The usefulness of the combined growth hormone (GH)-releasing hormone and arginine stimulation test in the diagnosis of radiation-induced GH deficiency is dependent on the post-irradiation time interval


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The diagnostic usefulness of the insulin tolerance test (ITT) in patients with radiation-induced GH deficiency (GHD) is well established, whereas that of the combined GHRH plus arginine stimulation test (AST) is unproven. Both tests were undertaken in 49 adult survivors (aged 16–53.7 yr), who were previously irradiated for nonpituitary brain tumors or leukemia, and 33 age-, gender-, and BMI-matched controls. The aims of the study were to examine the impact of the time interval after irradiation on the pattern of GH responsiveness to the two provocative tests and to establish the role of the GHRH + AST in the diagnosis of radiation-induced GHD.

The median (range) peak GH responses to either test were significantly lower (P < 0.0001) in the patients [GHRH + AST, 19.9 (range, 2.7–103.5) μg/liter; ITT, 5 (0.2–34.8) μg/liter] than in normals [GHRH + AST, 55 (5.7–173.5) μg/liter; ITT, 23.8 (4.2–80) μg/liter]. In patients and normal controls, the median peak GH response to the GHRH + AST was significantly greater (P < 0.0001) than the response to the ITT. However, the ratio of the peak GH response to the GHRH + AST over that achieved with the ITT (discordancy ratio) was significantly higher (P = 0.007) in the patients (median, 3.45; range, 0.8–53.5) compared with normals (median, 2; range, 0.34–18.6), consistent with dominant hypothalamic damage and relatively preserved somatotroph responsiveness.

The peak GH response to the ITT fell significantly within 5 yr of irradiation with little further change over the subsequent 10 yr. In contrast, the peak GH response to the GHRH + AST barely changed within 5 yr of irradiation but subsequently declined significantly over the next 10 yr. Thus, the evolution of change in GH responsiveness to the two different stimuli over time was markedly different, resulting in a significantly raised discordancy ratio of 6 within the first 5 post-irradiation years, which then normalized over the next 10 yr. The peak GH responses to the GHRH + AST and the discordancy ratio were negatively correlated with the time interval after irradiation (r = −0.40, P = 0.0037; and r = −0.4, P = 0.0046, respectively).

On a practical clinical level, the discordancy between the GH test results was important; 50% of those classified as severely GH-deficient patients by the ITT were judged normal or only GH insufficient by the GHRH + AST.

In conclusion, these findings suggest that hypothalamic dysfunction occurs early and somatotroph dysfunction occurs late, following radiation damage to the hypothalamic-pituitary axis. This time dependency of somatotroph dysfunction may reflect either secondary somatotroph atrophy due to hypothalamic GHRH deficiency or delayed direct radiation-induced damage to the pituitary gland. The high false-negative diagnosis rate for severe GHD makes the GHRH + AST an unreliable test in clinical practice when GH status is explored in the early years after cranial irradiation with the intention to treat. (J Clin Endocrinol Metab 88: 95–102, 2003)

CRANIAL IRRADIATION IS a potent cause of hypopituitarism, the severity of which is both dose- and time-dependent (1, 2). The hypothalamus is believed to be more radiosensitive than the anterior pituitary (3–6), and GH deficiency (GHD) is usually the first and frequently the only manifestation of radiation-induced hypopituitarism (7–10). With the increase in childhood cancer survival rates, radiation-induced hypothalamic-pituitary (h-p) dysfunction has become a frequent cause of isolated GHD in both children and the adult survivors (11, 12). Under these circumstances (isolated GHD), two GH provocative tests are generally required to make the diagnosis with certainty (13). Furthermore, the usefulness of measuring surrogate markers of GH status, such as IGF-I and IGFBP-3 levels, in patients with radiation-induced GHD has been questioned (14–17).

It is generally agreed that the insulin tolerance test (ITT) is the most reliable GH provocative test for the diagnosis of radiation-induced GHD (13, 18–20). A variety of other GH provocative tests, however, are used either as an alternative to the ITT or as a second test. More recently, it has been claimed that the combination of arginine plus GHRH may provide an excellent test for the diagnosis of GHD. The work of Aimaretti et al. (21) has validated the test in patients with presumed direct pituitary damage from tumor and/or surgery; well defined cut-off levels for both normal individuals and GHD patients have been provided. The question remains, however, how might the combined GHRH plus arginine stimulation test (AST) perform in a patient with primary hypothalamic disease? In this context, patients with radiation-induced GHD, in whom, the primary site of radiation damage is believed to be within the hypothalamus (3,
may well exhibit false positive responses to the combined GHRH + AST. We have, therefore, performed a comparative study of the GHRH + AST vs. the ITT in a large cohort of cranially irradiated patients with a putative diagnosis of GHD to examine the usefulness of the former test in such patients.

