed by Achenbach *et al.* (23), was used as a standardized measure of social competence and behavioral problems in children aged 2–18 yr and was completed by the parents. The Youth Self Report (YSR), a checklist evaluating similar aspects as the CBC, was completed by patients older than 11 yr. In this study, the Dutch and French versions were used (23, 24). The CBC and the YSR consist of a total social competence scale (including activity, school, and social competence) and a behavior scale (including eight subscales). In this report, we emphasized the data from four behavioral subscales at which the mean scores appeared to be most relevant: attention problems (poorly concentrated, acting young, nervous, daydreaming, impulsive, clumsy), social problems (teased, preferring younger children, not getting along, overweight), withdrawal (shy, secretive, underactive), and anxiety/depression (lonely, sad, worthless, fearful, guilty).

Table 2. Growth data of Turner patients before and after 1 and 2 yr of GH therapy.

	Group A (3–6 yr; n = 9)			Group B (7–12 yr; n = 13)			Group C (13–16 yr; n = 9)		
	Baseline	Yr 1	Yr 2	Baseline	Yr 1	Yr 2	Baseline	Yr 1	Yr 2
Ht SD score (in terms of growth norms for normal girls)	21.7 ± 0.9	21.1 ± 0.9[a]	20.8 ± 1.0[a]	22.6 ± 0.6	22.1 ± 0.8[a]	22.1 ± 1.0[a]	23.2 ± 0.5	22.7 ± 0.8[a]	22.3 ± 1.0[a]
Ht SD score (in terms of growth norms for untreated Turner girls)	0.5 ± 1.1	1.3 ± 1.1[a]	1.7 ± 1.3[a]	20.1 ± 0.7	0.8 ± 0.8[a]	1.4 ± 0.9[a]	0.3 ± 0.8	1.1 ± 0.8[a]	1.4 ± 0.9[a]
Ht velocity (cm/yr)	5.7 ± 1.3	9.0 ± 1.1[a]	7.4 ± 1.1[a]	3.5 ± 0.8	8.4 ± 1.2[a]	7.4 ± 2.3[a]	2.7 ± 0.8	5.9 ± 1.6[a]	4.3 ± 1.6[a]
Bone age (TW2 RUS, yr)	3.6 ± 0.7	6.1 ± 0.5[a]	7.6 ± 0.3[a]	9.3 ± 2.0	11.1 ± 1.7[a]	12.6 ± 1.5[a]	12.2 ± 0.9	13.1 ± 0.5[a]	13.9 ± 0.5[a]

Data are the mean ± SD.
[a] $P \leq 0.05$ *vs.* baseline.

For the CBC, individual raw scores were transformed into T scores (mean = 50, SD = 10) using the American norms (23). These T scores were transformed into SD scores. The behavioral problem scores were considered to be borderline when the SD score was more than 1.6 (T score, > 66; 95th percentile) and within the clinical range when the SD score was above 2 (T score, > 70; 98th percentile). The Self-Esteem Inventory (SEI), developed by Coopersmith, was completed by patients older than 8 yr (25). The total self-esteem comprises four subscales: social, general,

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school, and family self-esteem. These subscales measure how the child evaluates, respectively, her social contacts, herself in general, herself at school, and herself within the family. The social desirability or "lie" subscale measures the degree of wanting to present herself as she thinks that she is socially best accepted. For the SEI, the individual scores were transformed into SD scores using the American norms (25). In school age children and young adolescents (groups B and C), the intellectual abilities were assessed by the Wechsler Intelligence Scale for Children-Revised (WISC-R). The age- and sex-appropriate standards used were provided by the respective Dutch and French manuals (26, 27).

Other screening instruments were used to evaluate the psychological functioning of the child: the observation of play, including the use of anatomical dolls; the Scenotest; and drawing. Semi-structured interviews were developed to evaluate the perception of height and injections and to determine the specific behavioral and affective characteristics of each child with Turner's syndrome. The interviews were designed according to the systemic theory and family therapy (28–30). The evaluation involved interviews with the patient and her parents, as well as with the patient alone and with each of the seven pediatric endocrinologists taking care of the families. Upon written request, the semi-structured interviews will be forwarded to the reader.

