

The importance of this study is that it suggests that the final height of patients with TS who are treated with GH is increased by using very low doses of systemic estradiol, rather than routine estrogen therapy, to induce puberty. The gain seems equivalent to that achieved with 1 year of GH therapy alone. A trial with a larger number of patients will be required to confirm these data and to determine the long-term consequence of this intervention strategy on bone mineralization.

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The Psychological Consequences of Turner Syndrome and Review of the National Cooperative Growth Study Psychological Substudy

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ABSTRACT. *Objective.* To present longitudinal data on the psychological profile of a cohort of girls with and without Turner syndrome (TS) treated for 3 years with growth hormone (GH).

Methods. Among a sample of 283 children with short stature, 37 girls with TS were recruited at 27 US medical centers. Of the original cohort, 22 girls with TS, 13 girls with isolated growth hormone deficiency (GHD), and 12 girls with idiopathic short stature were followed through 3 years

of GH therapy. All were school-age, were below the 3rd percentile for height, had low growth rates, and were naive to GH therapy. Psychological tests (the Wide Range Achievement Test and the Slosson Intelligence Test) were administered to the clinical groups within 24 hours of their first GH injection and yearly thereafter. Control subjects were 25 girls with normal stature matched for age and socioeconomic status, who were tested only at baseline. One parent of each subject also completed the Child Behavior Checklist for that subject.

Results. At baseline, the clinical groups had more internalizing behavioral problems, had fewer friends, and participated in fewer activities than did the control subjects. The groups did not differ in mean IQ or academic achievement, but the TS group did have more problems in mathematics achievement. Height and growth rate significantly increased in the clinical groups over the 3 years of GH therapy, but IQ and achievement scores did not. Significant linear reductions were noted in both Internalizing and Externalizing Behavior Problems after GH treatment, with the TS group having fewer behavior problems before and after GH treatment than did the GHD-idiopathic short

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stature group. Decreases in specific Child Behavior Checklist subscales, including attention, social problems, and withdrawal, also were seen in the clinical groups after GH therapy.

Conclusions. The comprehensive treatment of girls with TS should include educational and behavioral interventions in addition to traditional medical therapies. *Pediatrics* 1998;102:488–491; *Turner syndrome, growth hormone deficiency, idiopathic short stature.*

ABBREVIATIONS. TS, Turner syndrome; GH, growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; WRAT–R, Wide Range Achievement Test–Revised; SIT, Slosson Intelligence Test; CBCL, Child Behavior Checklist; ANOVA, analysis of variance.

Turner syndrome (TS), a chromosomal abnormality characterized by an absence of or structural defect in one of the X chromosomes, occurs in ~1 of every 2500 female births. Short stature and infertility almost always are associated with TS, and additional physical anomalies and skeletal and medical problems may be present. There is considerable phenotypic variation among affected persons; in some cases, the features are quite evident and in others, they are more subtle.¹

Research has shown consistently that persons with TS are at increased risk for selective impairment in the cognitive, behavioral, and social domains.^{2,3} Some investigators cite experiential and environmental factors such as juvenilization, heightism, and overprotective parenting as primary causative factors. Others suggest that the genetic, hormonal, and medical problems associated with TS are likely to affect brain development and thus influence learning, social interactions, and behavior patterns.⁴ One group has attempted to link the specific cognitive and social difficulties associated with TS by noting their similarity to the combination of visuospatial problems, difficulties in learning mathematics, and poor social skills that are associated with a nonverbal learning disability.⁵

Mental retardation, except in those with a small ring X chromosome, is not common in persons with TS, but other cognitive impairments are frequently evident. Rovet's study suggests that girls with TS are two to four times as likely as unaffected girls to have some type of cognitive difficulty. Deficits in processing visuospatial information are described most often, and difficulties in executive functioning (eg, verbal fluency, planning skills, and flexibility), memory, and attention also are noted.⁶

Studies in girls and women with TS have not shown a high prevalence of severe psychopathology, but less serious emotional disturbance or poor adjustment is noted frequently. The behavioral profiles differ by age, with younger girls with TS having been described as hyperactive, immature, and anxious, and with anxiety, depression, and unsatisfactory relationships being more typical in older girls.⁷ In the largest TS cohort studied to date, Skuse and associates have reported that up to one quarter of the subjects with TS in their sample had adjustment

problems that were sufficient to warrant referral for psychiatric assessment and clinical intervention.⁸

