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# The Natural History of Partial Growth Hormone Deficiency in Adults: A Prospective Study on the Cardiovascular Risk and Atherosclerosis

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**Background:** Partial GH deficiency (GHD) in adults is poorly studied.

**Objective:** The objective of the study was to investigate the natural history and clinical implications of partial GHD.

**Study Design:** This was an analytical, observational, prospective, case-control study.

**Patients:** Twenty-seven hypopituitary patients (15 women, ages 20–60 yr) and 27 controls participated in the study.

**Main Outcome Measures:** Measures included GH peak after GHRH plus arginine [(GHRH+ARG), measured by immunoradiometric assay]; IGF-I (measured after ethanol extraction) z-SD score (SDS); glucose, insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels; and common carotid arteries intima-media thickness (IMT) measured periodically.

**Results:** At study entry, partial GHD patients had significantly lower IGF-I and HDL-cholesterol levels and homeostasis model assessment index than controls. During the 60 months of median follow-up, 11 patients had severe GHD (40.7%), seven normalized their GH response (25.9%), and nine showed persistently partial GHD (33.3%). Patients with developed severe GHD at baseline had similar age and body mass index and lower GH peak ($11.5 \pm 1.8$ *vs.* $14.3 \pm 1.5$ and $12.8 \pm 1.1$ $\mu$g/liter, $P = 0.008$) and IGF-I SDS ($-0.88 \pm 0.48$ *vs.* $0.15 \pm 0.58$ and $-0.42 \pm 0.78$; $P = 0.01$) than the patients with normal GH secretion or partial GHD. Severe GHD was accompanied by decreased IGF-I SDS and increased total to HDL cholesterol ratio, triglycerides, homeostasis model assessment index, and carotid intima-media thickness; normalization of GH secretion was accompanied by increased IGF-I SDS. By receiving-operator characteristic analysis, predictors of severe GHD were a baseline GH peak after GHRH+ARG of 11.5 $\mu$g/liter (sensitivity 64%, specificity 94%) and a baseline IGF-I SDS of $-0.28$ (sensitivity 91%, specificity 63%).

**Conclusions:** Of 27 patients with partial GHD after pituitary surgery, 40.7% developed severe GHD and 25.9% normalized their GH response. With the assay used, changes in the GH peak response to GHRH+ARG were accompanied by changes in the IGF-I SDS, metabolic profile, and carotid IMT. A peak GH of 11.5 $\mu$g/liter or less and IGF-I SDS $-0.28$ or less were highly predictive of delayed deterioration of GH secretion. **(*J Clin Endocrinol Metab* 91: 2191–2200, 2006)**

THE EXISTENCE OF a clinical syndrome of GH deficiency (GHD) in adults has been accepted only in recent years (1, 2). Adult GHD syndrome is characterized by abnormal body composition, reduced bone mineralization, unfavorable lipid profile, reduced cardiac performance, endothelial dysfunction, early atherosclerosis, and impaired quality of life (3, 4). These abnormalities are associated with reduced life expectancy (5–8).

Currently, GHD in adults is diagnosed by peak GH response to pharmacological stimuli such as insulin-induced hypoglycemia (ITT) or GHRH plus arginine (GHRH+ARG) test. Severe adult GHD is diagnosed by a GH peak less than 3 $\mu$g/liter to ITT or of less than 9 $\mu$g/liter to GHRH+ARG with currently available RIA or immunoradiometric assay (IRMA) methods (9). More recently, evidence is accumulating that the GH cutoffs proposed by the Growth Research Society Consensus Statement in 1998 (9) should be revised because at least two important factors affect the results: the age and body mass index (BMI) of the patients. In fact, during the so-called transition age, *i.e.* the period of transition from adolescence to adulthood between 16 and 25 yr of age (10), higher cutoff levels are required to correctly diagnose GHD: GH peak after ITT was proposed to be less than 5 $\mu$g/ liter from Clayton *et al.* (10) and less than 6.1 $\mu$g/ liter from Maghnie *et al.* (11), thus approximately twice the adult threshold. Moreover, it is well known that GH secretion decreases in obesity and thus lower cutoff levels should be applied in obese patients to avoid overestimation of GHD diagnosis. In fact, in obese hypopituitary patients both Biller *et al.* (12) and Corneli *et al.* (13) have reported that the diagnostic cutoff by the GHRH+ARG test should be lowered to 4.1–4.2 $\mu$g/liter, thus approximately half the adult threshold.

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Abbreviations: BMI, Body mass index; CI, confidence interval; CV, coefficient of variation; GHD, GH deficiency; GHRH+ARG, GHRH plus arginine; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IMT, intima-media thickness; IRMA, immunoradiometric assay; ITT, insulin-induced hypoglycemia; LDL, low-density lipoprotein; PRL, prolactin; ROC, receiving-operator characteristics; SDS, SD score.

The validity of GH cutoffs after ITT or GHRH+ARG is supported, however, by the evidence that they are correlated with clinical signs. In childhood, the peak GH cutoff to ITT to diagnose GHD was validated against the height velocity both before and after GH therapy (14). In adults, we reported that peak GH after GHRH+ARG correlated well with impaired lipid profile (15), reduced bone density (16), and reduced cardiac performance (17). The validation of these tests is essential, because both in America and Europe GH replacement is permitted only in the patients with severe GHD diagnosed on the basis of such tests.

However, the use of cut points or thresholds establishing the normal GH response to a stimulation test is arbitrary despite the correctness of all the statistical procedures. In GHD, GH secretion may not be completely absent but may rather reflect a continuum between normal and abnormal (18).

In fact, by using the GHRH+ARG test, there is a so-called gray zone that separates the normal GH response (*i.e.* $>$ 16.5 $\mu$g/liter) and the severe GHD (*i.e.* $<$ 9 $\mu$g/liter) in lean subjects: patients having such a response are generally classified as partial GHD. Partial GHD in adults is not recognized as a pathological condition. Nevertheless, adult patients with partial GHD also present some alterations in terms of increase of total and low-density lipoprotein (LDL) cholesterol levels (15), reduction of diastolic filling (at rest and at peak exercise) (17), reduction of systolic performance at peak exercise, and exercise performance (17). Murray *et al.* (19) also recently reported an increase of fat mass and a decrease of lean body mass in patients with partial GHD diagnosed by ITT. Similarly, Tauber *et al.* (20) reported an abnormal body composition in adolescents with partial GHD.

Diagnosis and clinical implications of partial GHD in adults are poorly investigated. This is a clinical issue because among patients with organic hypopituitarism, partial GHD occurs in 16% (15), 18% (16), 27% (17), or 38% (19) of patients who are not allowed to currently receive GH replacement with potential future impairment of life quality and duration. Similarly, no information is available on the natural history of partial GHD in adults.

To investigate the natural history of partial GHD in adult patients, we designed this analytical, observational, prospective, case-control study. During a median period of follow-up of 60 months, we found that one third of the patients showed persistently partial GHD, whereas the remaining patients had either deterioration (40.7%) or normalization of GH secretion (25.9%). These results indicate that prolonged follow-up with periodic GH testing is indicated in adult patients with partial GHD.

## Subjects and Methods

### *Study design*

This was an analytical, observational, prospective, case-control study to explore the natural history of partial GHD in adults. The patients underwent yearly follow-ups, whereas controls were studied at the study entry and at the same time (± 3 months) of last follow-up of the corresponding patient.

### *Inclusion criteria*

Inclusion criteria included: 1) GH peak after the GHRH+ARG test between 9.1 and 16.5 $\mu$g/liter, according to the Growth Research Society guidelines (9); 2) in the context of an organic pituitary disease; 3) follow-up of at least 24 months (24–60 months).