STATISTICAL ANALYSIS

This descriptive, nonrandomized study consisted of an in-depth investigation of a limited number of patients. No control group was studied. Comparisons between the data obtained within each age group, before and after 1 and 2 yr of GH therapy, were made by ANOVA with correction for repeated measurements, followed by *post-hoc* Fisher's protected least significant difference test. Comparisons of the SD score data between the age groups were performed by ANOVA followed by Scheffe's F test for multiple comparisons. The correlation between various data was calculated by regression analysis. The level of significance was set at $P < 0.05$. No adjustment was made for multiple comparisons.

Results

AUXOLOGY

In the three age groups, the mean pretreatment height SD score (**Table 2**) and individual values (**Fig. 1**) were within the normal range for Turner patients. When calculated in terms of growth norms for normal girls, the pretreatment height SD score was lower with age (**Fig. 1**). During the first and second years of GH treatment, mean height velocity and mean height SD score, calculated in terms of growth norms for normal as well as Turner girls, increased significantly in the three groups (**Table 2**). In group B, the increase in height SD score after 2 yr was more marked in terms of growth norms for Turner girls (+1.5) than in terms of growth norms for normal girls (+0.5). Some patients in group B showed a reduction in height SD score, particularly during the second year of treatment

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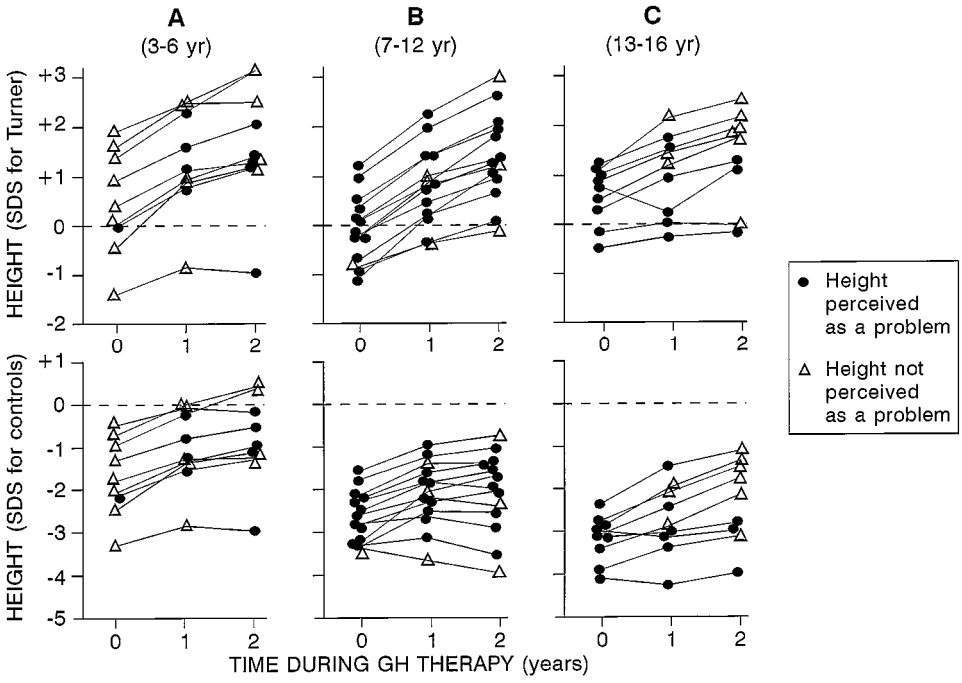
(**Fig. 1**). During the 2 yr of therapy, the mean progression in bone age was greater in group A (+4.0 yr) than in group B (+3.3 yr) and group C (+1.7 yr; **Table 2**).

