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Serum Levels of Insulin-Like Growth Factor I in 152 Patients with Growth Hormone Deficiency, Aged 19–82 Years, in Relation to Those in Healthy Subjects*

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ABSTRACT

Serum insulin-like growth factor I (IGF-I) levels within normal range for age have been reported to be common in adults with GH deficiency (GHD). Therefore, serum IGF-I levels were determined in 152 consecutive patients (71 women and 81 men) with evidence of hypothalamic-pituitary disorders or previous cranial radiation, who fulfilled the presently used criteria for GHD *i.e.* peak GH response below 3 μg/L at stimulation test. Patients treated for acromegaly were excluded. Forty-three patients, aged 19–63 yr, had childhood onset GHD, and 109, aged 23–82 yr, had adult-onset GHD. Their IGF-I levels were expressed in SD scores in relation to normal reference values based on 448 healthy subjects, aged 20–96 yr (247 women and 201 men). In healthy subjects a linear inverse correlation, without gender difference, was found between logarithmic transformed IGF-I levels and age ($r = -0.774$; $P < 0.001$). In contrast, no age dependency was found in GHD patients. All patients with childhood-onset GHD had IGF-I values below −2 SD, significantly lower than those in adult-onset GHD patients (−6.2 ± 0.3 *vs.* −3.2 ± 0.2 SD score; $P < 0.001$). In patients with adult-onset GHD, 34% of the IGF-I levels were within normal range, increasing to 40% in the subgroup above 60 yr of age, in whom 86% were diagnosed with hypothalamic-pituitary tumors. Normal IGF-I was more common in men than in women, but no difference was observed between patients with panhypopituitarism and those with partial pituitary insufficiency. High frequencies of IGF-I levels within the normal range were found in GHD patients with pituitary tumors (20 of 57 nonsecreting pituitary adenomas, 5 of 15 prolactinomas, 6 of 12 Cushing's disease, and 4 of 25 craniopharyngiomas), but in only 2 of 43 patients with GHD due to other causes.

In conclusion, an IGF-I level below −2 SD seems to be of diagnostic value in GHD with onset in childhood or early adulthood, whereas values within normal range are common in patients over 60 yr of age, especially those with pituitary tumors. The outcome of GH replacement therapy may reveal whether the addition of IGF-I as a diagnostic criterion is of predictive value in older patients. (*J Clin Endocrinol Metab* **84:** 2013–2019, 1999)

THE BENEFITS of GH treatment in adults with GH deficiency (GHD) are now well recognized (1), even though the criteria for deciding which patients to treat are not yet fully established. Adult GHD is divided into two categories, childhood-onset and adult-onset GHD, and heterogeneity between the entities has been demonstrated before and during GH treatment (2). The diagnosis of GHD in children is partly based on auxology, including height velocity. In patients with suspected GHD acquired during adult life, this obvious criterion is absent, and the diagnosis has to be based on the patient's history, *i.e.* evidence of hypothalamic-pituitary disease or previous cranial irradiation and biochemical measurements. Serum insulin-like growth factor I (IGF-I) is GH dependent (3) and has been addressed as a marker for GHD (4–7). The usefulness of IGF-I estimation in serum in the diagnosis of adult GHD is, however, a matter of contention (8).

With attention to differences in etiology and age at onset of GHD, the aim of the present study was to further explore the diagnostic value of serum IGF-I determinations. Moreover, the value of GH replacement therapy is now being explored in elderly patients defined as having GH-deficiency. Accordingly, an extended reference range with healthy older subjects was needed for the comparison of IGF-I values.

Subjects and Methods

Healthy subjects

The normal range of IGF-I was determined in sera from 448 apparently healthy subjects (247 women and 201 men), aged 20–96 yr, with an extended number of subjects of older ages compared to that previously described (9). Thus, the reference range was composed of 229 blood donors, aged 20–71 yr, 128 other healthy subjects, aged 24–84 yr, and 91 healthy elderly individuals, aged 79–96 yr. The subjects were equally distributed in each decade with respect to number and gender, except for the ages above 80 yr, where the women were in majority, probably reflecting the normal sex ratio at that age (Table 1). The healthy subjects were recruited among hospital staff and by an advertisement in the local paper. The elderly individuals were also recruited by information at a pensioners' meeting and enquiries to the home service organization (collected by A.-L.M.). None had diabetes or other endocrine diseases or had received estrogen therapy. The elderly subjects were living independently at home. Height and weight were registered in 349 subjects. In women, the mean height was 162.4 cm (range, 140–178 cm), the mean weight was 64.9 kg (range, 43–100 kg), and the mean body mass index (BMI) was 24.6 kg/m^2 (range, 17.1–37.5 kg/m^2). Corre-

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sponding values in men were 177.7 cm (range, 161–195 cm), 80.0 kg (range, 58–115 kg), and 25.3 kg/m^2 (range, 18.8–32.9 kg/m^2).

