Prevalence of GH deficiency in cured acromegalic patients: impact of different previous treatments

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Abstract

Objective: Radiotherapy (RT) for pituitary adenomas, including GH-secreting ones, frequently leads to GH deficiency (GHD). Data on the effects of surgery alone (S) on dynamic GH secretion are limited. The aim of the study was to investigate the occurrence of GHD in acromegalic patients treated with different therapeutic options.

Design and methods: Fifty-six patients in remission from acromegaly, (33 F & 23 M, age: 54 ± 13 years, body mass index (BMI): 28.4 ± 4.1 kg/m², 21 with adequately substituted pituitary deficiencies) treated by S alone (n = 33, group 1) or followed by RT (n = 23, group 2), were investigated for GHD by GHRH plus arginine testing, using BMI-adjusted cut-offs. Several metabolic and cardiovascular parameters (waist circumference, body fat percentage, blood pressure, fasting and post-oral glucose tolerance test glucose, HbA1c, insulin resistance and lipid profile) were evaluated in all the patients and 28 control subjects with known diagnosis of GHD.

Results: Serum GH peak after challenge was 8.0 ± 9.7 μg/l, without any correlation with post-glucose GH nadir and IGF-1 levels. The GH response indicated severe GHD in 34 patients (61%) and partial GHD in 15 patients (27%). IGF-1 were below the normal range in 14 patients (25%). The frequency of GHD was similar in the two treatment groups (54% in group 1 and 70% in group 2). No significant differences in metabolic parameters were observed between acromegalic patients and controls with GHD.

Conclusions: Severe GHD may occur in about 60% of patients treated for acromegaly, even when cured after S alone. Thus, a stimulation test (i.e. GHRH plus arginine) is recommended in all cured acromegalic patients, independently from previous treatment.

Introduction

Acromegaly is an extremely disabling disease caused by chronic GH and insulin-like growth factor 1 (IGF-1) hypersecretion and associated with increased cardiovascular morbidity and mortality. The aims of treatment mainly consist of restoring normal hormonal secretion, thus controlling the symptoms related to GH excess and reducing the mass effects of the pituitary tumour. The biochemical control of the disease is of crucial importance for the normalization of mortality. To this aim, despite the remarkable improvement in neurosurgery, the majority of patients require various therapeutic approaches including radiotherapy (RT) and medical treatment. Thus, the efforts to achieve the disease control might induce the development of GH deficiency (GHD) in a certain proportion of patients. At present, data on the effect of different therapeutic strategies for the cure of acromegaly on the occurrence of GHD are lacking. As far as conventional RT is concerned, it has been reported that it may induce GHD in many patients with pituitary adenomas, such as non-functioning, ACTH- or prolactin-secreting adenomas (1). Although with a minor frequency, the same is true also for radiosurgery (2). Regarding acromegalic patients, it is known that RT may induce GHD in about 30–50% of treated patients (3–5) and radiosurgery in about 6% (6). On the contrary, few and contrasting studies conducted on small series of patients are present in the literature about the impact of transsphenoidal surgery (S) alone (4, 7–9). In a previous report, our group demonstrated that in a large series of acromegalic patients cured by neurosurgery alone, both GH and IGF-1
levels significantly decreased during a long-term follow-up, suggesting the occurrence of GHD at least in some of them (10).

The aim of the present study was to investigate the prevalence of GHD in acromegalic patients treated either with S alone or with S followed by RT.

Materials and methods

Patients

A total of 56 patients with previous diagnosis of acromegaly (33 F & 23 M, age: 54±13 years, body mass index (BMI): 28.4±4.1 kg/m²) and considered cured according to the current guidelines (11) was investigated. At the time of diagnosis, serum GH and IGF-1 levels were 27.8±28.7 µg/l and 122±43 nmol/l respectively; 31 patients had a macroadenoma, with extrasellar localization in 22 of them. The patients were studied after a median period of 60 months (range: 12–336) from the disease remission that corresponded to a median period of 144 months (range: 12–444) from the first treatment for acromegaly. At the time of evaluation, 21 patients had known anterior pituitary deficiencies (38%), such as isolated hypoadrenalism (n=5), isolated hypogonadism (n=3), isolated hypothyroidism (n=2) or multiple deficiencies (n=11), all being adequately substituted before starting the study protocol. Moreover, 17 patients had glucose metabolism alterations (30%), 4 being affected with diabetes mellitus and 13 with impaired glucose tolerance. Finally, 16 patients were obese (29%), 25 patients were overweight (45%) and the remaining 15 had a normal body weight.