INTERVIEWS

PERCEPTION OF HEIGHT AND INJECTIONS

In patients younger than 6 yr, height was not perceived as a problem before starting GH therapy (**Fig. 1**). This was in contrast to all but 1 of the patients older than 6 yr. After 1 yr of treatment, height was still not perceived as a problem in 5 of the 7 patients younger than 6 yr at that time, including a patient with a height SD score of −2.8 *vs.* that in normal girls. In this group, perception of height as a problem was not consistent with actual stature, as some treated patients with height greater than −1 SD complained about height. After 2 yr of GH therapy, height remained a problem in the vast majority of patients older than 6 yr, particularly in group B (10 of 13 patients). In contrast, height remained a problem in only 3 of 9 patients in group C (**Fig. 1**). At the pretreatment interview, it appeared that the perspective of a treatment using daily injections was frightening for all patients in the 3 groups regardless of age. After 1 yr, the injections remained a problem in 4 of the 9 patients in group A and in a minority of patients (3 of 22) in groups B and C.

Fig. 1. Height changes during 2 yr of GH therapy in 31 girls with Turner's syndrome divided into 3 age groups. The data were calculated in terms of growth norms for untreated Turner girls (*upper panels*) or normal girls (*lower panels*). For each individual patient, the data are connected by *lines*, and the *symbols* indicate whether height was perceived as a problem at each of the 3 evaluations.



EXPECTATION ABOUT ADULT HEIGHT

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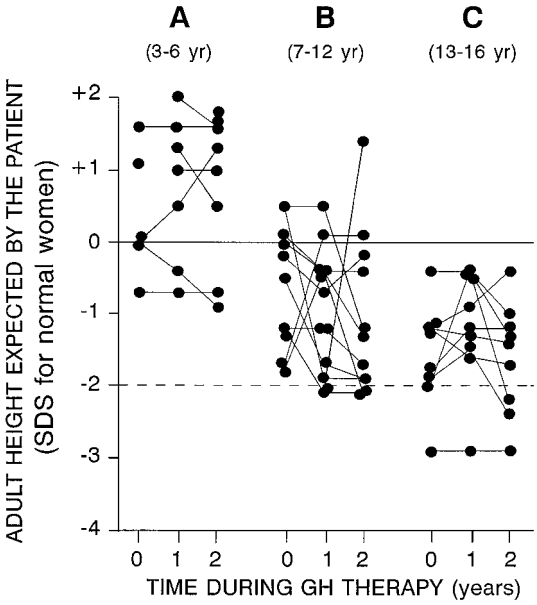
The adult height anticipated by most patients was high in the three groups and appeared to decrease with age (**Fig. 2**). The older the patient, the more realistic was the expectation. However, most patients in group C still had overly optimistic expectations (adult height above −2 SD of normal women). No correlation was found between expected adult height and growth response to therapy.

PSYCHOSOCIAL PROBLEMS

In group A, hyperactivity, talkativeness, lack of concentration, impatience, and a tendency to dominate became obvious through observation during the interview sessions as well as through the complaints by the parents. These problems remained unchanged during the 2 yr of follow-up. In group B, the patients themselves expressed suffering from being teased about short stature. The parents were concerned about a tendency to withdraw. The interviews revealed that the patients invested more in schoolwork than their siblings, and they obtained less satisfactory results. The majority of patients did not participate in any social, cultural, or sports activity and were rather passive at home. In group C, the adolescents expressed feelings of inferiority at the start of the study. The complaints about a lack of self-confidence tended to decrease during the 2 yr of follow-up. After 2 yr, a tendency to minimize problems became obvious.

Fig. 2. Adult height expected by 31 girls with Turner's syndrome divided into 3 age groups. The expected adult height was transformed into the SD score (in terms of growth norms for adult women). The data obtained from each individual patient, before and during 2 yr of GH therapy, are connected by *lines*.



TESTING

INTELLIGENCE

The mean intelligence quotient (IQ) was significantly lower ($P < 0.05$) in group B (mean ± SD, 91 ± 15) than in group C (105 ± 14). Half of the patients (11 of 22) had average IQs ranging between 96–

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109. Two had IQs above average (113 and 116), and 2 were gifted (122 and 124). Six patients had borderline IQs ranging between 74–85, and 1 had mild mental retardation (68).