**Patients and Methods**

**Patients**

Adult patients who fulfilled the study entry criteria were identified in the late effects clinic. Patients were invited if they had a history of receiving cranial irradiation for leukemia or a brain tumor anatomically distinct from the h-p region, and if they had been shown to be free from tumor recurrence, or any other medical condition that might influence their GH/IGF-I status. The study was approved by the South Manchester Local Research Ethics Committee, and informed consent was obtained from all patients before testing.

The patient cohort consisted of 49 adult patients (16 females and 33 males) aged 16–53.7 yr (median, 23 yr). The body mass index (BMI) ranged from 16.9–38.8 kg/m² (median, 24 kg/m²). Forty-seven patients had received whole brain irradiation and/or focal irradiation. Two patients had received total body irradiation (TBI) only (Table 1). All patients with leukemia or lymphoma and four patients with brain tumors had also received combination chemotherapy.

Of the 49 patients, 36 (13 females and 24 males) had received their cranial irradiation during childhood, at an age of 1.3–15.5 yr (median, 9 yr). The remaining 13 (3 females and 10 males) were irradiated at an age of 16–49 yr (median, 23.5 yr). Patients were tested 1.5–29.4 yr (median, 11.7 yr) after irradiation.

An age-, gender-, and BMI-matched healthy control group was studied for comparative purposes. This consisted of 33 subjects (9 females and 24 males), aged 17.3–56.5 yr (median, 22.8 yr), with a BMI that ranged from 16.3–28.9 kg/m² (median, 22.9 kg/m²).

Among the 49 patients, 1 had partial ACTH deficiency, and 1 had partial TSH deficiency; 4 patients had primary hypothyroidism; 2 females had chemotherapy-induced ovarian failure; and 11 males had partial TSH deficiency; 4 patients had primary hypothyroidism; 2 females had chemotherapy-induced ovarian failure; and 11 males had partial TSH deficiency; 4 patients had primary hypothyroidism; 2 females had chemotherapy-induced ovarian failure; and 11 males had partial TSH deficiency; 4 patients had primary hypothyroidism; 2 females had chemotherapy-induced ovarian failure; and 11 males had partial TSH deficiency; 4 patients had primary hypothyroidism; 2 females had chemotherapy-induced ovarian failure; and 11 males had partial TSH deficiency; 4 patients had primary hypothyroidism; 2 females had chemotherapy-induced ovarian failure; and 11 males had partial TSH deficiency; 4 patients had primary hypothyroidism; 2 females had chemotherapy-induced ovarian failure; and 11 males had partial TSH deficiency; 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Discordancy ratio

The discordancy ratio is defined as the ratio of the peak GH response to the combined GHRH + AST over that achieved in response to the ITT. It is perceived that the combined test measures pituitary integrity (somatotroph responsiveness), whereas the ITT tests hypothalamic integrity. Thus, a high ratio would be expected if hypothalamic damage predominates (with preserved somatotroph responsiveness), whereas a normal ratio is expected if pituitary damage and/or atrophy contribute significantly to the subnormal GH status. The discordancy ratio has no diagnostic value for an individual patient, and a very wide range may be observed in both normals as well as patients. However, in this study it was estimated to evaluate the relative contribution of hypothalamic vs. pituitary damage in cranially-irradiated patients in relation to the time interval after irradiation.

Statistics

The data were expressed as mean ± SD if normally distributed, or as median and ranges if the data were skewed. Simple correlations to examine the relationship between variables were performed using the Spearman rank order correlation test. Differences between groups were examined by the t test if the data were normally distributed (parametric) or the Mann-Whitney rank-sum test if the data were nonparametric (skewed). Kruskal-Wallis one-way ANOVA was used to compare normally distributed multiple independent groups, whereas ANOVA on ranks was used if the data were skewed.