### *Exclusion criteria*

Exclusion criteria included: 1) present or previous concomitant diseases affecting cardiac function, such as diabetes mellitus, coronary artery diseases, or long-standing hypertension (n = 16); 2) abnormal renal and/or hepatic function (n = 3); 3) BMI above 30 kg/m$^2$ (n = 22); 4) severe GHD based on a GH peak after GHRH+ARG 9 $\mu$g/liter or less [n = 75 (9)]; and 5) normal GH reserve based on a GH peak after GHRH+ARG test greater than 16.5 $\mu$g/liter [n = 17 (9)].

### *Patients*

From January 1, 1998, to December 31, 2002, of 160 hypopituitary patients diagnosed at the Department of Molecular and Clinical Endocrinology and Oncology of the University "Federico II" of Naples, 27 patients (12 men, 15 women, aged 20–60 yr) were diagnosed to have a partial GHD because of a pituitary tumor and/or its treatment. All the patients had been previously operated on by transsphenoidal route for nonfunctioning pituitary adenoma (n = 17), meningioma (n = 3), prolactin (PRL)-secreting adenoma (n = 5), or ACTH-secreting adenoma (n = 2). None of the patients received radiotherapy. Normal residual pituitary function was found in 12 patients (44.4%), whereas deficiency of various degrees was found in the remaining 15 patients: isolated LH deficiency in six; FSH and LH deficiency in five patients; FSH, LH, and TSH deficiency in one; FSH, LH, and ACTH deficiency in one; FSH, LH, TSH, and ACTH in one; and FSH, LH, and arginine vasopressin deficiency in one. Before undergoing GH testing, the patients had to receive stable replacement therapy with L-$T_4$ (50–100 $\mu$g orally daily), cortisone acetate (25–37.5 mg/d), intranasal desmopressin (5–20 $\mu$g/d), testosterone-enanthate (250 mg im monthly) in men and transdermal estrogens associated with progesterone in premenopausal females, according to individual patients' endocrine status. Adequacy of replacement therapy was periodically assessed by measuring serum-free thyroid hormones, testosterone, urinary free cortisol and blood pressure, and serum $Na^+$ and $K^+$ measurements. At study entry, these hormonal parameters were in the normal range for age in all patients. The five patients with prolactinoma received treatment with cabergoline at doses ranging from 1 to 2.5 mg/wk. None of the patients had ever received GH treatment. Sixteen patients were nonsmokers (59.3%), five were ex-smokers, and the remaining six were mild smokers (less than 15 cigarettes per day); 12 patients had a normal weight, whereas 15 were overweight (25.3–29.7 kg/m$^2$). Patients' profiles are shown in Table 1.

### *Controls*

Of 174 healthy subjects (92 women, 82 men, aged 18–80 yr), recruited among the medical and paramedical personnel of our Department and their relatives (21), 27 were matched with the patients for age (± 1 yr) and gender and agreed to serve as controls. The protocol of the study was approved by the Ethical Committee of the "Federico II" University of Naples, and all subjects gave their informed consent to the study. Twelve controls were nonsmokers (44.4%), three were ex-smokers, and 12 were mild smokers (less than 15 cigarettes per day); 14 controls had a normal weight and 13 were overweight (25.2–27.4 kg/m$^2$). The comparison between patients and controls at study entry is shown in Table 2.

### *Study protocol*

Six to 12 months after surgery, when hypopituitarism was replaced in the subset of affected patients, the following parameters were studied: GH peak after GHRH+ARG; serum IGF-I assay and calculation of the SD score (SDS) for age and gender; glucose, insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels after an overnight fasting; and common carotid arteries intima-media thickness (IMT) by ultrasonography. The total to HDL cholesterol ratio, index of cardiovascular risk (22), the LDL cholesterol levels [by the formula:

**TABLE 1.** Profile of the 27 patients at the diagnosis of partial GHD

| Patient no., sex | Age (yr) | BMI (kg/m$^2$) | MRI findings | | | Hormone deficits | GH peak after GHRH+ARG ($\mu$g/liter) | | IGF-I z-SDS | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Tumor type | Volume (ml) | | | At diagnosis | At last follow-up | At diagnosis | At last follow-up |
| | | | | At diagnosis | At last follow-up | | | | | |
| 1. F | 20 | 27 | NFA | 220.5 | 160.8 | FSH, LH, ACTH | 10.7 | 6.5 | −1.44 | −1.89 |
| 2. F | 20 | 23.3 | NFA | 0.0 | 0.0 | LH | 12.5 | 8.8 | −0.66 | −1.00 |
| 3. F | 30 | 24.4 | NFA | 19.8 | 22.0 | FSH, LH | 11 | 4.7 | −1.00 | −2.12 |
| 4. F | 30 | 22.5 | ACTH-sec | 0.0 | 0.0 | None | 13.4 | 14.6 | −0.50 | 0.00 |
| 5. F | 32 | 25.6 | NFA | 0.0 | 0.0 | FSH, LH | 12.3 | 33.3 | −1.00 | −0.30 |
| 6. F | 33 | 26.7 | NFA | 123.9 | 139.6 | FSH, LH, TSH, ACTH | 14.1 | 7.5 | −1.50 | −2.00 |
| 7. F | 35 | 29.7 | NFA | 0.0 | 0.0 | None | 10.2 | 7.5 | −0.50 | −1.45 |
| 8. F | 40 | 27.8 | PRL-sec | 101.2 | 87.5 | None | 10.9 | 12.7 | −1.00 | −0.50 |
| 9. F | 45 | 25.6 | PRL-sec | 94.7 | 112.3 | None | 9.8 | 3.7 | −0.23 | −2.00 |
| 10. F | 50 | 27.8 | Meningioma | 0.0 | 0.0 | None | 12.6 | 30.4 | −0.25 | 0.36 |
| 11. F | 51 | 26.7 | NFA | 43.8 | 52.3 | None | 16.1 | 25.7 | 0.80 | 1.20 |
| 12. F | 52 | 21.5 | NFA | 33.8 | 43.9 | None | 15.9 | 27.9 | 1.00 | 0.95 |
| 13. F | 52 | 24.3 | NFA | 0.0 | 0.0 | None | 13.3 | 13.8 | −0.25 | 0.00 |
| 14. F | 53 | 27.7 | NFA | 0.0 | 0.0 | None | 14.4 | 13.5 | 0.50 | −0.10 |
| 15. F | 56 | 26.8 | Meningioma | 107.0 | 201.6 | None | 12.1 | 12.7 | 0.44 | 0.00 |
| 16. M | 33 | 26.7 | NFA | 0.0 | 8.8 | FSH, LH | 13.5 | 7.7 | −1.00 | −2.00 |
| 17. M | 34 | 25.8 | ACTH-sec | 0.0 | 0.0 | LH | 12.4 | 14.4 | −1.50 | −0.40 |
| 18. M | 35 | 16.1 | NFA | 38.2 | 30.1 | LH | 13.4 | 13.4 | −1.29 | 0.00 |
| 19. M | 36 | 22.3 | NFA | 35.3 | 32.9 | LH | 14.1 | 9.5 | −0.50 | −1.00 |
| 20. M | 40 | 24.2 | PRL-sec | 216.6 | 138.6 | LH | 13.8 | 21.1 | 0.50 | 0.55 |
| 21. M | 41 | 26.6 | NFA | 183.4 | 192.7 | None | 11.5 | 7.1 | −0.28 | −0.99 |
| 22. M | 43 | 25.6 | PRL-sec | 813.0 | 562.9 | FSH, LH, DI | 10 | 4.4 | −1.50 | −1.84 |
| 23. M | 47 | 24.6 | NFA | 0.0 | 0.0 | FSH, LH | 12.7 | 14.7 | −0.75 | −1.00 |
| 24. M | 48 | 24.1 | PRL-sec | 45.7 | 55.0 | LH | 15.2 | 27.8 | 0.00 | 0.30 |
| 25. M | 54 | 23.1 | NFA | 220.6 | 210.2 | FSH, LH, TSH | 9.3 | 6.1 | −1.10 | −1.88 |
| 26. M | 57 | 26.9 | meningioma | 60.9 | 65.3 | FSH, LH | 1.4.1 | 31.3 | 0.00 | 0.44 |
| 27. M | 60 | 23.3 | NFA | 0.0 | 0.0 | None | 12.2 | 13.1 | 0.55 | 0.30 |

NFA, Clinically nonfunctioning adenomas; ACTH-sec, ACTH-secreting adenoma; PRL-sec, PRL-secreting adenoma; F, female; M, male.