STANDARDIZED QUESTIONNAIRES

In group A, the mean attention problem score on the CBC was high at the 3 evaluations (**Fig. 3**). The individual attention problem scores were borderline or in the clinical range in a quarter of the patients at the start of treatment and in half of the patients after 2 yr. On the other subscales (**Fig. 3** and **Table 3**), the scores were within the normal range and remained so throughout the study. In group B, the mean attention problem score was elevated as well, with individual scores being borderline or in the clinical range in half of the patients before and after 2 yr of therapy. A high mean score on the social problem subscale was observed at the 3 evaluations, indicating social behavior inadequate for age. The individual social problem scores were borderline or clinical range in 3 of 13 patients at the start and in5 of13 after 2 yr of treatment. High mean behavior problem scores were also observed on the withdrawal and anxiety depression subscales (**Fig. 3**), and low mean social competence scores were observed on the activities, social, and school subscales (**Table 3**). No significant changes in mean score were seen throughout the study, except on the social competence subscale in group B. On the SEI (**Fig. 4**), the mean social self-esteem score was low in group B at the start of treatment and remained so throughout the study. In contrast, the mean family self-esteem score was high at the 3 evaluations. In group C, a high mean score was observed on the social problem subscale of the CBC, with a nonsignificant decrease during follow-up (**Fig. 3**). On the other behavior problem subscales (**Fig. 3** and **Table 3**), the scores were within the normal range and remained so throughout the study. On the activities and social subscales of the social competence scale, low mean scores were observed, with no change during the study (**Table 3**). On the YSR, the mean social problem score was high at the start of treatment and decreased significantly after 2 yr of treatment (**Table 4**). High mean scores were also obtained on the anxiety-depression subscale of the CBC (**Fig. 3**) and YSR (**Table 4**), and they showed some decrease during follow-up. Low mean scores of social competence were obtained on the YSR, and no changes were seen throughout the study (**Table 4**). It is noteworthy that the mean scores of the parents (CBC) were lower than those of the patients (YSR) on all subscales. On the SEI, the mean social and general self-esteem scores showed a significant increase throughout the study (**Fig. 4**). These score changes might be biased because the mean social desirability scores increased significantly throughout the study. A biasing effect of IQ was unlikely because the baseline SEI scores were not significantly correlated with the IQ scores. Neither were the baseline SEI scores correlated with the dysmorphy scores, indicating that variations in self-esteem were not simply determined by variations in physical appearance.

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Fig. 3. Mean (±SD) problem score (SD score) obtained on four behavioral subscales of the CBC in three age groups of Turner girls studied before and after 1 and 2 yr of GH therapy.

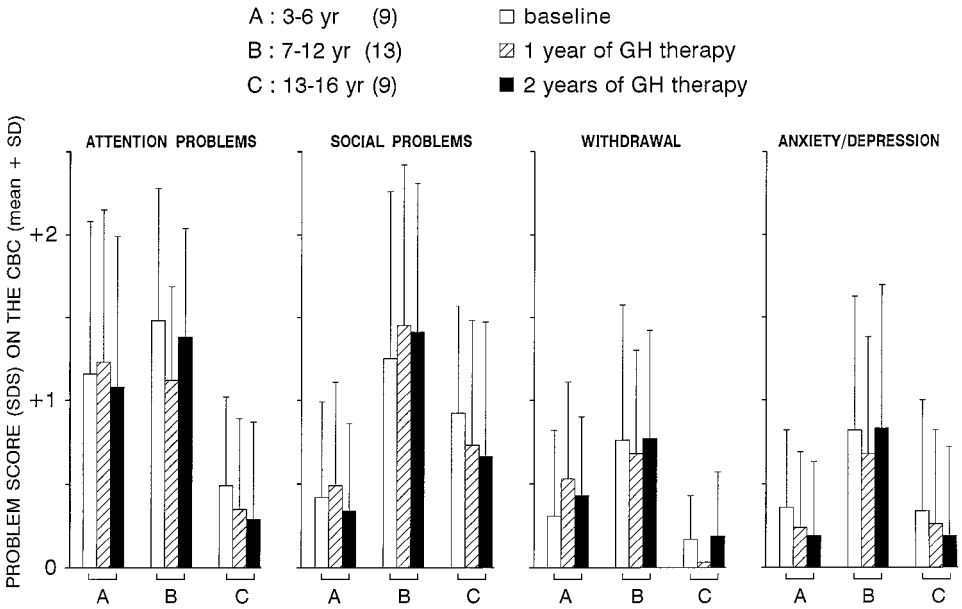

Table 3. Behavior problem and social competence scores on the Child Behavior Checklist in three age groups (A, B, and C) of Turner patients at baseline and after 1 and 2 yr of GH therapy.