Backward stepwise multiple linear regression was used to examine the relationship between the independent variables [length of follow-up (i.e. time interval between irradiation and testing), age at irradiation, gender (male = 1, female = 2), and BED] and the dependent variable (peak GH response to the GHRH + AST and the ITT or the discordancy ratio). Log transformation of skewed data was undertaken to produce or approximate a normal distribution before running the linear regression analysis. The validity of the regression analysis was verified by standard tests; both the normality and the homoscedasticity test had to be passed, and the test power achieved was 0.8 or greater. P value less than 0.05 was taken as significant.

Results

The combined GHRH + AST vs. ITT

The peak GH responses to the combined GHRH + AST and the ITT were significantly correlated (r = 0.64; P = 0.00; Fig. 1). The peak GH responses to the combined GHRH + AST were significantly (P < 0.0001) higher than those achieved with the ITT both in normals and the patients’ cohort (Fig. 2). The peak GH responses to the GHRH + AST and the ITT were significantly (P < 0.0001) lower than those achieved in normal individuals (Fig. 2).

There was a moderate but significant negative correlation (r = −0.40; P = 0.0037) between the peak GH responses to the combined GHRH + AST and the time interval (years) after irradiation (Fig. 3), but no correlation with the age at irradiation or the BED. In contrast, a weak negative correlation was observed between the peak GH responses to the ITT and the BED (r = −0.35; P = 0.014), but no correlation with the time interval after irradiation or the age at irradiation.

Backward stepwise multiple linear regression analysis showed that the best fit model to predict the log peak GH responses to the GHRH + AST and the ITT was dependent on the time after irradiation (P = 0.0026 and 0.026, respectively).

The diagnostic sensitivity of the combined GHRH + AST was compared with that of the ITT. Sixteen patients were diagnosed with severe GHD based on their responses to the ITT, of whom only 8 (50%) were classified severely GHD with the combined GHRH + AST (concordant results); in the other 8 (50%), the results were either consistent with GHI or
were normal. A similar pattern of discordancy was seen in 7 of 10 patients (70%) who were GHI to the ITT but normal to the combined test (Table 2).

**Discordancy ratio**

The discordancy ratio was significantly \(P = 0.007\) higher in patients (median, 3.45; range, 0.8–53.5) than in normals (median, 2; range, 0.34–18.6). A significant negative correlation was found between the discordancy ratio and the time interval after irradiation \(r = -0.40; P = 0.0046\). In contrast, the discordancy ratio positively correlated with the BED \(r = 0.4; P = 0.004\) and the PRL level \(r = 0.61; P = 0.00\).

Backward stepwise multiple linear regression analysis showed that the best-fit model to predict the log discordancy ratio was dependent only on the time interval after irradiation \(P = 0.001\).

Subgroup analysis of the peak GH responses to both tests in relation to the time interval after irradiation showed that the decline in peak GH responses to the combined GHRH + AST lags behind that seen with the ITT; the latter, being mostly affected in the first 5 yr, with little and only insignificant decline thereafter, contrasted with the late decline in the GH response to the combined test that mostly (and significantly) occurred after the first 5 yr of radiotherapy (Table 3 and Fig. 4). The combined effects of these changes resulted in a much higher increase \(P < 0.05\) in the discordancy ratio in the first 5 yr compared with normals and also with those patients who had received their radiotherapy more than 5 yr previously. The ratio subsequently declined but remained slightly but insignificantly \(P > 0.05\) higher than normals.

The discordancy ratio in patients with either normal peak GH responses to both tests or severe GHD to both tests remains slightly elevated but not significantly higher than normals (data not presented).

### Table 2. Classification of patients according to GH status determined by their responses to the combined GHRH + AST and the ITT using defined cut-off levels

<table>
<thead>
<tr>
<th></th>
<th>GHRH + AST</th>
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</thead>
<tbody>
<tr>
<td>GHD (&lt;9)</td>
<td>8a</td>
</tr>
<tr>
<td>GHI (9–16.5)</td>
<td>6</td>
</tr>
<tr>
<td>Normal (&gt;16.5)</td>
<td>2</td>
</tr>
</tbody>
</table>

Data represent the number of patients within the defined GH cut-off levels (μg/liter; shown in parentheses) for both tests.