Thirty-three patients had been previously treated with S alone (group 1) while 23 had been also irradiated (17 by conventional fractioned RT and 6 by radiosurgery with Leksell-gamma-knife technique, group 2). RT or radiosurgery were performed at least 5 years before the beginning of the study. Clinical and hormonal characteristics of the two treatment groups are summarized in Table 1. In particular, groups 1 and 2 were comparable in terms of age and sex, while the time from first treatment (but not that from disease remission) was longer and BMI values were higher in group 2.

A total of 28 sex-, age- and BMI-matched patients (17 M & 11 F, age: 46.3±11.5 years, BMI: 27.3±4.2 kg/m²) followed in the Unit of Endocrinology and Diabetology (Fondazione IRCCS Ospedale Maggiore Policlinico, Milan, Italy) for different hypothalamus–pituitary diseases and previously diagnosed as affected with severe adulthood onset GHD were also investigated for hormonal and metabolic parameters (control group). In particular, 18 patients had non-functioning pituitary adenomas, 2 had craniohypophyngiomas, 2 had traumatic brain injury, 2 had primary empty sella and 4 had other hypothalamic–pituitary diseases (i.e. hypophysitis, histiocitosis X, sellar mass or idiopathic hypopituitarism). Twenty of these patients had been previously submitted to S, followed by RT in four cases, and 26 had isolated or multiple hypopituitarism. They had a mean GH peak after the combined GHRH plus arginine test of 3.2±2.5 µg/l (range: 0.2–8.9). The IGF-1 concentrations were below the normal range for age in 19 subjects (68%) and below −1.0 s.d. score in 25 subjects (89%).

Study protocol

The complete remission of acromegaly was further confirmed by a new 2-h oral glucose tolerance test (OGTT, 75 g) for the evaluation of the GH nadir

| Table 1 Clinical and hormonal data of cured acromegalic patients treated with neurosurgery alone (group 1) or followed by radiotherapy (group 2). |
|-------------------------|-----------------|-----------------|---|
|                         | Group 1         | Group 2         | P  |
| n                       | 33              | 23              | –  |
| Sex (M/F)               | 16/17           | 7/16            | NS |
| Age (years)             | 55.6±13.4       | 51.7±11.2       | NS |
| Follow-up from first treatment (months) | 119±97          | 219±123         | <0.01 |
| Follow-up from disease remission (months) | 107±91          | 89±126          | NS  |
| BMI (kg/m²)             | 27.6±3.5        | 29.7±4.8        | 0.06 |
| BMI <25, 25–30, >30 kg/m² (n) | 9/16/8          | 4/9/10          | NS  |
| BF (%)                  | 32.6±8.1        | 38.4±7.1        | 0.05 |
| Pituitary deficiencies (no/isolated/multiple) | 26/3/4          | 8/8/7           | <0.01 |
| NT, IGT, DM (n)         | 23/8/2          | 15/5/2          | NS  |
| Dyslipidaemia (no/yes)  | 19/14           | 11/12           | NS  |
| Blood hypertension (no/yes) | 20/13          | 18/5            | NS  |
| Post-glucose GH nadir levels (µg/l) | 0.18±0.21       | 0.33±0.27       | <0.05 |
| GH peak levels after GHRH + Arg (µg/l) | 10.5±1.15       | 4.3±3.9         | <0.05 |
| Severe GH deficiency (no/yes) | 15/18          | 7/16            | NS  |
| IGF-1 levels (SDS)      | −0.8±1.1        | −0.9±1.1        | NS  |
| Low IGF-1 for age-range (n) | 10 (30%)        | 7 (30%)         | NS  |

M, male; F, female; BMI, body mass index; BF, body fat; NT, euglycemic; IGT, impaired glucose tolerance; DM, diabetes mellitus; GHRH + Arg, GH releasing hormone plus arginine testing; SDS, standard deviation scores.