GHD patients

One hundred and fifty-two consecutive patients, aged 19–82 yr, with GHD of various etiologies participated in this study (Table 2). Patients with acromegaly were excluded. Etiologies referred to as "others" were hypophysitis (n = 3), intrauterine infection (n = 1), meningoencephalitis (n = 1), intracranial hemorrhage (n = 1), congenital lues (n = 1), surgery, not due to pituitary tumor (n = 1), neurosarcoidosis (n = 1), and meningioma (n = 1). One hundred and seven patients had panhypopituitarism. In 43 patients (20 females and 23 males), GHD was diagnosed before 20 yr of age, *i.e.* childhood onset, whereas 109 patients (51 females and 58 males) acquired their GHD as adults. All patients received regular adequate substitution therapy for pituitary insufficiency, except for GHD. Cushing's disease was treated and inactive, and the prolactinoma patients had normal PRL levels due to either previous treatment or current medication with dopamine receptor agonists. Twenty patients with childhood-onset GHD had received previous GH treatment withdrawn several years before this study. GHD was biochemically defined according to Consensus Guidelines 1997 (10) as a peak GH response below 3 μg/L to insulin-induced hypoglycemia. When an insulin test was contraindicated, especially in elderly patients, arginine or glucagon stimulation tests were performed, with the same cut-off value for GH. In addition, diurnal GH profiles, sampled every 20 min throughout 24 h using the continuous withdrawal technique (11), were determined in 58 patients, none with values above 3 μg/L. In fact, in this patient group, only 4 patients had GH values above 2 μg/L in stimulation tests or diurnal profiles.

TABLE 1. Reference values of serum IGF-I concentrations in relation to age

Age (yr)	n (women/men)	IGF-I (μg/L)		
		−2 SD	Mean	+2 SD
20–29	59 (34/25)	147	256	444
30–39	53 (23/30)	125	218	379
40–49	47 (22/25)	107	186	323
50–59	60 (31/29)	91	158	275
60–69	58 (28/30)	78	135	235
70–79	69 (36/33)	66	115	200
80–89	88 (61/27)	56	98	171
90–96	14 (12/2)	48	84	145

Values are the geometrical mean ± 2 SD. Data represent values in each decade based on the regression analysis performed when all (n = 448) subjects were included.

Assays

IGF-I was determined in serum or plasma by RIA after separation of IGFs from IGF-binding proteins (IGFBPs) by acid-ethanol extraction and cryoprecipitation. To minimize interaction of IGFBPs, des(1–3)-IGF-I was used as the ligand, and high affinity antibodies were employed (12). The detection limit was 8 μg/L. Including the extraction step, the intraassay coefficients of variation (CVs) were 4.3% (at 149 μg/L), 3.9% (at 217 μg/L), and 8.6% (at 526 μg/L), whereas the interassay CVs were 9.6% (at 146 μg/L), 7.7% (at 209 μg/L), and 8.8% (at 317 μg/L), respectively.

Two different assays have over time been used to determine serum or plasma levels of GH. First, a RIA with polyclonal antibodies was used, and the separation was performed with a second antibody (13). The detection limit was 0.2 μg/L, and the intra- and interassay CVs were 3.0% and 10%, respectively. Later a commercially available kit, a two-site fluoroimmunometric GH assay based on two monoclonal antibodies, was used (DELFIA hGH, Wallac, Inc., Turku, Finland) with a detection limit of 0.04 μg/L. The intra- and interassay CVs were 5.0% and 8%, respectively. Standards used in the different assays were both calibrated against the WHO First International Reference Preparation 80/505. The equation for the linear regression line comparing the two methods is: $y = 1.01x + 0.32$ (r = 0.97), where x is the DELFIA, and y is the RIA.