**PRL**

The PRL levels in patients (median, 186.5 μg/liter; range, 67–1327 μg/liter) were not significantly different \(P = 0.8\) compared with normals (median, 205 μg/liter; range, 116–528 μg/liter). The PRL levels were significantly higher \(P = 0.005\) in those who received a BED greater than 45 Gy (median, 213 μg/liter; range, 67–1327 μg/liter) compared with those who received a lower BED (median, 116 μg/liter; range, 90–522 μg/liter). The PRL level was significantly lower \(P = 0.004\) in patients with severe GHD to both tests (median, 139 μg/liter; range, 67–749 μg/liter) compared with those who were severely GHD to the ITT only (median, 58 μg/liter; range, 189–1327 μg/liter).

The PRL levels significantly correlated with the BED \(r = 0.41; P = 0.003\) and with the discordancy ratio \(r = 0.61; P = 0.0001\).

### IGF-I

Age- and gender-corrected IGF-I sd scores were used for comparison. The mean IGF-I sd score \((-1.085 ± 1.35)\) was significantly lower in the patients \(P = 0.0013\) than in the normal controls \((-0.16 ± 1.0)\). Patients with severe GHD to both the ITT and the GHRH + AST (concordant GHD) had the lowest IGF-I sd score, but there was no significant difference from the IGF-I sd score of other patient groups (Fig. 5). There was no correlation between the IGF-I sd score and the peak GH responses to either test.

### Discussion

GHD is a frequent complication of radiation damage to the h-p axis. Its incidence and severity are related to the intensity of the radiation schedule and the duration of follow-up (1, 2). There is now robust evidence that radiation damage to the h-p axis is primarily hypothalamic (1, 26). It is the hypothalamic site of damage that is believed to be responsible for the phenomenon of radiation-induced GH neurosecretory dysfunction (4, 27–29), which occurs after certain radiation doses. In addition, previous studies using a GHRH stimulation test demonstrated the preservation of somatotroph responsiveness in the presence of severe GHD in irradiated patients (3, 6, 22, 23).

Intensive irradiation, as may be used for nasopharyngeal carcinoma for example, can produce direct pituitary damage that can lead to attenuation in the anterior pituitary hormone responses to direct pituitary stimulation (26, 30–32). However, little is known about the evolution of somatotroph...
dysfunction after h-p axis irradiation with less intensive schedules such as those used for nonpituitary brain tumors and leukemia. Furthermore, assessment of somatotroph function has been traditionally performed using GHRH stimulation. The GH response to the latter test is highly variable, and a failed response may be seen in normal individuals. This variability has been attributed to the level of somatostatinergic tone at the time of testing (33–35). Therefore, the addition of arginine, which is believed to inhibit hypothalamic somatostatin release (36–38), allows the GHRH to maximally explore somatotroph reserve with very little variability. The attraction of using a combination of arginine with GHRH is emphasized by the well defined cut-off levels in normals and GHD patients with excellent reproducibility (21, 39). For these reasons, we have used this test firstly, to accurately assess somatotroph function/integrity after cranial irradiation, and secondly, to explore its usefulness in the diagnosis of radiation-induced GHD in comparison with the “gold standard” ITT.

The most important findings in this study were probably those that reflected the impact of length of follow-up (time since irradiation) on the pattern of peak GH responses to both tests. As expected, the peak GH responses to both tests in patients were significantly lower than those achieved in the normal controls. Although there was a significant correlation between the peak GH responses to both tests in patients, the attenuation in the GH responses to the ITT was more severe compared with that seen with the combined test; the latter produced GH responses that were on average 3.5-fold higher than the ITT in the patients, compared with GH responses that were 2-fold higher than the ITT in normal individuals. This resulted in the significantly higher discordancy ratio in the patients compared with that seen in normals. This indicates relative preservation of somatotroph function or a predominance of hypothalamic dysfunction.

Across the whole cohort, there was a significant negative correlation between the peak GH response to the combined test and the time interval after irradiation, indicating that somatotroph dysfunction is time-dependent and progressive; a similar relationship was not found with the ITT. Consequently, there was a significant and gradual decline in the discordancy ratio with longer follow-up periods. Backward regression analysis using the age at irradiation, sex, BED, and the time since irradiation (follow-up period) as the independent variables showed that the variability in the linear regression model for the log peak GH responses to the ITT, the GHRH + AST, or the discordancy ratio can be mostly predicted by the time since irradiation.

