Decreased growth hormone response to growth hormone-releasing hormone in Turner's syndrome: Relation to body weight and adiposity

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Abstract. A decreased growth hormone response to various secretagogues has been described in Turner's syndrome, but the mechanisms responsible for this decrease are unknown. Seventeen prepubertal girls with Turner's syndrome (age 6.4 to 15.7 years; height −0.2 to −5.4 so, bone age −3.7 to −0.3 so; weight 93 to 169% of ideal body weight) underwent a stimulation test with GHRH (0.5 µg/kg). Plasma GH and prolactin were measured by radioimmunoassay from −30 to +120 min and insulin-like growth factor-I at time 0. These values were compared with those observed in lean children with constitutional short stature. Peak plasma GH after GHRH was 17.0±3.6 µg/l (mean±SEM), significantly lower (p<0.001) than in the short lean children (39.2±5.1 µg/l). In Turner's syndrome patients, the peak GH value was negatively correlated with the percentage of ideal body weight (r = −0.58, p<0.02) and of body fat (r = −0.59, p<0.02). Plasma prolactin levels in Turner's syndrome did not rise after GHRH and showed a normal circadian variation, from 8.0±1.0 µg/l at 08.30 h to 5.0±0.7 µg/l at 11.00 h (mean±SEM). Mean (±SEM) baseline plasma insulin-like growth factor-I concentrations was 0.88±0.14 kU/l, higher than in the short lean children (0.49±0.08 kU/l, p<0.05). We conclude that the decreased GH response to GHRH of girls with Turner's syndrome is related, at least in part, to their excess body weight and fat and is associated with higher IGF-I levels than in short lean children.

Girls with Turner's syndrome have abnormal growth patterns and short final stature (1). The mechanisms responsible for their slow growth remain unknown, but probably involve some resistance of the growth plate to the action of growth hormone or insulin-like growth factor-I (IGF-I) (2). Although severe GH deficiency is rare in Turner's syndrome, subtle abnormalities of GH secretion have been described: patients older than 9 years have decreased spontaneous night-time and 24-h plasma GH levels and decreased GH response to classic stimulation tests (3-4). The GH response to GH-releasing hormone administration has recently been shown to be decreased as well (5,6). As we and others have shown that children and adults with idiopathic obesity have a blunted GH response to GHRH (7-11), and as Turner's syndrome girls tend to be overweight for height, a phenomenon that increases with age (1), we hypothesized that the obesity of these patients should be taken into account in interpreting their GH response to GHRH.

Patients and Methods

Seventeen girls with Turner's syndrome were studied. Their clinical and biological characteristics are summarized in Table 1. Chronological age ranged from 6.4 to 15.7 years (mean 11.1); bone age expressed in so for chronological age ranged from −3.7 to −0.3 (mean −1.7); height ranged from −0.2 to −5.4 so below the mean for age (mean −3.1) according to the standards of Tanner (12); weight expressed as % of the 50th centile of weight for height age (ideal body weight) ranged from 93 to 169% (mean 122%).

All patients were prepubertal (Tanner stage I for breast and pubic hair development), except one girl with
XO/XX mosaicism who had breast stage II. None had received estrogens, androgens or GH before the study. The controls consisted of a previously described group of 12 prepubertal children with constitutional short stature (13). The body weight of these children was 87-100% of ideal body weight and they are therefore hereafter referred to as short lean children; their mean age was 10.6±0.8 years, similar to that of the girls with Turner's syndrome in the present study (Table 1).

The patients were admitted at 08.00 h after an overnight fast. At 08.30 h, a butterfly needle was placed in a forearm vein and a saline solution was started. At 09.00 h an iv bolus of 0.5 μg/kg GHRH 1-44-NH2 (Somatorenline®, Labaz-Sanofi, Brussels, Belgium) was given. Blood was withdrawn at -30, 0, 15, 30, 60, 120 min for GH and PRL determinations. Samples for IGF-I determinations were taken at time 0 min. The protocol was approved by the Ethical Committee of the School of Medicine of the Free University of Brussels. The purpose of the study was explained to the parents and to the patients and informed consent was obtained.

Plasma GH and PRL levels were determined by RIA using kits purchased from Pharmacia (Sweden) and Serono (Switzerland), respectively. Plasma IGF-I levels were measured by RIA after acid-ethanol extraction (to remove the interference of IGF binding proteins), as previously described (7). The sensitivity of the RIAs was 1 μg/l for GH, 0.5 μg/l for PRL, and 0.1 kU/l for IGF-I. Mid-curve intra- and inter-assay coefficients of variation were 5 and 6%, 4 and 12%, and 10 and 15% for GH, PRL and IGF-I, respectively. Bone age was assessed by the method of Greulich & Pyle (14). The percentage of body fat was calculated by the equation of Mellits & Cheek (15). Comparisons between groups were performed by the Mann-Whitney U-test. Correlations between variables were analysed by linear regression. A probability of less than 0.05 was considered significant. In the table and in Fig. 1, the data are summarized as means ±SEM.