Until recently, endocrine treatment of patients with TS had focused primarily on estrogen replacement to induce pubertal maturation. With the availability of biosynthetic growth hormone (GH), it has become possible to use GH to lessen the marked height deficit in these patients.⁹ The impact of GH therapy on behavior, however, has yet to be assessed in girls with TS or in girls in general. In addition to the present study, Rovet and Holland have reported preliminary results from an ongoing longitudinal study that is evaluating psychological functioning in school-age girls with TS who are randomized to GH treatment or no treatment. After 2 years, the increase in the growth rate was significantly greater in the girls treated with GH than in the control group. The growth rate was not correlated with family or school functioning, but there was a correlation between increased growth rate and the girls' perceptions of themselves as being more intelligent, being more attractive, having more friends, being more popular, and experiencing less teasing than found in the untreated girls.¹⁰

The effects of GH therapy on the growth velocity and the final height of girls with TS are encouraging, but there is little information on the effects of GH therapy on the educational, social, and behavioral functioning not only in girls with TS but also in girls with other indications for such therapy.

The current study was designed to present longitudinal data on the psychological profile of a cohort of girls with or without TS who were treated with GH for 3 years in the National Cooperative Growth Study.

METHODS

Subjects

As part of a longitudinal behavioral study of GH therapy, 283 short children were recruited at 27 US medical centers. All were below the 3rd percentile for height, had low growth rates, and were naive to GH therapy. Data also were collected on 146 children of normal stature (10th to 90th percentile) who were matched for age, sex, and socioeconomic status and were used as control subjects.¹¹ There were 37 girls with TS, 27 girls with isolated growth hormone deficiency (GHD), and 24 girls with idiopathic short stature (ISS) in the original cohort. Of these, 22 with TS, 13 with GHD, and 12 with ISS were followed through 3 years of GH treatment. Of the 67 girls in the control group, 25 were matched for age and socioeconomic status with the girls in the clinical groups for this report. Socioeconomic status was determined by the raw scores on the Hollingshead Four Factor Index of Social Status.¹²

There were no significant demographic differences between the girls who started GH treatment and those who completed it. Because the baseline demographics, growth measurements, and cognitive and behavioral measurements were not different in the girls with GHD and those with ISS, they were combined into one comparison group (GHD-ISS). GHD was defined as a peak stimulated GH level of <10 µg/L.

Selected growth measures and demographics for the TS, GHD-ISS, and control groups are shown in Table 1. No significant differences between the clinical groups in pretreatment growth rate, bone age, or chronologic age were observed. The girls in each group lived in predominantly middle- to upper-middle-class, two-parent families, with both parents having at least a high school education. On the basis of reports from the parents, the groups did not differ in the percentage of girls who had failed a grade in school, had used special education services, or had been diagnosed with a learning disability or attention problem.

TABLE 1. Baseline Demographics

| | TS (<i>n</i> = 22) | GHD-ISS (<i>n</i> = 25) | Control Subjects (<i>n</i> = 25) | <i>P</i> |
|--------------------|---------------------|--------------------------|-----------------------------------|----------|
| Age (y) | 10.1 (2.7) | 10.3 (2.0) | 11.0 (2.8) | — |
| Height SDS | -3.3 (0.7) | -3.1 (0.7) | — | NS* |
| Bone age (y) | 8.7 (2.9) | 9.1 (2.4) | — | NS* |
| Height (cm) | 119.8 (12.8) | 125.1 (11.6) | 145.4 (16.6) | <.001† |
| Growth rate (cm/y) | 4.7 (1.4) | 4.8 (1.3) | — | NS* |
| SES | 43.4 (9.6) | 46.2 (12.0) | 42.8 (8.7) | — |

* TS vs GHD-ISS; † TS and GHD-ISS vs controls. Values are mean (SD).

The controls were matched with the clinical groups for age and socioeconomic status. SDS indicates standard deviation score; SES, socioeconomic status.