Progressive attenuation in peak GH responses to the ITT with time is not a new finding. However, the tempo of time-dependent reduction in the GH responses to both tests is different; the ITT is mostly affected in the early years after irradiation, whereas the combined GHRH + AST (or somatostroph function) is mostly affected in subsequent years. To highlight these temporal changes, patients were divided into four subgroups according to the length of follow-up. All groups had received similar median BED. In the first 5 yr after irradiation, there was only a minimal and insignificant drop in the peak GH response to the combined test compared with normals. Later on, however, the decline in GH response was substantial. In contrast, the peak GH response to the ITT was reduced considerably in the first 5 yr after irradiation with little further reduction subsequently. The combined effects of these evolutionary patterns resulted in a much higher discordancy ratio in the first 5 yr after irradiation compared with normals and with those patients who had been irradiated more than 5 yr previously. Subsequently, the discordancy ratio declined but remained slightly but insignificantly higher than in normals. Thus, the data suggest that, whereas hypothalamic damage is the primary pathology, somatotroph dysfunction is a late secondary outcome. Our findings are in accord with previous studies that showed impaired GH responses to the ITT within 3 months of irradiation, and certainly in the first 12 months (8, 40), and a very high incidence of GHD that may reach its maximum in the first 5 yr after cranial irradiation in childhood (2).

The presence of a high discordancy ratio is a reflection of predominant hypothalamic damage, whereas a normalized ratio indicates the presence of established pituitary dysfunction. Interestingly, there was a significant positive correlation between the discordancy ratio and the serum PRL level. A high PRL level is a sign of hypothalamic damage (1, 41) and, therefore, this correlation provides additional but indirect evidence that an elevated discordancy ratio reflects hypothalamic damage.

Delayed somatotroph dysfunction can be attributed to time-dependent secondary atrophy as a consequence of diminished hypothalamic release of the (trophic) GHRH and/or delayed direct radiation-induced damage of the somatotroph. There is some circumstantial evidence to support both mechanisms. In support of the former mechanism, previous studies have shown reversibility of somatotroph re-

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**TABLE 3.** Age at testing and XRT, BMI, the BED of XRT, PRL level, GH responses to provocative stimuli, and the discordancy ratio of the patient groups in relation to the time interval since irradiation (median and ranges)

<table>
<thead>
<tr>
<th>Time interval since XRT</th>
<th>&lt;5 yr (n = 11)</th>
<th>5–10 yr (n = 10)</th>
<th>10–15 yr (n = 14)</th>
<th>&gt;15 yr (n = 14)</th>
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<tr>
<td>Age at testing (yr)</td>
<td>22.7 (16–53.7)</td>
<td>20.25 (16.5–48.6)</td>
<td>22.5 (16–52)</td>
<td>29.75 (18–37.3)</td>
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<tr>
<td>Age at XRT (yr)</td>
<td>20.7 (11.8–49)</td>
<td>12.25 (5–42.6)</td>
<td>9.5 (1.3–41)</td>
<td>7.5 (1.5–11.5)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>21.9 (17.1–31)</td>
<td>21.7 (18.6–34.3)</td>
<td>23.45 (16.9–38.8)</td>
<td>25.7 (18.6–38.7)</td>
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<td>BED (Gy)</td>
<td>58.3 (30.2–103.3)</td>
<td>58.3 (23–73.3)</td>
<td>58.3 (28–90)</td>
<td>52.19 (27.25–66.8)</td>
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<td>PRL (mU/liter)</td>
<td>190 (117–912)</td>
<td>234 (107–801)</td>
<td>174 (90–1327)</td>
<td>168.5 (67–749)</td>
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<td>GH peak to ITT (µg/liter)</td>
<td>4.8 (1.6–20)</td>
<td>4.8 (0.2–20.5)</td>
<td>6.2 (0.8–29.3)</td>
<td>4.0 (0.4–34.8)</td>
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<td>Discordancy ratio</td>
<td>6.05 (2.1–22.6)</td>
<td>4.32 (1.48–53.5)</td>
<td>3.39 (0.8–14.13)</td>
<td>2.34 (0.85–14.1)</td>
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### Footnotes
- **Darzy et al.** GHRH + AST and Radiation-Induced GHD in J Clin Endocrinol Metab, January 2003, 88(1):95–102
- **Downloaded from**: https://academic.oup.com/jcem/article-abstract/88/1/95/2846010 by guest on 22 December 2018
sponsiveness in patients with GHRH deficiency after prolonged treatment with daily GHRH injections (42), although similar studies have not been performed in irradiated patients. Arguments for the second mechanism are derived from our own findings and some earlier literature; normally, one would expect to see a persistently elevated PRL level in the cranially irradiated patients due to continuous diminished inhibition of PRL secretion by the damaged hypothalamus. We could not demonstrate this in our cohort of patients. The suggestion of direct radiation-induced pituitary damage is supported by the observation that the PRL levels were significantly lower in patients with severe GHD to both tests, i.e. patients with established somatotroph unresponsiveness/atrophy, who had the longest follow-up period of 18.2 ± 6.0 yr, compared with those who were severely GHD to the ITT only and had a follow-up period of 10 ± 10.6 yr. This is in accord with the findings of Littley et al. (43) who had previously demonstrated that an early rise in PRL levels after irradiation for pituitary adenomas was followed by a gradual decline in subsequent years. These observations suggest that direct radiation-induced damage of the pituitary gland evolves slowly with time and might contribute to the delayed onset of somatotroph dysfunction.