LDL = total cholesterol − HDL cholesterol − (triglycerides/5)] and estimate of insulin resistance by the homeostasis model assessment (HOMA) score [(23) fasting serum insulin ($\mu$U/ml) × fasting plasma glucose (mmol/liter)/22.5] were calculated. The conversion factors (milligrams per deciliter to millimoles per liter) for lipids and glucose were as follows: cholesterol, 0.02586; triglycerides, 0.01129; and glucose, 0.05551.

A study of the pituitary region by magnetic resonance imaging (1.0–1.5 T scanners, slice thickness 2–3 mm, axial, coronal and sagittal projections before and after the administration of 0.1 mmol gadolinium chelate) was performed at study entry and yearly during the follow-up in all patients to diagnose potential tumor recurrence.

In all the patients showing changes in the GH peak after GHRH+ARG during the study so that the initial classification should be changed, a second test was performed within 3 months to confirm the diagnosis of severe GHD or normal GH secretion. The metabolic profile and common carotid ultrasonography were performed at the time of the second test, when the diagnosis was confirmed.

### *Carotid ultrasonography*

Common carotid artery ultrasound imaging was carried out with a Vingmed Sound CMF 725 equipment (Horten, Norway) by means of a 7.5-MHz annular phased array transducer. Details on the technique were reported elsewhere (24, 25). Right and left carotid arteries were scanned longitudinally, 2.5 cm proximal and 1 cm distal to the bifurcation. When

**TABLE 2.** Comparison between patients and controls at study entry

| | Partial GHD patients | Controls | *P* |
|---|---|---|---|
| No. | 27 | 27 | |
| Women/men | 15/12 | 15/12 | |
| Age (yr) | 41.7 ± 11.0 | 41.8 ± 11.1 | 0.99 |
| BMI (kg/m$^2$) | 25.0 ± 2.7 | 23.8 ± 2.9 | 0.16 |
| GH peak after GHRH+ARG ($\mu$g/liter) | 12.7 ± 1.8 | 45.8 ± 16.8 | <0.0001 |
| Serum IGF-I levels ($\mu$g/liter) | 172.1 ± 24.5 | 240.4 ± 46.8 | <0.0001 |
| IGF-I SDS | −0.46 ± 0.75 | 0.38 ± 0.74 | <0.0001 |
| Total cholesterol (mmol/liter) | 4.7 ± 0.5 | 4.6 ± 0.5 | 0.4 |
| HDL cholesterol (mmol/liter) | 1.4 ± 0.2 | 1.6 ± 0.2 | 0.038 |
| LDL cholesterol (mmol/liter) | 3.0 ± 0.6 | 2.8 ± 0.6 | 0.16 |
| Total to HDL cholesterol ratio | 3.3 ± 0.6 | 3.0 ± 0.7 | 0.13 |
| Triglyceride levels (mmol/liter) | 1.1 ± 0.2 | 1.1 ± 0.2 | 0.81 |
| Fasting glucose levels (mmol/liter) | 4.7 ± 0.6 | 4.4 ± 0.4 | 0.012 |
| Fasting insulin levels (mIU/liter) | 7.0 ± 2.0 | 5.7 ± 1.9 | 0.016 |
| HOMA index | 1.5 ± 0.5 | 1.1 ± 0.5 | 0.012 |
| Right common carotid artery IMT (mm) | 0.70 ± 0.11 | 0.64 ± 0.12 | 0.055 |
| Left common carotid artery IMT (mm) | 0.71 ± 0.11 | 0.65 ± 0.12 | 0.078 |
| Mean common carotid artery IMT (mm) | 0.71 ± 0.11 | 0.65 ± 0.12 | 0.056 |

satisfactory B-mode imaging of common carotid artery wall was achieved, M-mode images were taken for several cardiac cycles to obtain the best quality measurements of IMT. Quantitative and semiquantitative indices were evaluated by echo-Doppler ultrasonography placing the sample volume (set at 75% of lumen caliber) in the middle of the vessel lumen. The variability in IMT measurement for our instrument was 0.03 mm. Our intraobserver variability for repeated measurements of carotid artery diameter is 0.01 ± 0.02 mm. The average value of IMT between right and left common carotid arteries was calculated and reported as mean IMT. Flow indices of both carotids were investigated by measuring blood systolic and diastolic peak velocities. The epidemiological data currently available indicate that a value of IMT at or above 1 mm at any age is associated with a significantly increased risk of myocardial infarction and/or cerebrovascular disease (26). Presence, location, and size of plaques were also evaluated at the level of common carotid arteries. All measurements were made by one investigator (S.Sp.) who was blind in respect to patients or controls study and to the results of GH testing in the patients.

### *Assays*

Serum GH levels were measured by IRMA using commercially available kits (HGH-CTK-IRMA; Sorin, Saluggia, Italy). The sensitivity of the assay was 0.02 μg/liter. The intra- and interassay coefficients of variation (CVs) were 4.5 and 7.9%, respectively. Plasma IGF-I was measured by IRMA after ethanol extraction using materials from Diagnostic System Laboratories Inc. (Webster, TX). The normal range in men 20 yr or younger, 21–30, 31–40, 41–50, 51–60, 61–70, and more than 70 yr old was 180–625, 118–475, 102–400, 100–306, 95–270, 88–250, and 78–200 μg/liter, respectively, whereas in women it was 151–530, 118–450, 100–390, 96–288, 90–250, 82–200, 68–188 μg/liter, respectively. The sensitivity of the assay was 0.8 μg/liter. The intraassay CVs were 3.4, 3.0, and 1.5% for low, medium, and high points of the standard curve, respectively. The interassay CVs were 8.2, 1.5, and 3.7% for low, medium, and high points of the standard curve.

### *Statistical analysis*

Results were expressed as mean ± SD unless otherwise specified. The statistical analysis was performed by SPSS Inc. (Cary, NC) package using nonparametric tests. The within-group comparisons and those between controls and patients at study entry and end were performed using the Wilcoxon matched paired test. The comparison among patients with severe GHD, normal GH secretion, or partial GHD was performed using the Kruskal-Wallis test followed by the Dunns test. Correlation coefficients were calculated by measuring the Pearson or Spearman coefficients for the variables normally or not normally distributed. Cutoff threshold for GH peak after GHRH+ARG and of IGF-I SDS to predict subsequent development of severe GHD was analyzed by a receiving-operator characteristics (ROC) curve calculated using MedCalc Software for Windows (MedCalc, Mariakerke, Belgium). The significance was set at 5%.