Behavior problems	Baseline	Yr 1	Yr 2
Somatic complaints			
Group A	0.36 ± 0.31	0.58 ± 0.52	0.40 ± 0.35
Group B	0.76 ± 0.82	0.69 ± 0.67	0.51 ± 0.57
Group C	0.28 ± 0.50	0.28 ± 0.46	0.40 ± 0.83
Thought problems			
Group A	0.26 ± 0.54	0.20 ± 0.37	0.43 ± 0.56
Group B	0.46 ± 0.69	0.39 ± 0.52	0.55 ± 0.58
Group C	0.44 ± 0.57	0.25 ± 0.49	0.14 ± 0.43
Delinquent problems			
Group A	0.36 ± 0.53	0.34 ± 0.60	0.48 ± 0.73
Group B	0.49 ± 0.66	0.42 ± 0.59	0.56 ± 0.68
Group C	0.34 ± 0.59	0.21 ± 0.42	0.14 ± 0.36
Aggressive behavior			
Group A	0.42 ± 0.66	0.66 ± 0.89	0.64 ± 0.83
Group B	0.58 ± 0.65	0.60 ± 0.72	0.55 ± 0.78
Group C	0.21 ± 0.45	0.16 ± 0.46	0.07 ± 0.20
Externalizing			
Group A	−0.14 ± 1.17	0.08 ± 1.39	0.26 ± 1.20
Group B	0.35 ± 1.00	0.37 ± 0.98	0.26 ± 1.02
Group C	−0.49 ± 1.01	−0.78 ± 1.00	−0.99 ± 0.82
Internalizing			
Group A	−0.01 ± 0.74	0.09 ± 0.84	−0.06 ± 0.80
Group B	0.73 ± 0.96	0.67 ± 0.74	0.68 ± 0.65
Group C	−0.34 ± 1.12	−0.41 ± 0.89	−0.77 ± 1.33

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Total			
Group A	0.16 ± 0.16	0.34 ± 0.97	0.21 ± 1.02
Group B	0.81 ± 0.93	0.68 ± 0.76	0.75 ± 0.68
Group C	−0.31 ± 1.28	−0.44 ± 1.02	−0.89 ± 1.24
Social competence			
Activities			
Group B	−0.68 ± 0.70	−0.88 ± 0.54	−0.62 ± 0.61
Group C	−1.09 ± 0.93	−1.19 ± 0.68	−1.19 ± 0.88
Social			
Group B	−0.64 ± 0.65	−0.87 ± 0.73	−1.36 ± 0.67[a]
Group C	−1.03 ± 0.87	−0.84 ± 0.81	−1.14 ± 0.98
School			
Group B	−1.05 ± 0.74	−0.96 ± 0.99	−1.28 ± 0.89
Group C	−0.17 ± 0.88	−0.65 ± 1.09	−0.60 ± 0.99
Total			
Group B	−0.97 ± 0.51	−1.24 ± 0.43	−1.45 ± 0.52
Group C	−1.13 ± 0.91	−1.25 ± 0.74	−1.57 ± 0.94

Scores are expressed as SD scores (mean ± SD).
[a] $P \leq 0.05$ *vs.* baseline.

No significant correlation was found between the height gain during therapy and the individual differences in attention problem score, social problem score, and social selfesteem score. This was found analyzing the data from each of the three groups separately as well as analyzing the entire set of data together.

Fig. 4. Mean (±SD) self-esteem score (SD score) obtained on four subscales of the SEI in two age groups of Turner girls studied before and after 1 and 2 yr of GH therapy.