Study protocol

Serum samples for the determination of IGF-I were taken in the morning after an overnight fast in all subjects, except for the blood donors, who had had their regular morning meal. However, levels of IGF-I seem to be unaffected by meals, as in most studies (14–17) no diurnal variation has been found in healthy subjects.

The ethics committee of the Karolinska Hospital approved the study, and the subjects gave informed consent.

Statistics

Results are presented as the mean ± SEM if not otherwise stated. Unpaired t test or Mann-Whitney rank sum test assessed the comparability of two groups. Correlation coefficients were determined from simple and multiple least linear regression analysis. The nonnormally distributed serum IGF-I values were log transformed before analysis to more closely approximate a Gaussian distribution. The age-dependent reference range for serum IGF-I concentrations was calculated by simple least linear regression analysis; the regression line represents the mean, and the prediction interval is represented by ±2 SD, where SD is the residual deviation of the regression errors. The value of acceptance for statistical significance was set at $P < 0.05$. Statistical analyses were performed using SigmaStat for Windows (Jandel Scientific GmbH, Erkarth, Germany).

TABLE 2. Characteristics of 152 patients defined as having GH deficiency

	Childhood onset		Adult onset		Total (n = 152)
	Females (n = 20)	Males (n = 23)	Females (n = 51)	Males (n = 58)	
Age (yr)	33 (19–63)	34 (19–54)	51 (26–74)	58 (23–82)	49 ± 1
Ht (cm)	163 (146–182)	171 (157–191)	164 (155–174)	178 (165–192)	171 ± 1
Wt (kg)	71 (41–121)	78 (48–114)	72 (49–120)	86 (56–133)	78 ± 1
BMI (kg/m^2)	26.7 (16.6–42.3)	26.4 (18.8–38.3)	26.8 (17.9–48.1)	27.1 (15.2–46.8)	26.9 ± 0.5
Etiology					
Nonsecreting pituitary adenoma	2	3	17	35	57
Craniopharyngioma	4	7	8	6	25
Prolactinoma	2	0	8	5	15
Cushing's disease	1	0	9	2	12
Idiopathic	4	8	1	3	16
Irradiation, not due to pituitary tumor	4	1	1	3	9
Trauma, Sheehan's syndrome	2	0	5	1	8
Other	3	2	1	4	10
Panhypopituitarism/partial pituitary insufficiency	12/8	18/5	29/22	48/10	107/45

Data are the mean ± SEM or the number of patients; within *parentheses* are ranges.

Results

Serum IGF-I in healthy subjects

Serum levels of IGF-I in healthy subjects were age dependent, declining with age (r = −0.774; $P < 0.001$; n = 448; Fig. 1 and Table 1). A logarithmic scale was used on the *y*-axis because the transformed data of IGF-I approximated a normal distribution more closely. The equation for the regression line in women was: ^{10}log [IGF-I (μg/L)] = 2.585 − 0.00715 × age (yr) (r = −0.768; $P < 0.001$); the equation in men was: ^{10}log [IGF-I (μg/L)] = 2.566 − 0.00647 × age (yr) (r = −0.775; $P < 0.001$). No significant difference was found between the slopes. Thus, an age-dependent reference range (geometrical mean ± 2 SD) in healthy subjects, independent of gender, was calculated based on the equation for the regression line in all subjects: ^{10}log [IGF-I (μg/L)] = 2.581 − 0.00693 × age (yr), with SD = 0.120. The variation (SD) was constant for ages between 20–80 yr, although it increased at ages above 80 yr. However, a common regression line for all ages was calculated. Thus, the prediction interval became slightly larger in ages younger than 80 yr than if the subjects older than 80 yr were excluded.

A positive correlation was found between serum levels of IGF-I and body height in women and men separately (r = 0.511; $P < 0.001$ and r = 0.386; $P < 0.001$, respectively) and together (r = 0.452; $P < 0.001$; Table 3). In multiple regression analysis, when age was taken into account, the relation was still significant if women and men were calculated together. However, only a small increase in the r^2 value, from 0.516 to 0.533, was observed in the multivariate correlation compared to the univariate correlation between IGF-I and age. Body weight correlated positively to IGF-I in men (r = 0.224; $P = 0.007$) and in all subjects (r = 0.241; $P < 0.001$; Table 3), but the relation disappeared when age was taken into account. Exclusively in women an inverse relationship was found between IGF-I and BMI (r = −0.161; $P = 0.021$), which was also lost when age was considered.