## Results

### *Baseline study*

As shown in Table 2, partial GHD patients had significantly lower IGF-I and HDL cholesterol levels and higher glucose and insulin levels and HOMA index than controls. In the patients group, the IGF-I SDS was significantly correlated with total cholesterol ($r = -0.44$; $P = 0.021$); HDL cholesterol ($r = 0.57$; $P = 0.002$); total to HDL cholesterol ratio ($r = -0.62$; $P = 0.006$); triglyceride ($r = -0.72$, $P < 0.0001$), glucose ($r = -0.56$; $P = 0.002$), and insulin levels ($r = -0.59$; $P = 0.001$); and HOMA ($r = -0.65$; $P = 0.0005$). In the control group, the IGF-I SDS was significantly correlated only with HDL cholesterol ($r = 0.6$; $P = 0.0009$), total to HDL cholesterol ratio ($r = -0.5$; $P = 0.008$), and triglyceride levels ($r = -0.48$, $P = 0.012$). There was no difference in baseline endocrine and metabolic pattern between patients lean (n = 12) or overweight (n = 17): residual tumor volumes (47.7 ± 73.6 *vs.* 116.6 ± 205.5 ml; $P = 0.28$), GH peak after GHRH+ARG (13.1 ± 1.8 *vs.* 12.3 ± 1.6 μg/liter; $P = 0.29$), and z-SDS score (−0.33 ± 0.72 *vs.* − 0.56 ± 0.78; $P = 0.44$) were similar in the two groups. Details are shown in Fig. 1. In the subgroup of overweight patients, but not in the lean, the IGF-I SDS was still significantly correlated with total cholesterol ($r = -0.61$; $P = 0.015$), LDL cholesterol ($r = -0.71$; $P = 0.0025$), total to HDL cholesterol ratio ($r = -0.77$; $P = 0.0009$), and triglyceride levels ($r = -0.81$; $P = 0.0002$).

### *Follow-up study*

During the 24–72 months of follow-up (median 60 months), retesting with GHRH+ARG showed that 11 patients developed severe GHD (40.7%), seven normalized their GH response (25.9%), and nine showed a persistently partial GHD (33.3%). Nevertheless, the GH peak at last follow-up was significantly correlated with that at study entry both in the patients and controls (Fig. 2). The percent changes of GH peak after GHRH+ARG were significantly greater in the patients developing severe GHD [95% confidence interval (CI) −50.4 to −34.3%] and in those normalizing GH secretion (95% CI 59.5–141.9%) than in the partial GHD (95% CI 1.4–13.5%) and controls (95% CI 2.7–24.3%). Individual percent GH changes and mean values in different groups are shown in Fig. 3.

The patients who developed severe GHD did not differ from the others for age or BMI (Table 3) at baseline, whereas they showed a GH peak after GHRH+ARG and IGF-I SDS significantly lower than the patients who normalized GH secretion or those who remained partial GHD (Table 3). They also had a higher prevalence of multiple pituitary deficiency,

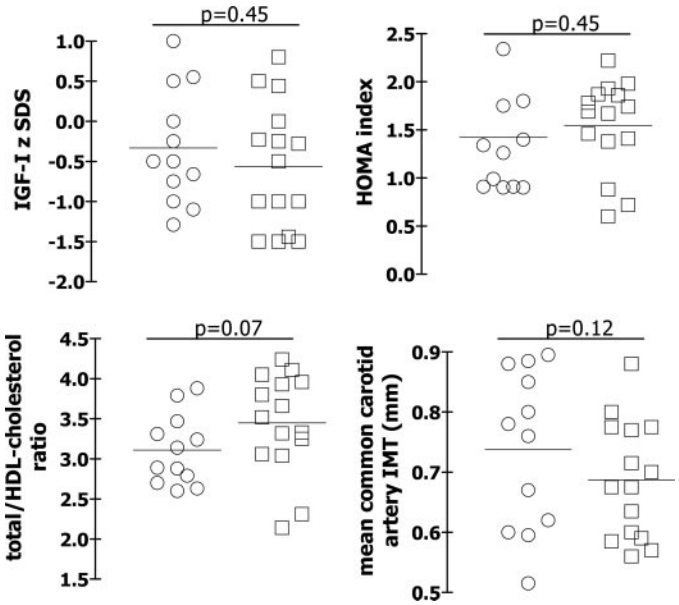


FIG. 1. Individual results of the z-SDS of IGF-I levels (*top*, *left*), HOMA index (*top*, *right*), total to HDL cholesterol ratio (*bottom*, *left*), and mean IMT at common carotid arteries (*bottom*, *right*) in the 27 patients at study entry subdivided according to their BMI in normal weight [<25 kg/m$^2$; n = 12 (○)] and overweight [25–30 kg/m$^2$, n = 15 (□)]. Mean values in each group are also shown as *continuous lines*. Statistical significance by Mann-Whitney test is also indicated.

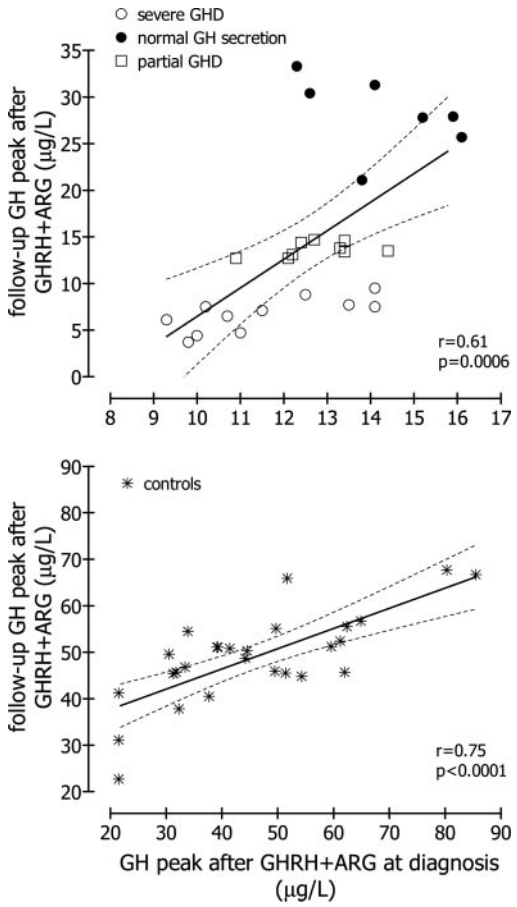


FIG. 2. Peak GH after GHRH+ARG at study entry and last follow-up in the controls (*top*) and entire series of patients (*bottom*). The *continuous line* indicates the regression line and the *interrupted lines* indicate the 95% CIs of regression. ○, Patients developing severe GHD; ●, patients normalizing GH secretion; □, patients with persistent partial GHD; *, controls.

compared with the other two groups. Severe GHD developed after a median period of 36 months (range 12–48 months) from first testing and was associated with decreased IGF-I SDS, impairment of metabolic profile, and increased IMT at common carotid arteries (Table 4). Normalization of GH secretion was found in 25.9% of the patients after a median period of 48 months from first testing and was associated with increased IGF-I SDS without any change in lipid or tolerance profile (Table 5). A slight increase in carotid IMT was also found in this group (Table 5). In the nine patients with biochemically confirmed partial GHD, there were no changes in IGF-SDS in the metabolic profile, but there was an increase of IMT at common carotid arteries (Table 6).