FIG. 4. Box and whisker plots representing the peak GH responses to the ITT (A), the GHRH + AST (B), and the discordancy ratio (C) in normals and patients according to the time interval since irradiation. The lower boundary of the box indicates the 25th percentile, a line within the box marks the median, and the upper boundary of the box indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles, respectively. P values are derived from comparison of each patient group with the normal control group. Note that BED was not different among the groups (Table 3).
It is generally agreed that adult GH replacement therapy should be considered in patients with severe GHD in the appropriate clinical context (44). Thus, analysis of the pattern of the individual GH responses to the combined GHRH + AST, compared with the actual GH status defined by the GH response to an ITT, is more relevant to clinical practice. In our cohort, 16 patients (33%) were diagnosed severely GHD to the ITT. Only eight of them (50%) showed responses consistent with severe GHD to the combined test (concordant results), whereas the other eight (50%) showed GH responses to the combined test that classified them as either GHI or normal (discordant results). Similarly, 70% of patients who were GHI to the ITT showed normal responses to the combined test. The latter is more relevant to pediatric practice in which GH replacement is considered for less severe forms of GHD. A 50–70% discordancy rate is probably an underestimate, given the fact that our patients had mean follow-up periods in excess of 10 yr. On the basis of our findings, it is anticipated that the discordancy rate (false negative diagnosis) will be extremely high if patients are tested in the early years after irradiation. Thus, the combined test may be clinically misleading. However, in contrast to its low sensitivity, the combined GHRH + AST has a very high specificity (90%) for the diagnosis of severe GHD if appropriate cut-off levels for a particular GH assay are used. More recently, a much lower peak GH response (<5 μg/liter) to the combined GHRH + AST was recommended to maximize specificity for the diagnosis of severe GHD (45). Applying this cut-off level to the results of our patient cohort gives rise to an even greater degree of discordancy, further substantiating the poor utility of this test in the irradiated patients.

The IGF-I levels were significantly lower in patients compared with the normal controls. However, and in accord with previous studies (14–17), IGF-I SD scores were not discriminating; IGF-I SD score less than −2 was only found in 3 of the 8 patients with discordant severe GHD. Of the 8 patients with discordant GH responses, none of the 10 patients with GHI defined by the ITT, and 5 of the 23 patients with normal GH status to both tests. The latter finding is of interest and may indicate that some patients with apparently normal GH status may actually have GH neurosecretory dysfunction. In addition, the mean IGF-I SD score was lower in patients with severe GHD to both tests (discordant GHD) compared with other patient groups, although the difference did not reach statistical significance, possibly due to the small sample size (type 2 error). This suggests that patients with established somatotroph atrophy may have the most severe degree of GHD. It is, however, premature to draw this conclusion without studying physiological GH secretion over 24 h in these patients.

In conclusion, this study has demonstrated that hypothalamic dysfunction is an early complication of radiation damage to the h-p axis, whereas somatotroph dysfunction, characterized by attenuation of GH responses to the combined GHRH + AST is a late complication that mostly occurs more than 5 yr after irradiation. This time dependency of somatotroph dysfunction can be attributed to either secondary somatotroph atrophy due to hypothalamic GHRH deficiency or to delayed and slowly evolving direct radiation-induced damage to the pituitary gland. In addition, the high false negative diagnosis rate makes the combined GHRH + AST an unreliable test in clinical practice when GH status is explored in the early years after cranial irradiation with the intention to treat. It is, however, reasonable to conclude that a failed GH response to the combined GHRH + AST reflects the presence of radiation-induced GHD reliably.

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