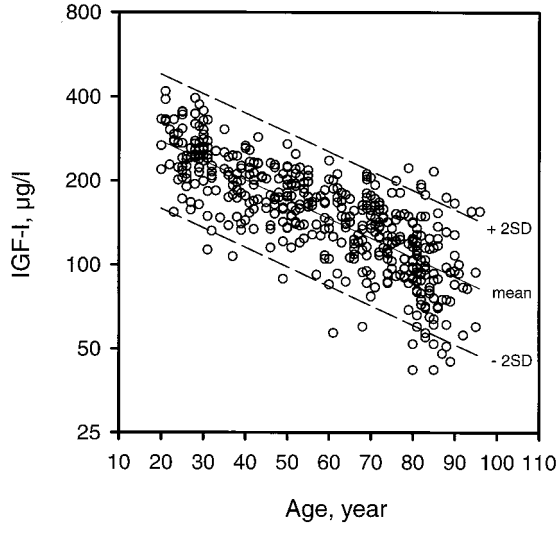

FIG. 1. Serum IGF-I concentrations (on a logarithmic scale) in relation to age in healthy subjects (n = 448). Normal reference values (the geometrical mean ± 2 SD) are indicated by *solid* and *dashed lines*, respectively.

TABLE 3. Simple linear correlation coefficients between IGF-I and age, body height, body weight, and BMI, respectively, in patients with GH deficiency and in healthy subjects registered with height and weight

	Age	Ht	Wt	BMI
All patients (n = 152)				
IGF-I	0.134	0.421[a]	0.240[b]	0.036
Childhood onset (n = 43)				
IGF-I	−0.217	0.325[c]	0.171	0.025
Adult onset (n = 109)				
IGF-I	−0.039	0.405[a]	0.225[c]	0.024
Adult onset, IGF-I <−2SD (n = 72)				
IGF-I	−0.109	0.423[a]	0.222	0.032
Adult onset, IGF-I >−2SD (n = 37)				
IGF-I	−0.726[a]	0.126	0.316	0.251
Healthy subjects (n = 349)				
IGF-I	−0.718[a]	0.452[a]	0.241[a]	−0.088

[a] $P < 0.001$.
[b] $P < 0.01$.
[c] $P < 0.05$.

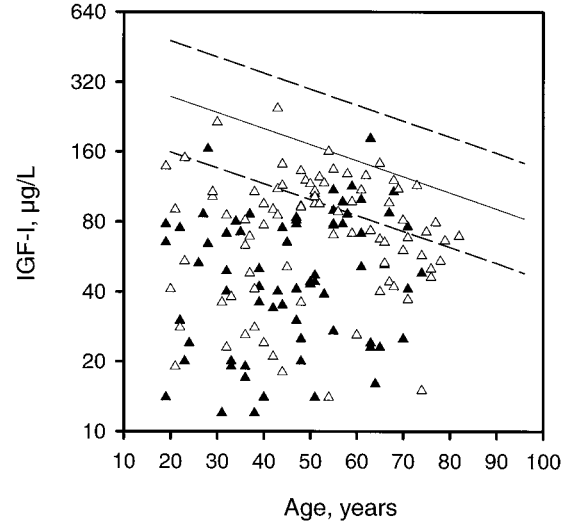

FIG. 2. Serum IGF-I concentrations in GHD patients. ▲, Women (n = 71); △, men (n = 81). The normal range for age (the geometrical mean ± 2 SD) is indicated.

Serum IGF-I in GHD patients

Compared to the age-dependent reference range in healthy subjects, the majority (76%) of GHD patients had IGF-I values below −2 SD (Fig. 2). When all patients were included, no correlation was found between levels of IGF-I and age (r = 0.134; $P = 0.100$). The number of patients with IGF-I values within the normal range increased with increasing age: 4% for ages 20–39 yr (n = 48), 30% for ages 40–59 yr (n = 61), and 40% for ages above 60 yr (n = 43). Mean IGF-I was lower in women than in men (57 ± 4 μg/L *vs.* 81 ± 5 μg/L; $P < 0.001$), also when corrected for age; IGF-I-SD was −5.0 ± 0.3 in women and −3.3 ± 0.3 in men ($P < 0.001$). For all patients (n = 152), only five had serum IGF-I levels above −2 SD for 20-yr-old healthy individuals (159 μg/L); one had craniopharyngioma, two had nonsecreting pituitary adenomas, one had Cushing's disease, and one had idiopathic GHD.