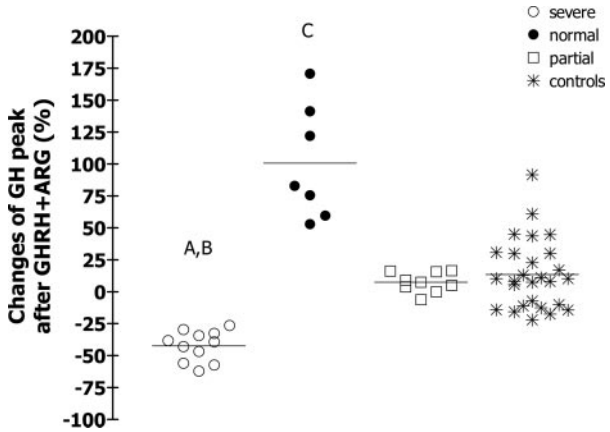


FIG. 3. Percent changes of peak GH after GHRH+ARG during the study duration. A, $P < 0.0001$ *vs.* patients who normalized GH levels and *vs.* controls. B, $P < 0.01$ *vs.* patients with persistent partial GHD. C, $P < 0.05$ *vs.* patients with persistent partial GHD and *vs.* controls.

Individual results of IMT at common carotid arteries in the 11 patients who developed severe GHD, the seven who normalized GH secretion, and the nine with persistent partial GHD are shown in Fig. 4. Overall, increase in mean IMT was also found in the 27 controls (from 0.64 ± 0.2 to 0.66 ± 0.11 mm, $P = 0.003$), together with an increase of glucose levels (from 4.4 ± 0.4 to 4.6 ± 0.5 mmol/liter, $P = 0.024$). The percent increase of IMT in controls (3.4 ± 5.1%) was significantly lower than in patients developing GHD (6.1 ± 4.3%, $P = 0.028$) and those with partial GHD (5.6 ± 2.9%, $P = 0.041$) but similar to that found in patients who normalized GH secretion (2.3 ± 1.4%, $P = 0.67$).

None of the patients showed recurrence of pituitary tumors or regrowth of remnant tumors (Table 1). The residual pituitary function remained stable in all patients, but three of those developing severe GHD experienced a deterioration: two patients with isolated LH deficiency also developed FSH deficiency, and one with normal pituitary function developed FSH and LH deficiency.

### *Predictors of severe GHD or normal GH secretion*

By the ROC analysis, the best cutoffs of GH peak after GHRH+ARG and IGF-I SDS at baseline could distinguish the patients who developed severe GHD and those who normalized GH secretion. Best cutoff for peak GH was 11.5 µg/liter [sensitivity (95% CI) 64% (31–89%), specificity 94% (70–100%), positive predictive value 88%, negative predictive value 79%]. Best cutoff of IGF-I SDS was −0.28 [sensitivity 91% (59–100%), specificity 63% (35–85%), positive predictive value 63%, negative predictive value 91%]. By applying these two cutoffs to our population, we found that eight of 11 patients who developed severe GHD had a baseline peak GH after GHRH+ARG 11.5 µg/liter or less, compared with none of the seven who normalized GH secretion and one of the nine who had persistent partial GHD (Fig. 5). Similarly, 10 of 11 patients who developed severe GHD had a baseline IGF-I SDS −0.28 or less, compared with one of the seven who normalized GH secretion and five of the nine who had persistent partial GHD (Fig. 4). The combination of a baseline GH peak 11.5 µg/liter or less and IGF-I SDS −0.28 or less predicted the development of severe GHD in all cases, whereas baseline GH peak greater than 11.5 µg/liter and IGF-I SDS greater than −0.28 predicted the normalization of GH secretion in six of seven patients (85.7%). Of note, the remaining case had a peak GH of 12.3 µg/liter and an IGF-I SDS of −1 and had the lowest BMI in this series (21.1 kg/m$^2$).

**TABLE 3.** Endocrine and metabolic profile at study entry according to the peak GH after GHRH+ARG at last follow-up

| | Severe GHD patients | Normal GH patients | Partial GHD patients | *P* |
|---|---|---|---|---|
| No. | 11 | 7 | 9 | |
| Age (yr) | 35 ± 10 | 47 ± 8 | 45 ± 11 | 0.074 |
| BMI (kg/m$^2$) | 25.6 ± 2.1 | 25.3 ± 2.2 | 24.3 ± 3.6 | 0.80 |
| Prevalence of overweight subjects (%) | 63.4 | 57.1 | 44.4 | 0.69 |
| GH peak ($\mu$g/liter) | 11.5 ± 1.8$^{a,b}$ | 14.3 ± 1.5 | 12.8 ± 1.0 | 0.008 |
| IGF-I SDS | −0.88 ± 0.48$^{a}$ | 0.15 ± 0.68 | −0.42 ± 0.78 | 0.01 |
| Tumor volume (ml) | 155.6 ± 234.9 | 57.3 ± 74.0 | 27.4 ± 45.3 | 0.15 |
| Associated pituitary deficiencies | | | | |
| 0 | 3 | 3 | 6 | 0.21 |
| 1–2 | 4 | 4 | 3 | 0.58 |
| 3–4 | 4$^{a,b}$ | 0 | 0 | 0.033 |
| Total cholesterol (mmol/liter) | 4.7 ± 0.5 | 4.5 ± 0.4 | 4.7 ± 0.5 | 0.34 |
| LDL-cholesterol (mmol/liter) | 3.2 ± 0.5 | 2.9 ± 0.4 | 2.9 ± 0.7 | 0.55 |
| HDL-cholesterol (mmol/liter) | 1.4 ± 0.1 | 1.4 ± 0.2 | 1.5 ± 0.2 | 0.98 |
| Total/HDL ratio | 3.5 ± 0.5 | 3.2 ± 0.4 | 3.1 ± 0.7 | 0.80 |
| Triglycerides (mmol/liter) | 1.1 ± 0.2 | 1.1 ± 0.1 | 1.1 ± 0.2 | 0.93 |
| Glucose (mmol/liter) | 4.9 ± 0.5 | 4.6 ± 0.6 | 4.5 ± 0.6 | 0.96 |
| Insulin (mIU/liter) | 7.7 ± 1.6 | 6.8 ± 2.6 | 6.4 ± 1.8 | 0.24 |
| HOMA index | 1.7 ± 0.4 | 1.4 ± 0.6 | 1.3 ± 0.5 | 0.39 |
| Mean IMT CCA (mm) | 0.67 ± 0.11 | 0.78 ± 0.10 | 0.70 ± 0.10 | 0.037 |

*P* values refer to statistical comparison among groups. CCA, Common carotid arteries.
[a] $P < 0.05$ *vs.* patients with normalized GH secretion; statistical difference by Kruskal-Wallis test followed by Dunns test among groups.
[b] $P < 0.05$ *vs.* patients with partial GHD.

## Discussion

This is the first observational prospective study to investigate the natural history of partial GHD in adult patients with hypothalamus-pituitary tumors. We demonstrated that among the patients showing a partial GHD at their evaluation for pituitary deficiency after surgical treatment of pituitary tumors, 40.7% subsequently developed severe GHD, whereas 25.9% normalized their GH secretion. Importantly, deterioration of GH secretion was predicted by a GH peak after GHRH+ARG 11.5 $\mu$g/liter or less and an IGF-I SDS of −0.28 or less. Of note, patients developing severe GHD also had multiple pituitary deficiency more frequently than the others. The biochemical diagnosis of severe GHD was accompanied by other alterations such as impairment of lipid profile, with increased total to HDL cholesterol ratio, triglyceride levels, and glucose tolerance, with increased insulin resistance and IMT at common carotid arteries, indicating early atherosclerosis. Slight increase of IMT was found in the control population as well as the patients who normalized GH secretion, but the magnitude of the effect was greater in the patients who developed GHD and those showing persistent partial GHD.