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levels, except in the four diabetic patients, and by the measure of serum IGF-1 concentrations. In a different day, all the patients underwent a GHRH plus arginine testing for the evaluation of GH peak (GHRH1–29; GEIRE; Serono: 1 µg/kg i.v. at 0 min; arginine hydrochloride, 0.5 g/kg i.v. over 30 min from 0 to 30 min, up to a maximum of 30 g). Blood samples for GH evaluation were taken at 0, 15, 30, 45, 60, 90 and 120 min. This test has been previously validated by other authors for the diagnosis of GHD in the acromegalic population (5, 8). According to more recent criteria, severe GHD has been defined by GH peak <11.5 µg/l if BMI was below 25 kg/m², <8.0 µg/l if BMI was between 25 and 30 kg/m² and <4.2 µg/l if BMI was over 30 kg/m² (12). Partial GHD was defined when GH peak was comprised between the respective limit for severe GHD and 16.5 µg/l (13).

In all the patients, several metabolic parameters and cardiovascular risk factors, such as waist circumference, systolic and diastolic blood pressure, plasma glucose and serum insulin before and after 2-h OGTT, HbA1c and lipid profile (total and HDL-cholesterol, triglycerides), were evaluated. The basal insulin resistance was then calculated by homeostasis model assessment by the following formula: fasting insulin (mU/l)×fasting glucose (mmol/l)/22.5 (14). The areas under the curve for either glucose (gluAUC) or insulin (insAUC) during OGTT were also calculated.

Body composition was evaluated by whole-body bioelectrical impedance analysis, using a portable impedance analyser (RJL Systems, Detroit, MI, USA). Body fat percentage (BF%) was calculated using Segal’s regression equation (15) and the results were compared with those reported by Pichard et al. (16) in age- and sex-matched normal subjects.

Finally, all the patients were studied for neuroradiological imaging by magnetic resonance imaging of the pituitary region before and after gadolinium infusion.

All the described study procedures have been performed in a similar way in both the patients with cured acromegaly and the controls.

The study was approved by the local ethical committee. All the patients gave their written informed consent to participate in the study.

**Assays**

Serum GH levels were measured by two-site monoclonal immunofluorometric assay method (AutoDelfia kit, Wallac, Inc., OY, Turku, Finland). The standards were calibrated against the first WHO IRP 80/505 (1 ng = 2.6 mIU) and the detection limit was 0.01 µg/l (10), with intra- and inter-assay coefficients of variation (CV) of 2 and 1.7% respectively. Serum IGF-1 levels were determined by the commercial RIA kit from Medagnost (Tübingen, Germany) obtaining separation of IGF-1 from binding proteins by acidification in IGF-2 excess. The intra- and inter-assay CV were 3.2 and 8.9%, respectively and IGF-2 cross-reactivity <0.05%. The values were compared with an appropriate age-adjusted range as previously reported (10) and expressed also as SDS.

All the other biochemical and haematological parameters were measured by standard procedures.

**Statistical analysis**

All the results are expressed as mean ± s.d. unless otherwise stated. A paired or unpaired Student’s t-test was performed to compare different variables when data were normally distributed, or else the non-parametric Wilcoxon–Mann–Whitney test was used, as appropriate. The gluAUC and insAUC during OGTT were estimated according to the trapezoidal method. Fisher’s exact test or χ²-test were used to compare the number of patients. Correlations between different parameters were evaluated by linear regression analysis.

All the statistical examinations were assessed using Graph Pad Prism (version 5.01, 2007) and SPSS (version 11.0). Values of P < 0.05 were considered statistically significant.

**Results**

**Prevalence of GHD in cured acromegalic population**

In the population of acromegalic patients in disease remission, the mean basal GH levels were 0.56 ± 0.56 µg/l. GH nadir levels after glucose load were 0.25 ± 0.25 µg/l and IGF-1 concentrations were 18.1 ± 8.9 nmol/l (−0.8 ± 1.1 SDS). In particular, IGF-1 levels were below the normal range for age in 14 patients (25%), being below −1.0 SDS in 29 (52%).