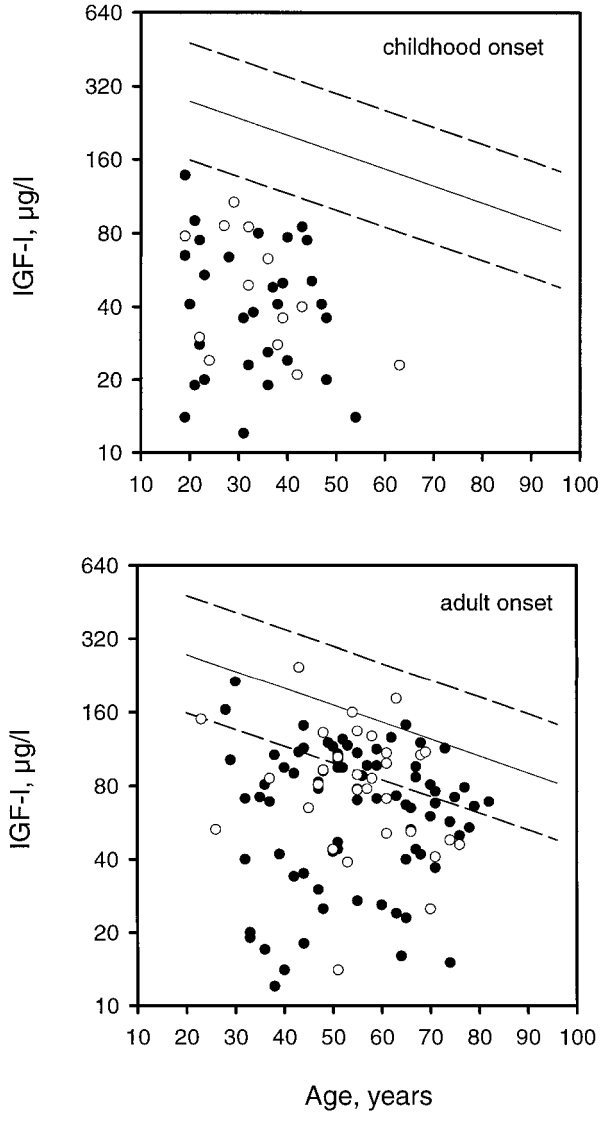

FIG. 3. Serum IGF-I concentrations in patients with childhood-onset GHD and adult-onset GHD, respectively. ●, Patients with panhypopituitarism; ○, patients with partial pituitary insufficiency. The normal range for age (the geometrical mean ± 2 SD) is indicated.

All patients with childhood-onset GHD had IGF-I levels below −2 SD (Fig. 3A). In contrast, among patients with adult-onset GHD, 34% had IGF-I levels within the normal range for age (Fig. 3B). The mean IGF-I was 48 ± 4 μg/L in childhood-onset GHD patients and 78 ± 4 μg/L in adult-onset GHD patients ($P < 0.001$), corresponding to −6.2 ± 0.3 and −3.2 ± 0.2 SD scores ($P < 0.001$), respectively, so a difference in age was also observed (34 ± 2 *vs.* 55 ± 1 yr; $P < 0.001$). In both groups, patients with panhypopituitarism were in the majority (70%). Similar age-corrected IGF-I levels were found in panhypopituitarism and partial pituitary insufficiency; the mean IGF-I SD score was −6.4 ± 0.4 *vs.* −5.8 ± 0.5 ($P = 0.443$) in patients with childhood-onset GHD and −3.5 ± 0.3 *vs.* −2.6 ± 0.4 ($P = 0.075$) in adult-onset GHD patients.

The patients were divided according to the etiology of GHD (Fig. 4). IGF-I concentrations were within the normal range in 4 of 25 (16%) craniopharyngiomas, in 20 of 57 (35%) nonsecreting pituitary adenomas, in 5 of 15 (33%) prolactinomas, and in 6 of 12 (50%) Cushing's disease patients. In patients with idiopathic GHD, corresponding values were 1 of 16 (6%), and in patients treated with radiation, not due to pituitary tumor, corresponding values were 1 in 9 (11%). All patients with Sheehan's syndrome (n = 5) as well as all patients with GHD due to trauma (n = 3) had IGF-I values below −2 SD for age in healthy subjects. In patients with GHD of other etiologies (n = 10), all had IGF-I values below −2 SD.