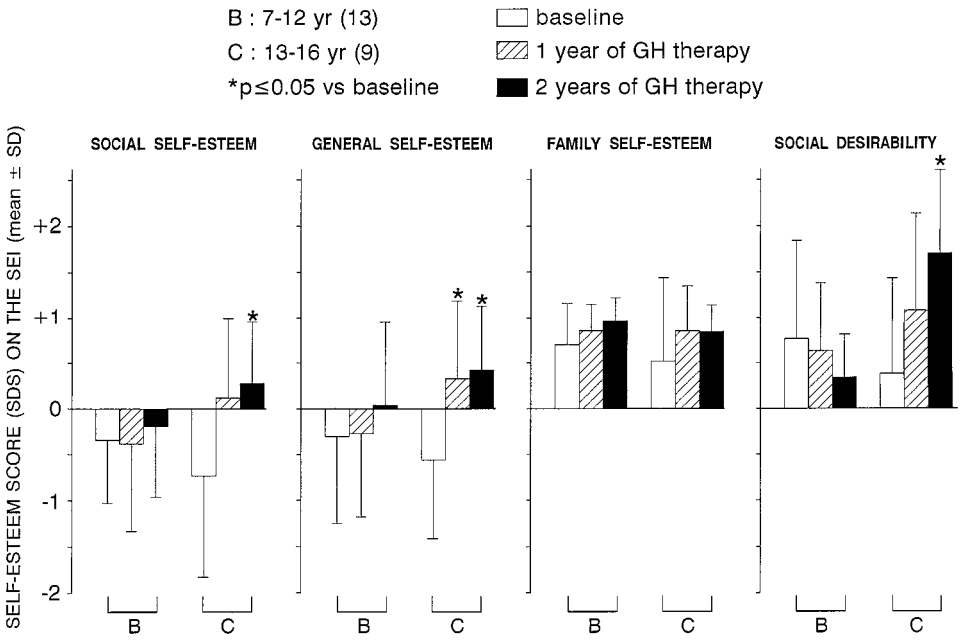

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Table 4. Behavior problem and social competence scores on the Youth Self Report in nine adolescent Turner patients (group C) at baseline and after 1 and 2 yr of GH therapy.

	Baseline	Yr 1	Yr 2
Behavior problems			
Attention problems	0.69 ± 0.89	0.41 ± 0.60	0.32 ± 0.42
Social problems	1.11 ± 0.80	1.07 ± 0.79	0.41 ± 0.57[a]
Withdrawal	0.44 ± 0.58	0.30 ± 0.46	0.13 ± 0.29
Anxiety/depression	0.74 ± 0.82	0.38 ± 0.49	0.22 ± 0.40
Somatic complaints	0.39 ± 0.51	0.12 ± 0.19	0.14 ± 0.34
Thought problems	0.28 ± 0.37	0.21 ± 0.43	0.12 ± 0.22
Delinquent behavior	0.44 ± 0.43	0.13 ± 0.40	0.13 ± 0.40
Aggressive behavior	0.25 ± 0.65	0.26 ± 0.49	0.14 ± 0.30
Externalizing	−0.19 ± 1.08	−0.39 ± 0.80	−0.42 ± 0.72
Internalizing	0.06 ± 1.44	−0.24 ± 0.92	−0.49 ± .094
Total	0.06 ± 1.35	−0.27 ± 0.77	−0.50 ± 0.90
Social competence			
Activities	−1.15 ± 1.10	−0.97 ± 1.31	−1.00 ± 0.78
Social	−1.44 ± 0.87	−1.24 ± 0.85	−1.29 ± 0.89
Total	−1.63 ± 0.73	−1.47 ± 0.83	−1.43 ± 0.84

Scores are expressed as SD scores (mean ± SD).

[a] $P \leq 0.05$ *vs.* baseline.

Discussion

In this study, the perception of short stature and GH therapy by Turner patients as well as their psychosocial functioning appeared to be different according to age, with only slight changes during 2 yr of GH therapy. Neurocognitive functioning and behavioral problems in Turner patients can be influenced by many other factors besides age. Among these factors, brain structure anomalies (31), karyotype subgroups (3, 32), parental origin of the remaining X chromosome (33), and estrogen deficiency (34) may play some role. In this study, we cannot exclude either the confounding effect of brain structure anomalies, which was not investigated, or the potential estrogen effects because estrogen therapy was initiated after 1 yr of study in six patients from the adolescent group. Although the majority of non-45 XO karyotypes were found in groups B and C, there were only two patients with ring X chromosome, which is associated with high risk of mental retardation (32). However, due to the small number of patients in each age group and because there are no control untreated patients, the possible role of those factors cannot be delineated. Therefore, the age-related aspects described in this study deserve confirmation in larger groups of patients, taking into account the effects of genetic, neurological, and endocrine factors as well.