The mean GH peak after the GHRH plus arginine test was 8.0 ± 9.7 µg/l (range: 0.02–54.0 µg/l). A negative correlation was observed between the GH peak and the duration of follow-up from the first treatment for acromegaly (P = 0.05, r = 0.24; Fig. 1A), but not between IGF-1 levels and the duration of follow-up from the first treatment for acromegaly (Fig. 1B). Another negative correlation was found between the IGF-1 levels at the last evaluation and the GH levels at the time of diagnosis (P < 0.01, r = 0.36). No other significant correlation was observed. Nevertheless, the patients with one or more other pituitary failures had lower GH peak with respect to the remaining ones (3.4 ± 3.5 vs 10.9 ± 11.1 µg/l, P < 0.005).

As a whole, 34 out of 56 cured acromegalic patients had severe GHD (61%), with a mean GH peak of 2.8 ± 2.1 µg/l (range: 0.02–6.6). Among the other 22 patients, 15 had a partial response to stimulus (27%) while 7 had a completely normal GH secretion. The prevalence of severe GHD was slightly higher in cured acromegaly than in population with pituitary failures. The prevalence of partial and severe GHD was in particular higher than in controls. In the population with GH failure, 17 of the 22 with pituitary failures had severe GHD (77%), but only 7 of the 34 cured acromegalic patients (21%) had severe GHD, with a significant difference of 56% (95% CI: 37%–75%; P = 0.002). The prevalence of partial GHD was 22% in the cured acromegalic group and 36% in the pituitary failure group, with a non-significant difference. The mean GHRH peak was also significantly higher in the group with pituitary failures (5.4 ± 6.7 µg/l vs 0.9 ± 3.0 µg/l, P = 0.003).

The prevalence of severe GHD was lower in cured acromegalic patients than in the healthy population of the same age, with a significant difference of 62% (95% CI: 41%–82%; P = 0.001). The prevalence of partial GHD was lower in the cured group (21%) than in the healthy population (36%), but the difference was not significant (P = 0.21). The mean GHRH peak was significantly lower in cured acromegalic patients than in the healthy population of the same age (5.4 ± 6.7 µg/l vs 14.4 ± 8.9 µg/l, P = 0.001) and the mean GH peak after the GHRH plus arginine test was also significantly lower (9.5 ± 7.3 µg/l vs 25.3 ± 11.4 µg/l, P < 0.001).

Finally, all the described study procedures have been performed in a similar way in both the patients with cured acromegaly and the controls.

The study was approved by the local ethical committee. All the patients gave their written informed consent to participate in the study.

**Assays**

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All the statistical examinations were assessed using Graph Pad Prism (version 5.01, 2007) and SPSS (version 11.0). Values of P < 0.05 were considered statistically significant.
patients with macroadenomas with respect to those with microadenomas at the time of diagnosis (68 vs 40%, \( P = 0.05 \)). Mean IGF-1 levels were significantly lower in severe GHD patients than in other ones (15.8 \( \pm \) 6.9 vs 21.8 \( \pm \) 9.2 nmol/l, \(-1.1 \pm 1.0 \) vs \(-0.3 \pm 1.1 \) SDS, \( P < 0.01 \)), being below the normal range in 11 and in 3 patients respectively (32 vs 14%, \( P = 0.05 \)). As expected, a higher percentage of GHD patients also had multiple pituitary failures (29 vs 4%, \( P < 0.05 \)). No other clinical, hormonal or metabolic parameter was significantly different between the patients with severe GHD and the other ones. Excluding the patients with partial GHD, some differences were found between the patients with severe GHD and those with normal GH secretion in terms of BMI (28.2 \( \pm \) 3.4 vs 25.8 \( \pm \) 2.0 kg/m\(^2\), \( P = 0.08 \)), BF% (35.6 \( \pm \) 8.6 vs 32.3 \( \pm \) 5.5%, \( P = 0.06 \)) and insAUC (5.5 \( \pm \) 3.1 vs 2.8 \( \pm \) 1.6 mU/l per 120 min, \( P < 0.05 \)).

**Impact of different treatments for acromegaly on GHD occurrence**

The percentage of severe GHD patients treated for acromegaly remained unchanged when subdividing the population into the two different treatment groups. In fact, 18 out of 33 patients in group 1, and 16 out of 23 in group 2 had severe GHD (54 vs 70%, \( P = 0.05 \)). The two groups also had similar mean IGF-1 levels (\(-0.8 \pm 1.1 \) vs \(-0.9 \pm 1.1 \) SDS, \( P = 0.09 \)), that were below the normal range for age in ten patients in group 1 and in seven patients in group 2 (30 vs 30%, \( P = 0.05 \)), being below \(-1.0 \) SDS in 18 and 11 patients respectively (54 vs 48%, \( P = 0.05 \)). Considering only the patients with severe GHD, they had both similar mean GH peak levels (3.4 \( \pm \) 2.4 \( \mu \)g/l in group 1 vs 2.0 \( \pm \) 1.4 \( \mu \)g/l in group 2, \( P = 0.05 \)) and comparable percentages of subjects with low IGF-1 levels (12% in group 1 vs 22% in group 2, \( P = 0.05 \)).