The diagnosis of GHD in both adults and children is based on peak GH responses to ITT or GHRH+ARG at appropriate cutoffs as indicated by the Consensus Guidelines of the Growth Hormone Research Society (9). The appropriateness of diagnosis is easily confirmed in children on the basis of auxological criteria, whereas in adults it is mandatory that GHD is diagnosed in the context of known or putative disease of the hypothalamic-pituitary region. From childhood to adulthood, the GH and IGF-I secretion is modified, showing an increase during puberty and a slow, progressive decrease

**TABLE 4.** Endocrine and metabolic profile at study entry and study end in patients developing severe GHD during the study, compared with their controls

| | Patients who developed severe GHD | | | Controls | | |
|---|---|---|---|---|---|---|
| | Study entry | Study end | *P* | Study entry | Study end | *P* |
| Age (yr) | 35 ± 10 | 38 ± 10 | | 35 ± 10 | 38 ± 9 | |
| BMI (kg/m$^2$) | 25.6 ± 2.1 | 25.1 ± 1.8 | 0.023 | 24.1 ± 2.8 | 23.0 ± 1.8 | 0.25 |
| GH peak ($\mu$g/liter) | 11.5 ± 1.8$^{a}$ | 6.7 ± 1.8$^{a}$ | 0.001 | 43.6 ± 17.2 | 47.3 ± 11.8 | 0.31 |
| IGF-I SDS | −0.88 ± 0.48$^{a}$ | −1.65 ± 0.45$^{a}$ | 0.001 | 0.17 ± 0.92 | 0.17 ± 0.77 | 0.73 |
| IGF-I level changes (%) | | −28.2 ± 15.3 | | | | |
| Total cholesterol (mmol/liter) | 4.7 ± 0.5 | 5.0 ± 0.3$^{a}$ | 0.07 | 4.5 ± 0.4 | 4.3 ± 0.8 | 0.57 |
| LDL cholesterol (mmol/liter) | 3.2 ± 0.5 | 3.5 ± 0.3$^{a}$ | 0.024 | 2.7 ± 0.7 | 2.6 ± 0.8 | 0.57 |
| HDL cholesterol (mmol/liter) | 1.4 ± 0.1 | 1.2 ± 0.1$^{a}$ | 0.007 | 1.5 ± 0.2 | 1.5 ± 0.2 | 0.82 |
| Total to HDL ratio | 3.5 ± 0.5 | 4.1 ± 0.4$^{a}$ | 0.003 | 3.0 ± 0.7 | 2.9 ± 0.6 | 0.72 |
| Triglycerides (mmol/liter) | 1.1 ± 0.2 | 1.3 ± 0.1 | 0.83 | 1.1 ± 0.3 | 1.2 ± 0.2 | 0.16 |
| Glucose (mmol/liter) | 4.9 ± 0.5$^{a}$ | 5.3 ± 0.3$^{a}$ | 0.014 | 4.4 ± 0.3 | 4.5 ± 0.4 | 0.13 |
| Insulin (mIU/liter) | 7.7 ± 1.6$^{a}$ | 8.8 ± 1.5$^{a}$ | 0.083 | 5.1 ± 1.0 | 5.2 ± 1.2 | 0.73 |
| HOMA index | 1.7 ± 0.4$^{a}$ | 2.1 ± 0.4$^{a}$ | 0.042 | 1.0 ± 0.2 | 1.0 ± 0.4 | 0.50 |
| Mean IMT CCA (mm) | 0.67 ± 0.11 | 0.73 ± 0.12$^{a}$ | 0.002 | 0.59 ± 0.09 | 0.61 ± 0.08 | 0.11 |

*P* values refer to statistical comparison between results at study entry *vs.* study end within each group using the Wilcoxon paired matched test. n = 11; female/male, 6/5. CCA, Common carotid arteries.
[a] $P < 0.01$ at the Wilcoxon paired matched test between the patients and controls at the same time points.

**TABLE 5.** Endocrine and metabolic profile at study entry and study end in patients normalizing GH secretion during the study, compared with their controls

| | Patients who normalized GH secretion | | | Controls | | |
|---|---|---|---|---|---|---|
| | Study entry | Study end | *P* | Study entry | Study end | *P* |
| Age (yr) | 47 ± 8 | 51 ± 10 | | 47 ± 8 | 50 ± 10 | |
| BMI (kg/m$^2$) | 25.3 ± 2.2 | 25.0 ± 2.1 | 0.62 | 24.6 ± 3.5 | 23.4 ± 1.8 | 0.22 |
| GH peak (μg/liter) | 14.3 ± 1.5[a] | 30.2 ± 5.3[a] | 0.016 | 38.8 ± 13.5 | 46.6 ± 6.6 | 0.087 |
| IGF-I SDS | 0.15 ± 0.68 | 0.50 ± 0.48 | 0.031 | 0.46 ± 0.60 | 0.49 ± 0.36 | 0.81 |
| IGF-I level changes (%) | | 5.6 ± 11.6 | | | | |
| Total cholesterol (mmol/liter) | 4.5 ± 0.4 | 4.6 ± 0.5 | 0.37 | 4.8 ± 0.5 | 4.7 ± 0.4 | 0.81 |
| LDL cholesterol (mmol/liter) | 2.9 ± 0.4 | 2.9 ± 0.6 | 0.81 | 3.0 ± 0.6 | 2.8 ± 0.5 | 0.58 |
| HDL cholesterol (mmol/liter) | 1.4 ± 0.2 | 1.4 ± 0.1 | 0.94 | 1.5 ± 0.2 | 1.6 ± 0.2 | 0.47 |
| Total to HDL ratio | 3.2 ± 0.4 | 3.2 ± 0.6 | 0.94 | 3.2 ± 0.8 | 2.9 ± 0.4 | 0.37 |
| Triglycerides (mmol/liter) | 1.1 ± 0.1 | 1.1 ± 0.1 | 0.81 | 1.1 ± 0.2 | 1.2 ± 0.1 | 0.58 |
| Glucose (mmol/liter) | 4.6 ± 0.6 | 4.6 ± 0.4 | 1 | 4.5 ± 0.5 | 4.8 ± 0.7 | 0.29 |
| Insulin (mIU/liter) | 6.8 ± 2.6 | 6.2 ± 0.8 | 0.94 | 6.6 ± 2.7 | 5.9 ± 1.6 | 0.16 |
| HOMA index | 1.4 ± 0.6 | 1.3 ± 0.2 | 0.94 | 1.4 ± 0.7 | 1.2 ± 0.5 | 0.37 |
| Mean IMT CCA (mm) | 0.78 ± 0.10 | 0.80 ± 0.10 | 0.016 | 0.73 ± 0.14 | 0.74 ± 0.13 | 0.09 |

*P* values refer to statistical comparison between results at study entry *vs.* study end within each group using the Wilcoxon paired matched test. n = 7; female/male, 4/3. CCA, Common carotid arteries.

[a] $P < 0.01$ at the Wilcoxon paired matched test between the patients and controls at the same time points.

thereafter (27) so that GH cutoff should be adjusted for age. By using either the ITT or GHRH+ARG test, there is a gray zone between the threshold of normal GH response (>7 μg/liter and > 16.5 μg/liter, respectively, in adults) and that of severe GHD (<3 μg/liter and < 9 μg/liter, respectively) (9).