Table 3 summarizes relationships between IGF-I and age, body height, body weight, and BMI in the GHD patients. Despite previous GH treatment in 20 of 43 patients with childhood-onset GHD, they were shorter than those with adult-onset GHD (167.4 ± 1.5 *vs.* 172.0 ± 0.9 cm; $P = 0.009$), mainly due to differences in height among the males. Body weight and BMI did not differ significantly between childhood-onset GHD and adult-onset GHD. Positive correlations were found between levels of IGF-I and body height. A relationship to body weight was observed in the whole GHD patient group and in the subgroup with adult-onset GHD, which disappeared when body height was added in the regression analysis. No correlation was found between serum levels of IGF-I and BMI. In the subgroup of patients who acquired GHD as adults and had IGF-I levels within normal range, a significant negative correlation to age was found, probably due to the age-related cut-off value at −2 SD. In this group, levels of IGF-I were not related to body height, body weight, or BMI. Furthermore, in adult-onset GHD patients, no difference in BMI was found between those with IGF-I levels within the normal range and those with subnormal serum IGF-I concentrations (27.2 ± 0.7 *vs.* 26.7 ± 0.7).

Discussion

In the present study, serum concentrations of IGF-I were below the normal range for age in 76% of adult patients fulfilling presently used criteria for GH deficiency, *i.e.* evidence of hypothalamic-pituitary disease or previous cranial irradiation and peak GH response below 3 μg/L on a stimulation test (10). This is in line with the assumption that approximately 80% of adult patients with severe GHD are expected to have serum IGF-I levels more than 2 SD below age-related means by extrapolating the findings in pediatric endocrinology (1). The percentage of GHD patients with IGF-I levels within the normal range increased with age as previously observed (7, 18). Although only 4% of the adult GHD patients below 40 yr had IGF-I levels within the normal range, the percentage increased to 40% in those older than 60 yr. This pattern can be attributed to the age-dependent decrease in healthy subjects, and the age independence of serum IGF-I found in GHD patients. In the selection of patients considered to have reduced GH production, few serum markers are available. Apart from IGF-I and the acid-labile subunit, both of which are regulated by GH at the transcriptional level in human liver (19, 20), only IGFBP-3 and IGFBP-5 are reported to be GH dependent (21, 22).

The finding of normal IGF-I levels in patients assumed to have GHD due to GH unresponsiveness in a provocation test raises several questions. Firstly, is the GH peak level after