**Comparison between GHD cured acromegalic patients and GHD controls**

Comparing the 34 severe GHD patients treated for acromegaly with the 28 severe GHD patients treated for other pituitary diseases, no significant differences were found in the GH peak after stimulation test and in all the evaluated metabolic and cardiovascular parameters (Table 2), but GHD cured acromegalic patients had higher mean IGF-1 levels (\(-1.1 \pm 1.0 \) vs \(-1.8 \pm 0.7 \), \( P < 0.01 \)) with a lower proportion of subjects with IGF-1 below the normal range for age (32 vs 68%, \( P < 0.05 \)) and a lower percentage of subjects with hypopituitarism (47 vs 93%, \( P < 0.05 \)). Conversely, the seven acromegalic patients with normal GH secretion had slightly lower fasting insulin (3.9 \( \pm \) 2.5 vs 11.3 \( \pm \) 11.0 mIU/l, \( P = 0.09 \)) and slightly improved lipid

**Table 2** Biochemical and metabolic parameters in cured acromegalic patients and in patients followed for other pituitary diseases with severe GHD deficiency (GHD).

|M, male; F, female; SDS, standard deviation score; BMI, body mass index; BF, body fat; HOMA-IR, insulin resistance by homeostasis model assessment (13); NT, euglycemic; IGT, impaired glucose tolerance; DM, diabetes mellitus; TC, total cholesterol; TG, triglycerides.|
|---|---|---|
|**n**| Cured acromegalic patients with severe GHD| Control group with severe GHD| \( P \) |
|---|---|---|
|Sex (M/F)| 18/16| 17/11| NS |
|Age (years)| 54.9 \( \pm \) 12.5| 46.3 \( \pm \) 11.6| NS |
|IGF-1 levels (SDS)| \(-1.1 \pm 1.0\)| \(-1.8 \pm 0.7\)| \( < 0.01 \) |
|Pituitary deficiencies (no/isolated/multiple)| 14/5/11| 2/6/21| \( < 0.05 \) |
|BMI (kg/m\(^2\))| 28.2 \( \pm \) 3.4| 27.3 \( \pm \) 4.2| NS |
|BF (%)| 35.6 \( \pm \) 8.6| 36.8 \( \pm \) 9.0| NS |
|Glucose (mg/dl)| 85.7 \( \pm \) 14.1| 83.8 \( \pm \) 8.5| NS |
|Insulin (mU/l)| 5.9 \( \pm \) 3.7| 11.3 \( \pm \) 11.0| NS |
|HOMA-IR| 1.3 \( \pm \) 1.0| 2.5 \( \pm \) 2.7| NS |
|HbA1c (%)| 5.5 \( \pm \) 0.5| 5.3 \( \pm \) 0.4| NS |
|Glucose alterations (NT/IGT/DM)| 25/7/2| 25/3/0| NS |
|TC (mg/dl)| 210 \( \pm \) 45| 207 \( \pm \) 38| NS |
|c-HDL (mg/dl)| 58 \( \pm \) 18| 51 \( \pm \) 23| NS |
|TG (mg/dl)| 118 \( \pm \) 75| 112 \( \pm \) 41| NS |
|Dyslipidaemia (no/yes)| 20/14| 12/16| NS |
|Hypertension (no/yes)| 29/5| 19/9| NS |

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A | \( P = 0.05 \)
---|---
B | \( r = 0.24 \)

**Figure 1** Correlation between the duration of follow-up from the first treatment for acromegaly and serum GH peak after GHRH plus arginine testing (A) or serum IGF-1 levels at the last evaluation (B). White symbols: patients treated with neurosurgery alone (group 1); black symbols: patients treated with radiotherapy (group 2).
Discussion