Procedures

After informed consent had been obtained and within 24 hours of her first GH injection, each girl underwent a baseline assessment with the Wide Range Achievement Test-Revised (WRAT-R) and the Slosson Intelligence Test (SIT). The WRAT-R provides age-standardized achievement scores in reading, spelling, and mathematics. The SIT provides an age-standardized measure of verbal intelligence. One parent (typically the mother) completed the Child Behavior Checklist (CBCL). The CBCL provides an age- and sex-standardized assessment of a child's social competence and behavior problems. Each girl who was treated with GH therapy and the parent who participated at baseline were reassessed annually by using the same battery. The girls in the control group and their parents were tested at baseline only. The tests were administered at each medical center by specially trained nurse coordinators, as described previously.¹¹

Analyses

Height data, IQ, and achievement and CBCL standard scores were analyzed by using analysis of variance (ANOVA) for baseline group comparisons. A general linear model for repeated-measures ANOVA was performed for examining changes over time in the TS and GHD-ISS groups after the initiation of GH treatment. In addition, each group was assessed for the frequency of psychological risk factors by using an odds ratio statistic. Psychological risk in academic achievement was defined as a WRAT-R score <80, below-average IQ as a SIT score <85, reduced social competence as a CBCL score <35, and significant behavioral problems as a CBCL score >65.

RESULTS

Baseline Analyses

No significant differences between the groups in intelligence or academic achievement at baseline were seen, but there was a trend toward lower mathematics performance in the TS group ($P = .09$) (Table 2). On the CBCL Social Competence Scale, the parents of the girls in the TS and GHD-ISS groups reported that their children had significantly fewer friends ($P = .04$) and engaged in significantly fewer activities ($P = .05$) than did the parents of the control subjects. The TS and GHD-ISS groups also were reported to have significantly more internalizing behavior problems ($P = .01$) and social problems ($P < .006$) on the CBCL than were the control subjects. The groups did not differ significantly in attention or externalizing problems.

Changes Over 3 Years

Increased growth rates and increased height percentiles were observed in both clinical groups after 3 years of GH therapy. The growth spurt was greatest in both groups in the first year of treatment and they grew less over time ($P < .001$), but not less than at baseline. Height percentiles increased significantly in both groups over the course of GH treatment ($P < .001$), and

the TS group, which was the shorter group before treatment, remained the shorter group after treatment.

General linear model for repeated-measures ANOVA analyses indicated no significant changes in mean IQ or achievement. Social competence improved over time in the clinical groups as a whole, but the improvement was attributable to reported school improvements in the GHD-ISS group only. Significant linear reductions were noted in both the TS and the GHD-ISS groups in internalizing behavior problems ($F = 15.1$, $P < .001$) after GH treatment, but the TS group had fewer internalizing behavior problems both before and after GH treatment than did the GHD-ISS group. Significant decreases in specific CBCL subscales such as Social Problems ($F = 5.43$, $P = .002$), Attention ($F = 6.02$, $P = .001$), and Withdrawal ($F = 3.32$, $P = .02$) after GH therapy were seen in both groups (Table 3).

Psychological Risk Before and After GH Treatment

Almost twice the proportion of girls in the TS (11/22 [50%]) and GHD-ISS (13/25 [52%]) groups as in the control group (7/25 [28%]) had at least one psychological risk factor at baseline (odds ratio, 2.68). In the TS group, 6 (27%) were having learning problems in mathematics, and 7 (32%) had significant social interaction problems. Only 2 had both academic and behavioral problems. After GH treatment 4 (18%) of the girls with TS were no longer at risk, 7 (32%) remained at risk, and 1 (5%) became at risk. Ten girls (45%) in the TS group never had a psychological risk factor. Similarly in the GHD group, 6 girls (46%) were no longer at risk after GH treatment, 1 (8%) remained at risk, 2 (15%) became at risk, and 4 (31%) were never at risk. In contrast, 1 girl with ISS (8%) with a risk factor before GH treatment was not at risk after GH therapy, 5 (42%) remained at