Patients showing a peak GH response to ITT between 3 and 7 μg/liter or to GHRH+ARG between 9 and 16.5 μg/liter can be classified as having the condition of partial GHD (or GH insufficiency). The prevalence of partial GHD is not negligible because it has been reported to occur in 16–38% of patients in different series (15–17, 19). More recently, Corneli *et al.* (13) reevaluated the GH cutoffs to diagnose severe GHD in the adult hypopituitary population to provide a better differentiation between the patients with normal GH secretion and those with GHD according to their BMI. The highest sensitivity and specificity were for a GH cutoff of 11.5 μg/liter in the lean population (BMI < 25), therefore higher than that reported by the same group before (28). In the overweight and obese population the GH cutoff is lower, *i.e.* 8 and 4.2 μg/liter, respectively (13). Biller *et al.* (12) also previously reported similar GH cutoff in a large population of hypopituitary patients having a mean BMI of 30 kg/m$^2$, thus in the obese range. Therefore, in adult patients with hypothalamus-pituitary diseases, the diagnosis of GHD should be based on stimulation tests using appropriate cut-offs not only according to the pharmacological stimulus used (9, 12) but also for the age and the BMI of the patients. Nevertheless, the validity of the ITT or GHRH+ARG test to investigate the GH secretory status is corroborated by clinical and biochemical data that were found to be correlated with GH peak responses in both children (14) and adults (15–17, 19).

In the current cohort of patients diagnosed with partial GHD when threshold GH values were 9–16.5 μg/liter after GHRH+ARG, 17 overweight patients were included. Overweight patients were indistinguishable from lean patients as for the endocrine and metabolic profile. At second testing, seven of the 11 patients diagnosed as severe GHD were overweight: in none of these overweight patients was the peak GH at last follow-up between 8 and 9 μg/liter, which

**TABLE 6.** Endocrine and metabolic profile at study entry and study end in patients with persistent partial GHD during the study, compared with their controls

| | Patients with persistent partial GHD | | | Controls | | |
|---|---|---|---|---|---|---|
| | Study entry | Study end | *P* | Study entry | Study end | *P* |
| Age (yr) | 45 ± 11 | 49 ± 10 | | 46 ± 11 | 50 ± 10 | |
| BMI (kg/m$^2$) | 24.3 ± 3.6 | 24.1 ± 3.5 | 0.12 | 22.9 ± 2.7 | 22.2 ± 1.7 | 0.25 |
| GH peak (μg/liter) | 12.8 ± 1.0[a] | 13.7 ± 0.8[a] | 0.039 | 54.7 ± 16.1 | 51.6 ± 9.8 | 0.31 |
| IGF-I SDS | −0.42 ± 0.78[a] | −0.19 ± 0.38[a] | 0.43 | 0.58 ± 0.57 | 0.53 ± 0.36 | 0.73 |
| IGF-I level changes (%) | | 13.5 ± 29.9 | | | | |
| Total cholesterol (mmol/liter) | 4.7 ± 0.5 | 4.8 ± 0.4 | 0.65 | 4.5 ± 0.5 | 4.6 ± 0.4 | 0.57 |
| LDL cholesterol (mmol/liter) | 2.9 ± 0.7 | 3.0 ± 0.4 | 0.84 | 2.7 ± 0.6 | 2.7 ± 0.4 | 0.57 |
| HDL cholesterol (mmol/liter) | 1.5 ± 0.2 | 1.5 ± 0.1 | 0.82 | 1.6 ± 0.2 | 1.6 ± 0.1 | 0.82 |
| Total to HDL ratio | 3.1 ± 0.7 | 3.2 ± 0.4 | 0.94 | 2.8 ± 0.6 | 2.8 ± 0.3 | 0.73 |
| Triglycerides (mmol/liter) | 1.1 ± 0.2 | 1.1 ± 0.1 | 0.57 | 1.1 ± 0.1 | 1.1 ± 0.1 | 0.16 |
| Glucose (mmol/liter) | 4.5 ± 0.6 | 4.9 ± 0.4 | 0.15 | 4.4 ± 0.6 | 4.7 ± 0.5 | 0.13 |
| Insulin (mIU/liter) | 6.4 ± 1.8 | 7.5 ± 2.0 | 0.19 | 5.8 ± 1.9 | 5.7 ± 1.3 | 0.73 |
| HOMA index | 1.3 ± 0.5 | 1.6 ± 0.5 | 0.16 | 1.2 ± 0.6 | 1.2 ± 0.4 | 0.50 |
| Mean IMT CCA (mm) | 0.70 ± 0.10 | 0.74 ± 0.09 | 0.044 | 0.64 ± 0.11 | 0.66 ± 0.09 | 0.11 |

*P* values refer to statistical comparison between results at study entry *vs.* study end within each group using the Wilcoxon paired matched test. n = 9; female/male, 5/4. CCA, Common carotid arteries.

[a] $P < 0.01$ at the Wilcoxon paired matched test between the patients and controls at the same time points.

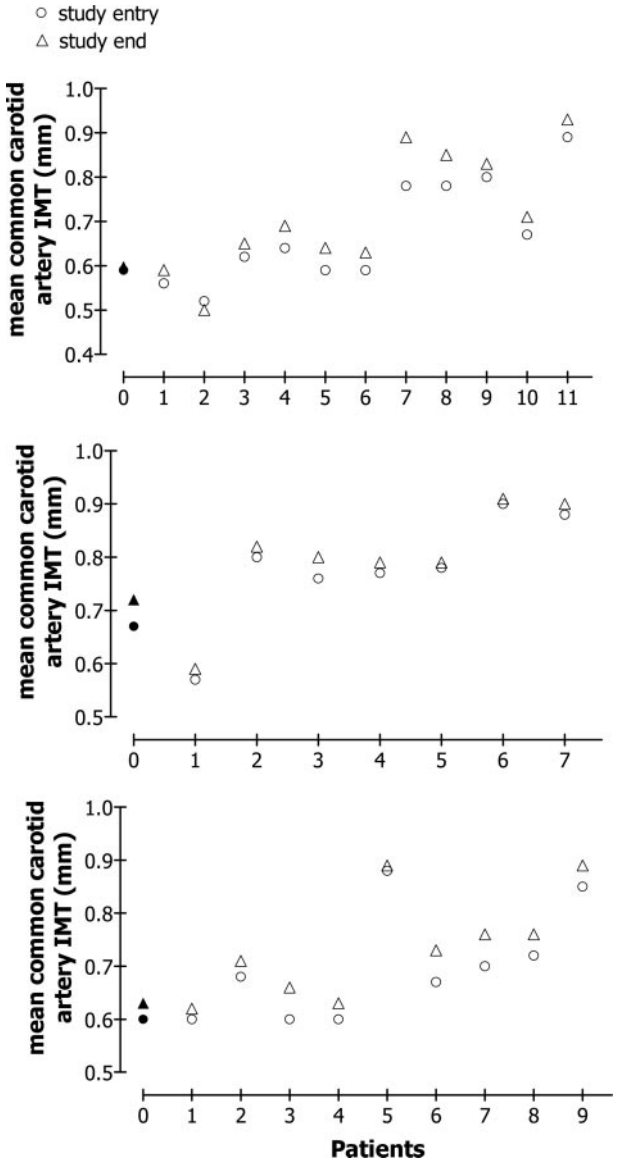


FIG. 4. Individual levels of the mean value of IMT measured at right and left common carotid arteries in the 11 patients who developed severe GHD (*top*), the seven who normalized GH secretion (*middle*), and the nine who showed persistence of partial GHD (*bottom*). *Open symbols*, Patients; *closed symbols*, median levels measured at study entry and study end in the sex- and age-matched controls for each group.

represents the new (13) and old (9) cutoff values to diagnose severe GHD. In contrast, among the nine diagnosed as having persistent partial GHD, none of the five lean patients had a GH peak between 9 and 11.5 $\mu$g/liter, which represents the old (9) and new (13) cutoff values to diagnose severe GHD. Thus, at least in the current series, no misleading diagnosis was made according to the newest threshold values for GH peak responses after GHRH+ARG in lean or overweight patients.