Before the age of 6 yr, the patients did not yet perceive height as a problem, and they accepted the injections with difficulty. In GH-treated patients, Leiberman (15) noted that satisfaction and

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compliance were high regardless of age at the start of treatment. We did not find such a satisfaction in Turner patients younger than 6 yr. At this early stage, the child does not yet have a realistic representation of height, and the rationale of treatment cannot be understood. According to the theory of Piaget (35) regarding cognitive development, the age period from 3–6 yr is characterized by magic and egocentric thinking; the child mixes reality and imagination. The young child with Turner's syndrome may hold firmly to the idea "I am tall, even the tallest of the whole class," even if she is objectively very short. In addition, affective development is characterized by investment in adults, particularly the parents, and comparison with peers is not yet so important. All children tend to idealize future perspectives without taking into account the real possibilities and limitations. Children younger than 6 yr in particular have difficulties projecting themselves into the future. This might explain the totally unrealistic expectations for adult height in these young patients. Turner girls younger than 6 yr showed several behavioral problems, such as hyperactive and impulsive behavior, poor concentration, talkativeness, and a need to dominate. Some of these features were confirmed by high attention problem scores on the CBC, which remained unchanged after 2 yr. Hyperactivity in young Turner girls was also described by Swillen *et al.* (5). Future studies in a larger number of young Turner patients might contribute to clarification of the etiology of the behavioral problems. In these young patients, it would also be interesting to study hypotheses such as the delayed neurological maturation hypothesis described by McCauley *et al.* in older patients (9–17 yr) (7). After 2 yr of GH therapy, the patients who were older than 6 yr perceived height in a more realistic way and compared themselves with peers. Height, however, was perceived as a problem by only five of nine patients, and social problems did not appear on the CBC, contrary to what could be expected at that age. These findings might be explained by the growth effects of GH therapy, which diminished the gap with peers. A long term follow-up of patients treated at a young age could further clarify whether perception of stature and GH therapy as well as psychosocial functioning in these young patients differ from those in patients starting GH therapy at an older age.

Turner patients, aged 7–12 yr, subjectively suffered from short stature. They had attained an age at which comparison with peers became important. They took into account and suffered from remarks by others. At this stage, the patients were aware of their dysmorphic appearance and began to realize the consequences of Turner's syndrome for pubertal development and fertility. Once they were 6 yr old, the patients showed high motivation, compliance, and satisfaction with GH therapy, as reported by others (36). This treatment created hope and required a great investment. This reinforced idealization and unrealistic expectations. According to Huisman *et al.* (36), the optimistic expectations for adult height in the patients were already striking before treatment and remained unchanged after 2 yr of therapy, in agreement with our findings. Although adult height expectations remained unrealistic, there was a decrease in some patients during therapy. This might be due to an age effect. There might also have been a biasing effect due to the psychologists having shared their concern about the unrealistic expectations of the patients with the pediatric endocrinologist. On the CBC, high scores on the attention problem, social problem, and anxiety/depression subscales were also found by Skuse *et al.* in a large group of girls with Turner's syndrome (4). A high rate of hyperactivity was reported by McCauley *et al.* in 97 untreated

girls with Turner's syndrome (1). Noteworthy, these studies were not set up in a longitudinal perspective. In our study, attention problems revealing distractibility, clumsiness, and poor school performance remained unchanged after 2 yr. In addition, as mean IQ was low in this group (6 of 13 had an IQ < 90), it was not surprising that school results remained moderate despite a great investment. We did not evaluate the effect of GH treatment on neurocognitive function. In a recent study comparing Turner patients treated with GH or a placebo, no evidence was found of an influence of GH on childhood brain development (37). On the CBC, social problems, indicating social immaturity, were still obvious after 2 yr. Apparently, the catch-up in growth did not lead to a catch-up in psychosocial functioning. Even after 2 yr of GH therapy, the patients continued to be perceived as younger. It is noteworthy that despite growth acceleration during GH treatment, the height gap compared to normal girls was not reduced in these patients, as their normal peers were growing rapidly on account of pubertal development. Most patients did not complain openly about being lonely and isolated, but they tended to withdraw before as well as during therapy. Their social self-esteem was rather low, in contrast to their family investment, which increased. They tended to avoid confrontation with peers and took refuge in the family. After 2 yr, the majority of patients reported that peer derision about short stature diminished, and they had learned to react better to remarks from peers. They also reported that GH treatment helped them in creating hope of catching up with peers. They felt supported by doing something for their short stature, the only symptom that they could influence at that moment. This positive effect of GH treatment, however, did not resolve the ongoing suffering in children between 7–12 yr of age.