TABLE 2. Selected Baseline Psychological Measures

| | TS (<i>n</i> = 22) | GHD-ISS (<i>n</i> = 25) | Control Subjects (<i>n</i> = 25) | <i>P</i> |
|-------------|------------------------|-----------------------------|--------------------------------------|----------|
| SIT IQ | 102.1 (11.2) | 104.6 (14.8) | 108.6 (16.7) | NS |
| WRAT-R | | | | |
| Reading | 98.0 (15.0) | 105.1 (17.6) | 98.0 (15.5) | NS |
| Spelling | 95.4 (19.3) | 98.7 (20.9) | 99.6 (15.3) | NS |
| Mathematics | 89.7 (15.7) | 101.8 (21.6) | 99.4 (20.1) | .09 |
| CBCL | | | | |
| Activities | 49.3 (6.6) | 48.1 (6.9) | 53.8 (10.3) | .05 |
| Social | 47.0 (8.8) | 46.0 (8.8) | 52.7 (11.0) | .006 |
| School | 46.2 (7.4) | 45.6 (9.6) | 49.4 (13.2) | NS |
| Internal | 50.6 (9.6) | 56.2 (12.9) | 47.0 (9.4) | .01 |
| External | 47.2 (9.1) | 51.5 (12.3) | 46.6 (9.6) | NS |

Values are mean (SD).

TABLE 3. Behavioral Changes Over 3 Years of GH Treatment

| Behavior Problems | Mean CBCL Subscale Score | | | | Effect Within Groups (F) | P* |
|--------------------|--------------------------|--------|--------|--------|--------------------------|------|
| | Baseline | Year 1 | Year 2 | Year 3 | | |
| Internalizing | | | | | 15.1 | .001 |
| TS | 51 | 46 | 45 | 44 | | |
| GHD-ISS | 57 | 54 | 50 | 52 | | |
| Social Problems | | | | | 5.43 | .002 |
| TS | 59.5 | 57.0 | 56.3 | 55.0 | | |
| GHD-ISS | 60.1 | 57.5 | 56.3 | 56.7 | | |
| Attention Problems | | | | | 6.02 | .001 |
| TS | 56.6 | 54.4 | 53.6 | 53.6 | | |
| GHD-ISS | 58.6 | 57.5 | 56.3 | 56.0 | | |
| Withdrawal | | | | | 3.32 | .02 |
| TS | 53.9 | 53.1 | 54.1 | 53.1 | | |
| GHD-ISS | 57.4 | 54.4 | 52.9 | 53.0 | | |

* Year 3 vs baseline. General linear model for repeated-measures ANOVA found significant effects on all measures within the groups, but did not find significant treatment effects between the groups.

risk, 2 (17%) became at risk, and 4 (33%) were never at risk.

DISCUSSION

Our findings support earlier reports that have described girls with TS as being vulnerable to psychological problems. At diagnosis, half of our TS group had at least one risk factor that warranted additional psychological assessment or prompt clinical intervention. Significant problems in academic achievement, especially in mathematics, and poor social interactions were evident and indicate a need for multidisciplinary management in the comprehensive care of these children. As Rovet notes, even subtle cognitive deficits may affect learning aptitude, may persist in adulthood, and may have a detrimental effect on the person's quality of life.⁶ We agree that girls with TS should be screened by psychoeducational specialists before they enter school and throughout their formal schooling to ensure proper educational placement and remediation. We also endorse the recommendations of McCauley and colleagues that the social skill functioning in girls with TS be monitored.⁷ Because poor peer relationships may result from difficulty in reading social cues and in knowing how to interact with others, the timely intervention of behavioral programs to improve socialization skills may make it easier for these girls to form more satisfying friendships. Finally, our findings suggest that girls with conditions other than TS who are referred for GH therapy may be at a greater risk for psychological problems than was believed previously. In fact, in most of the areas measured, the girls in the GHD and ISS groups had more psychological problems than did those in the TS group. More studies that focus on girls who are referred for GH therapy are needed to advance our understanding of their treatment needs.

In summary, our findings substantiate earlier reports that GH treatment increases the growth rate and the height in girls with TS and also may be associated with positive behavioral changes, but the specific role that GH treatment plays in this improvement remains unclear. The improved body image and greater self-esteem that result from increased height is one possible explanation, and the behav-

ioral and affective changes secondary to biochemical alterations of brain function are an interesting, but unsubstantiated, possibility. Additional study will help us better understand hormonal and neurobehavioral interactions and will also guide our treatment of girls with TS.

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