The present study demonstrates that severe GHD may occur in a high percentage of cured acromegalic patients, independently from the type of previous treatment for acromegaly. If confirmed, this observation could somehow explain why life expectancy may remain slightly reduced in acromegalic patients successfully treated with surgery alone with respect to the general population (17). In fact, in our series of cured acromegalic patients, evaluated by the GHRH plus arginine test, GH peak was consistent with a severe GHD in about 60% of the subjects. Most importantly, no significant difference in the percentage of severe GHD between patients treated with S alone and those treated also with RT (including both conventional RT and radiosurgery by gamma-knife) was observed. These results are in keeping with the held concept that RT may induce GHD in a quite high percentage of cured acromegalic patients (2–5), but for the first time states that also S alone may induce a deterioration of the residual GH secretion. In fact, to date, only scarce and contradictory data are available on the prevalence of GHD in only operated acromegalic patients (4, 7–9).

In terms of possible prognostic factors, it seems that the presence of a macroadenoma and higher GH levels at the time of diagnosis together with the concomitant existence of other pituitary failures (in particular multiple deficiencies) might be the best candidates to predict GHD in the population of patients successfully treated for acromegaly. On this connection, it is tempting to speculate that a more invasive therapeutic approach needed in most aggressive GH-secreting adenomas might increase the risk to develop pituitary failures, including severe GHD. In addition, also a longer duration of follow-up from the treatment seems to be a predictive factor for GHD occurrence. The present results might somehow suggest the intriguing possibility that the presence for many years of a pituitary mass and/or of an excess of GH and IGF-1 can damage in an irremediable way the normal somatotroph cells, but it is difficult to be ascertained. Nevertheless, only a prospective/longitudinal study with periodically repeated testing might better clarify whether it is going to progressively increase over the time.

It is also important to mention that, due to persistent qualitative abnormalities in GH secretion, it is not easy to diagnose GHD in cured acromegaly. In fact, there is still no definitive consensus on the best testing and on the criteria to define the GHD in this kind of population. Indeed, other authors previously validated the GHRH plus arginine test in acromegalic patients treated with either surgery or RT (5, 8).

As far as IGF-1 levels are concerned, they were below the normal range only in a minority of our patients treated for acromegaly and GH deficient (about 30% in both treatment groups with respect to 68% of the GHD control subjects). These findings suggest that IGF-1 concentrations might be even less informative in the suspected diagnosis of GHD in these patients as compared with other GHD patients (18, 19). Therefore, we can conclude that it is recommendable to periodically investigate all cured acromegalic patients with dynamic GH secretion evaluation, such as GHRH plus arginine test, independently from previous treatment for acromegaly and from IGF-1 levels.

As for metabolic evaluation, a slightly better BMI and insulin response was observed in patients treated for acromegaly with normal GH response to stimulus with respect to those with severe GHD. Due to the possible negative influence of an even minor GH secretion alteration on the metabolic condition, patients with partial GHD have been excluded from the analysis (20, 21).

Furthermore, we confirmed that there are no significant differences in terms of metabolic parameters between cured acromegalic patients and matched adults with other pituitary diseases with severe GHD, in agreement with previous observation (22). On the contrary, a recent study has reported a more impaired cardiovascular risk profile in ten GHD patients with previous acromegaly as compared with other GHD patients (23). On the other hand, the patients treated for acromegaly with normal GH secretion showed slightly lower insulin levels and better lipid profile with respect to controls with severe GHD. Starting from all these results, we might suggest that recombinant human GH (rhGH) therapy should be considered at least in a subgroup of cured acromegalic patients (i.e. with lower IGF-1 concentrations and/or altered body composition or metabolic condition). In fact, two previous studies already demonstrated some benefits of rhGH therapy on quality of life (19), body composition and serum lipid profile in cured acromegaly. However, the suggestion of an increased frequency of vascular events might represent a safety concern (23). Thus, specific studies on long-term effects of rhGH in this cohort of patients, with particular focus on cardiovascular parameters and mortality are now necessary before defining specific guidelines.

On the basis of the high percentage of severe GHD found in our series of cured acromegalic patients, we conclude that a dynamic evaluation of residual GH secretion, besides a complete clinical assessment, is mandatory in these patients, independently from previous type of treatment for acromegaly itself and particularly in those with other pituitary failures.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.
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