In all Turner girls aged 13–16 yr, short stature was a problem at the start of GH therapy, and treatment was perceived as the last chance to influence height. Although a considerable height difference from that of their peers remained after 2 yr, only one third of these adolescents still perceived height as a problem. As they knew that final height was almost attained, they tried to accept this inevitable reality. These findings were consistent with a study in untreated adult Turner patients, who expressed greater distress due to infertility compared with short stature (38). At the start of GH therapy, lack of self-confidence and low self-esteem were obvious in the majority of patients. In this study, the low self-esteem could be partly understood by the particular age period of adolescence during which all youngsters are searching for their own identity, and much importance is accorded to physical appearance. Comparisons with peers are particularly hard for Turner adolescents due to the obvious physical differences from peers: short stature, dysmorphic appearance, and absence of female development, which, together with infertility, do affect the sense of being a woman. We have assessed the severity of dysmorphic features in the three groups, because Turner stigmata might have been less visible in late diagnosed patients. Such an explanation was unlikely, as the mean dysmorphy score was slightly, but not significantly, lower in group C than in group B.

McCauley *et al.* (1) observed a decline in self-esteem in girls with Turner's syndrome as they moved into the adolescent period. These patients, however, were younger (mean age, 10.2 yr) than the adolescent group studied in the present work. According to the patients in this study, the perspective of estrogen replacement therapy created the hope of contributing to the patient's femininity just as GH therapy did for short stature. Ross *et al.* showed that estrogen therapy

resulted in improved self-concept and social behavior in Turner girls between 12–16 yr of age (34). This raised the question of whether the changes in self-esteem and behavior seen in adolescent Turner patients in this study could be related to estrogen therapy. Although this possibility was not excluded, only half of the adolescent patients were treated using estrogen, and such a treatment was only started after the first year of GH therapy. During this first year of study, however, a significant increase in self-esteem was already observed, indicating that some improvement might occur independently of estrogen therapy.

After 2 yr of GH therapy, there was some improvement in psychosocial functioning of the adolescent patients. They were less anxious-depressed and had a better self-image and greater social self-esteem. They considered themselves less socially immature. These data are consistent with the findings of Huisman *et al.* (36). On the SEI, social desirability scores increased considerably. The patients tended to minimize their problems as a way of coping with them. The adolescent patients wanted to present themselves as doing better. Their family investment was high. They felt secure and tended to take refuge in the family to avoid the often painful confrontation with peers. The very close relationship with their parents, particularly with their mother, and the feeling of guilt because of causing many problems to the parents could push the patients toward a minimization of their problems. This could also be a reason why they could not revolt against their parents as do other adolescents. Again, the observed changes might have been influenced by the treatment with GH. As we did not study a group of untreated patients for control purposes, the interpretation of these findings requires prudence. Nevertheless, it is interesting that no correlation was found between the changes in psychosocial functioning and the growth response to therapy in the three age groups.

In conclusion, this study shows that in Turner patients, perception of short stature, GH therapy, and expectation for adult height are different according to age. The psychological profile as well as the suffering caused by Turner's syndrome vary according to the cognitive and affective development and change only slightly during 2 yr of GH therapy. These data might provide a rationale for an age-based evaluation of indications for GH therapy and benefits from such a treatment in girls with Turner's syndrome. Treatment strategy should also take into account the possible adult height consequences of the rapid progression in bone maturation seen in young treated patients. This observation may indeed add to the questions about benefits from early onset of GH therapy.

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