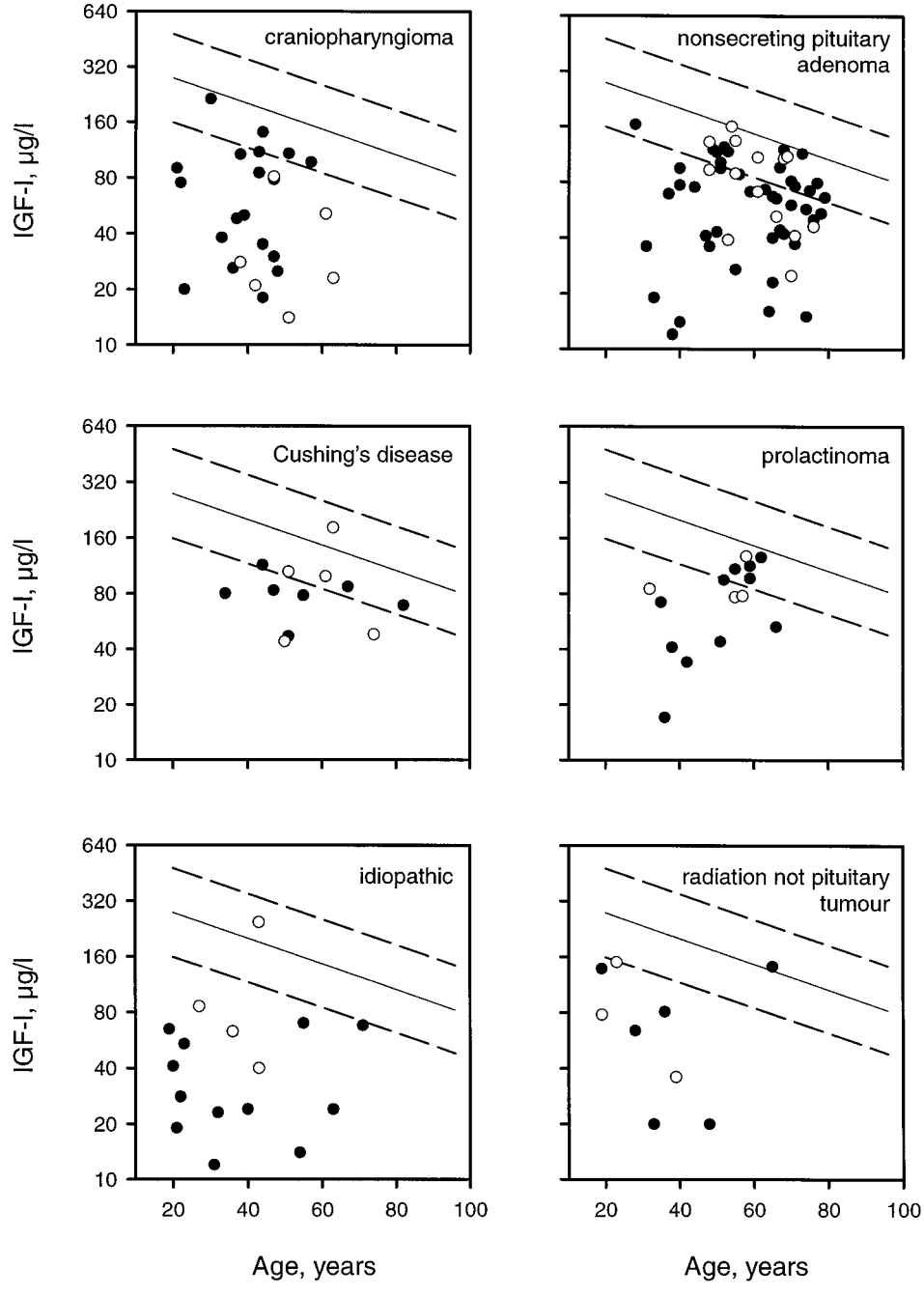

FIG. 4. Serum IGF-I concentrations in patients with GHD due to different hypothalamic-pituitary tumors (craniopharyngioma, nonsecreting pituitary adenoma, Cushing's disease, and prolactinoma), idiopathic GHD, and GHD due to radiation (not due to hypothalamic-pituitary tumors). ●, Panhypopituitarism; ○, partial pituitary insufficiency. The normal range for age (the geometrical mean ± 2 SD) is indicated.

provocation test a reliable index of endogenous GH production? The GH responses to insulin-induced hypoglycemia and arginine have low reproducibility (23, 24), and age-related reference values are lacking. GH secretion as well as the peak response to most provocative tests decrease with increasing age in healthy individuals (25). The peak GH response to arginine was below 3 µg/L in about 20% of healthy subjects over 60 yr of age (18). Thus, at least 20% of our older patients with pituitary disorders could have remaining GH production, which fulfills their requirements for age and results in a normal IGF-I SD score. Secondly, a cause of the discrepancy between GH response and IGF-I levels is obesity, which is characterized by normal serum IGF-I in the presence of low GH secretion (8). However, no difference in BMI was found between patients with normal and subnormal IGF-I levels, and as in the healthy subjects, no correlation was found between IGF-I and BMI. This is in contrast to the report by Svensson *et al.* (7), who found higher BMI values in patients with IGF-I levels within normal range. Thirdly, can another hormone replace GH as stimulator of IGF-I expression? Insulin, which is suggested to be involved in GH-regulated IGF-I production (26), was not measured in the present study, but no relationship was found between insulin and IGF-I in a previous study based on 23 GHD patients (9). Yet in a larger material of adult GHD patients, IGF-I correlated positively to insulin (7). It is not known whether GHD

patients with normal and subnormal IGF-I levels in relation to age differ concerning GH-dependent signs such as body composition. The observation of similar IGF-I SD scores in partial and total hypopituitarism indicates that the finding of normal IGF-I values among GHD patients is probably real. GH is assumed to be the first anterior pituitary hormone to be affected by surgery, radiation, or mass lesion of the hypothalamic-pituitary region. Thus, in multiple pituitary insufficiency, the probability of GHD being present is high (8).