It is important to mention that so far the patients with partial GHD have been studied very poorly. Tauber *et al.* (20) reported increased total body fat and decreased lean body mass in the partial GHD adolescents, compared with the

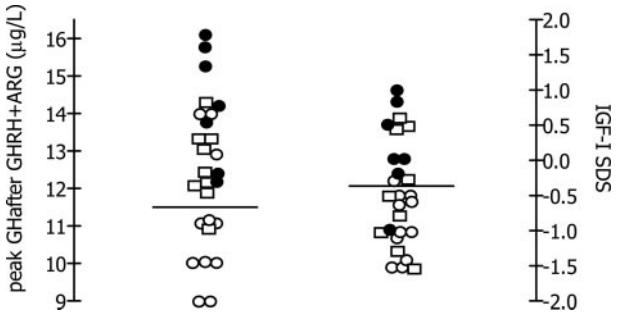


FIG. 5. Peak GH after GHRH+ARG (*left*) and IGF-I SDS (*right*) at study entry in the entire series of patients. ○, Patients developing severe GHD; ●, patients normalizing GH secretion; □, patients with persistent partial GHD. The *horizontal lines* indicate the cutoff levels indicated by the ROC analysis.

controls. Furthermore, 1 yr after withdrawing GH replacement, body composition alterations worsened further. In the adult population, Murray *et al.* (19) also showed that patients with partial GHD have an abnormal body composition with increased fat mass and reduced lean mass; increased waist to hip ratio; increased skinfold thickness over the biceps, triceps, and suprailiac regions; and increased sum of the regional skinfolds. In analogy with the pediatric growth data for patients with partial GHD, Murray *et al.* (19) showed that the degree of body composition changes was less than that observed in patients with severe GHD but well distinguished from a state of normal health. These data are also in line with some previous results in our cohort showing that partial GHD patients have impairment of lipid profile, cardiac performance, and exercise performance between the severe GHD patients, who had a worse status, and the non-GHD patients and controls, who had a better status. In the current study, we confirm that adult patients diagnosed as partial GHD on the basis of a peak GH after GHRH+ARG between 9 and 16.5 $\mu$g/liter, according to the cutoff accepted by the Growth Hormone Research Society (9) have a number of alterations when compared with sex- and age-matched healthy controls. Among the new findings, we found that partial GHD patients had higher glucose levels and insulin levels, worse insulin resistance, and higher IMT at common carotid arteries than controls. Early atherosclerosis is a well-documented condition of severe GHD adults (29–32) and can be improved by GH replacement therapy (33–35). Therefore, patients with partial GHD show alterations of body composition, lipid profile, and cardiovascular profile that could deserve more attention and potentially some treatment. In adult patients GH replacement is currently allowed worldwide only when severe GHD is diagnosed, thus excluding partial GHD patients.

There is evidence that the GHRH+ARG might be inaccurate in diagnosing GHD in some circumstances. In fact, because the GHRH+ARG test overcomes faint hypothalamic damage by producing also a direct stimulatory effect on the pituitary gland, it could be less accurate in patients with hypothalamic damage such as those receiving irradiation in the treatment protocol of their disease. Darzy *et al.* (36) compared the efficiency of ITT and GHRH+ARG in 49 adult survivors, who were previously irradiated for nonpituitary brain tumors or leukemia, and 33 age-, gender-, and BMI-

matched controls. They found that in both patients and controls, the median peak GH response to the GHRH+ARG was significantly greater than the response to the ITT. However, the discordance ratio (peak GH response to GHRH+ARG *vs.* ITT) was significantly higher in the patients, compared with controls, consistent with dominant hypothalamic damage and relatively preserved somatotroph responsiveness (36). Importantly, whereas the peak GH to ITT fell significantly within 5 yr of irradiation, the peak GH to GHRH+ARG barely changed in the same period. On a practical clinical level, the discordance between the GH test results was important; 50% of patients classified as severe GHD by the ITT were considered normal or only partial GHD by GHRH+ARG (36). Even if the current series did not include irradiated patients, we cannot rule out that some hypothalamic damage exists in some of them and thus that the GH peak after testing does not fully represent the GH secretory status and that these patients should thus be followed up carefully.

In fact, changes in the GH peak during the yearly follow-up were observed in 66.6% of the patients diagnosed as partial GHD after surgery because of pituitary tumor: 40.7% who developed severe GHD during the follow-up at a median time of 36 months and 25.9% who showed a normalization of the GH response to the test. Changes in the GH peak response to GHRH+ARG were accompanied by changes in the IGF-I SDS in both groups and impairment of lipid and glucose profile and increased IMT at common carotid arteries only in patients developing severe GHD. This further confirms the evidence of a clinical relationship between GH secretion, as studied by the GHRH+ARG test, and some metabolic features. Possible prediction of delayed impairment of GH secretion can be clinically useful. We found that a peak GH 11.5 $\mu$g/liter or less was highly predictive of deterioration of GH secretion as well as an IGF-I SDS −0.28 or less. Interestingly, Corneli *et al.* (13) found the same GH cutoff of 11.5 $\mu$g/liter to be diagnostic of severe GHD in another cohort of lean hypopituitary patients. Of note, only four of the 11 patients with a delayed diagnosis of severe GHD were lean, and all had first GH peak above 11.5 $\mu$g/liter. Therefore, no misdiagnosed severe GHD occurred in the current series.

It could be argued that changes in the GH response to the test could be simply due to variations of the GH inter- and intraassay CVs used and/or unsatisfactory test reproducibility. Certainly in the analysis of GH peak after any stimulus, the sensitivity of the assay used is relevant because old-fashioned RIAs overestimated GH levels, compared with the modern assays. Of note, we did not change the assay used during the period of the study, and the detection limit of our GH assay is in line with the most modern assays. As for the reproducibility, the GHRH+ARG test is considered more reproducible than other tests, including the ITT, in both young adults and elderly subjects (37). As further confirmation, in the current study, we found a high correlation between the GH peak after GHRH+ARG at the two tests in our control population and even in the patients' cohort. Changes in the GH peak in the two groups with modified diagnosis were significantly different from those with confirmed diagnosis, making unlikely the possibility that the results presented in the current study were simply due to poor assay reproducibility of the test.

There are a few hypotheses to explain our findings. One possible explanation for the delayed deterioration of GH secretion after surgery in some patients may be a secondary activation of an autoimmune process against pituitary cells after surgery. This is possible, even in the absence of other treatments, such as radiotherapy, well known to damage pituitary cell tissue, and relies on the demonstration of positive antibodies against vasopressin cells in 12% of patients with postsurgical diabetes insipidus (38). On the other hand, the prevalence of associated multiple pituitary deficiencies in the group developing severe GHD was higher than that found in the other two groups, so suggesting that the damage to the residual pituitary tissue was already greater at study entry, and new deficiencies also developed during the follow-up. The presence of multiple hormone deficiency is known to be associated with severe GHD (39): even if this finding is related to patients with severe and not partial GHD, the validity of the assumption remains. As for the patients who normalized their GH secretion, the majority did not have any remnant tumor or bear very small stable remnants, and three of seven patients did not have any other deficiency. GH secretion could then be recovered after surgery in a delayed fashion.

In conclusion, partial GHD in adult patients with hypothalamus-pituitary diseases is associated with lipid and glucose alterations and early atherosclerosis. Partial GHD may evolve to severe GHD or normal GH secretion in similar probability in one third of cases. With the assays used in our studies, baseline GH peak after GHRH+ARG 11.5 $\mu$g/liter or less associated with an IGF-I SDS −0.28 or less are highly predictive of deterioration of GH secretion in lean as well as overweight patients. A careful follow-up is thus indicated in patients with partial GHD to eventually decide on replacement treatments. The natural history and clinical implications of the patients with stably partial GHD remain to be clarified. Whether GH secretion will also change over time in this latter subset of patients should be established in longer follow-ups.

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