Results

Fig. 1 shows that, in girls with Turner's syndrome, the mean plasma GH levels 15 min after GHRH administration was 13.8±3.4 μg/l, significantly lower (p<0.001) than in control children (29.4±2.8 μg/l). The mean maximal plasma GH levels after GHRH in Turner's syndrome was 17.0±3.6 μg/l, significantly lower (p<0.001) than in short lean children, 39.2±5.1 μg/l (13). The peak plasma GH levels after GHRH in Turner's syndrome was negatively correlated with % ideal body weight (r=-0.58, p<0.02, Fig. 2) and with % body fat (r=-0.59, p<0.02). Plasma PRL levels in Turner's syndrome decreased from 8.0±1.0 μg/l at 08.00 h to 5.0±0.7 μg/l at 11.00 h, a reflection of its normal diurnal variation, and did not vary acutely after GHRH (not shown). Baseline plasma IGF-I concentration in Turner's syndrome was 0.88±0.10 kU/l (N=8, Table 1), significantly higher (p<0.05) than the value observed in short lean children (0.49±0.08 kU/l; N=11).

Fig. 2

Correlation between percentage of ideal body weight (IBW) and peak plasma GH during GHRH testing in girls with Turner's syndrome (r=-0.58, p<0.02).
Discussion

Girls with Turner’s syndrome have a blunted GH response to GHRH which is, at least in part, related to their excess body weight and body fat. This finding is similar to previous reports in obese children (7-9) and obese adults (10,11). The mechanisms responsible for the decreased response to GHRH in human obesity are complex: in obese children, a slight increase in circulating IGF-I concentrations has been described and it has been suggested that increased IGF-I levels may reduce GH secretion either directly at the level of the pituitary or indirectly through increased somatostatin release from the hypothalamus (7-9). In obese adults, however, circulating IGF-I levels are not elevated, suggesting that other factors play a role in the decreased GH responsiveness to GHRH associated with obesity: free fatty acids, glucose and insulin have been proposed as peripheral metabolic signals that may lead to the decreased GH response to GHRH observed in obese adults (10).

The normal basal PRL levels and the lack of an acute increase in PRL after GHRH in Turner’s syndrome suggest that the decreased GH responsiveness to GHRH of these patients is not due to a primary GHRH deficiency: we (13) and others (16) have shown that such an increase in PRL after GHRH is a hallmark of children with hypothalamic GHRH deficiency, although its precise mechanism remains unknown (17).

Plasma IGF-I concentrations in prepubertal girls with Turner’s syndrome have previously been found to be similar to those of prepubertal girls of normal height (18,19). In the present study, we compared the values of girls with Turner’s syndrome with those of a group of prepubertal chil-

Table 1.
Characteristics of the study population.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Chronological age (years)</th>
<th>Bone age (sd)</th>
<th>Height (sd)</th>
<th>Weight (% ideal body weight)</th>
<th>Body fat (%)</th>
<th>GH/GHRH (peak) (µg/l)</th>
<th>IGF-I (kU/l)</th>
<th>Karyotype</th>
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<td>93</td>
<td>-*</td>
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<td>32.4</td>
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Mean 11.1 ± 0.7
± sem 1.8 ± 0.3
± 0.3 ± 0.1
± 0.3 ± 0.08

* This patient was too short to calculate body fat according to Mellis & Cheek (15).
**p<0.05 and ***p<0.001 vs corresponding value in short lean children.
dren with a similar degree of shortness who had no abnormality of pituitary function and who were lean (13): mean plasma IGF-I levels were higher in Turner’s than in short lean children in the present sample as well as in our other two recent studies (20,21); these higher IGF-I levels in Turner’s syndrome may be induced by the hyperinsulinemia which has been reported in this condition (22) and/or may be a reflection of the putative end-organ resistance to IGF-I (2). At later ages, IGF-I levels in Turner’s syndrome become lower than normal, probably as a consequence of estrogen deficiency (18,19).

The degree of obesity of girls with Turner’s syndrome is variable. In the present sample, mean body weight was 121.9% of ideal body weight, whereas in the obese children we previously reported (7) it was 147% of ideal body weight. This may explain, at least in part, the fact that the GH responsiveness to GHRH is less blunted in the former than in the latter (peak GH 49 and 32% of that observed in the short lean children, respectively); it may also account for the fact that plasma IGF-I levels, even though they were higher in Turner’s syndrome than in short lean children, were not as high as those observed in children with idiopathic obesity (7).

The importance of obesity in the regulation of GH secretion and action in Turner’s syndrome is also suggested by the fact that GH treatment of short, overweight patients with Turner’s syndrome results in supraphysiological plasma IGF-I levels (20), a phenomenon not seen in short lean children (21) and consistent with the greater sensitivity of obese individuals to the IGF-I stimulating effect of exogenous GH (23).

It has been suggested that the abnormalities of GH secretion observed in Turner’s syndrome were related to estrogen deficiency. Schober et al. (6) have, however, shown that estrogen treatment does not modify the GH response to GHRH in Turner’s syndrome, suggesting that estrogens act on GH secretion through suprapituitary mechanisms; they also concluded that the abnormality of body weight and adiposity should be taken into account when GH values are evaluated in Turner’s syndrome.

In summary, we found that girls with Turner’s syndrome have decreased GH responses to GHRH and increased plasma IGF-I concentrations compared with short lean prepubertal children. The GH response to GHRH is inversely correlated with the degree of overweight and with the amount of body fat. In conclusion, among the many factors influencing GH secretion and action, obesity should be taken into account in studies of girls with Turner’s syndrome.

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