The overlap of IGF-I levels between GHD patients and healthy subjects in our study was less pronounced than that observed in previous studies, in which IGF-I values within normal range were found in 48–70% of GHD patients with mainly adult onset of disease (4–7). Moreover, in GHD patients over 60 yr of age, the percentage of those with normal IGF-I levels has been reported to be 2-fold higher than that in our study (18). Possible reasons for the fewer GHD patients with normal IGF-I in the present study could be the selection of healthy subjects for the reference range, the statistical analysis employed setting up the reference values, the IGF-I method, inclusion of GHD patients with childhood-onset disease, and/or the causes of GHD.

The number of individuals of different ages constituting the reference intervals is essential for improving the sensitivity and specificity of serum IGF-I levels (27). In the reference group of apparently healthy individuals, including ages from 20–96 yr, a linear inverse correlation was found between logarithmically transformed IGF-I levels and age. Thus, the normal mean value of serum IGF-I in a 90-yr-old individual corresponds to −4 SD of healthy young adults, 20 yr of age. A decline in serum IGF-I in adults with increasing age is well known from previous studies, based on smaller number of subjects and/or individuals less than 70 yr of age (9, 28–32). The use of logarithmically transformed data when evaluating the normal reference values was primarily due to nonnormal distribution of serum IGF-I values in the healthy subjects. The transformation results in a more narrow variation around the mean at low levels of IGF-I compared to high levels of IGF-I in terms of arithmetic values. As calculated from the regression analysis, the normal range for age constitutes an extensive variation around the mean; the −2 SD value is 57% of the mean, and the mean is 57% of the +2 SD value. For ages above 80 yr, the individual variations are greater, which might be due to varying levels of nutritional status and physical activity (33). Although apparently healthy, some were more physically active than others, and undernutrition cannot be ruled out among the elderly. No significant gender difference was found between the slopes of the regression lines, which is in agreement with the reports by Nyström *et al.* (32) and Juul *et al.* (30), but in contrast to those by Yamamoto *et al.* (28), Landin-Wilhelmsson *et al.* (29), and Kitano *et al.* (31). This discrepancy might be explained by a larger group in the present study and, as suggested by Nyström *et al.* (32), a wider range of age. Other explanations could be that the healthy individuals in the present study were not recruited from a population registry, and the analysis of IGF-I was performed by a method minimizing the interference of IGFBPs (12). This could be of importance in GHD patients, because they have high IGFBP-1/IGF-I ratios compared to healthy subjects (9).

Serum IGF-I levels were below −2 SD in all of our patients with childhood-onset GHD, where the original selection of children was based on retarded growth. When adult patients with childhood-onset GHD were reevaluated in a previous study, 7% had normal IGF-I levels (1). In both studies the included patients were selected by GH stimulation tests, with the exception of higher GH cut-off values in the study by De Boer *et al.* (1). Thus, in the present study serum IGF-I concentrations completely separated GHD patients with childhood-onset disease from healthy subjects and can be recommended for use in the reevaluation of the GHD diagnosis made during childhood. In contrast, IGF-I levels above −2 SD were found in 34% of the patients with adult-onset GHD; five were even within the normal range for young healthy adults. The mean IGF-I SD score was significantly higher in the adult-onset GHD patients, as previously observed by others (2, 8). In addition, a gender difference was found, with normal IGF-I levels being more common in men than in women with GHD.

The differences in IGF-I levels between childhood- and adult-onset GHD as well as the finding of fewer patients with normal IGF-I than in previous studies might be influenced by the underlying etiologies. Idiopathic hypopituitarism and craniopharyngioma dominated among childhood-onset GHD, whereas pituitary tumors, such as nonsecreting pituitary adenoma, prolactinoma, and Cushing's disease, dominated in patients with adult-onset GHD. In fact, the majority (86%) of patients over 60 yr of age, in which 40% had normal IGF-I levels, were diagnosed with hypothalamic-pituitary tumors. It cannot be excluded that apart from GH, an additional pituitary factor can regulate IGF-I expression.

In conclusion, in the identification of adult patients suitable for GH replacement therapy, measurement of serum IGF-I can be used as a diagnostic tool in younger adult patients. However, the IGF-I SD score seems less reliable in elderly patients, especially in patients with hypothalamic-pituitary tumors, partly due to the age-dependent decrease in IGF-I levels in healthy subjects. Nevertheless, it is still the treatment outcome that could ascertain which patients are GH deficient and thus most likely to respond to and benefit from GH replacement therapy.

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