# Characteristics and treatment responsiveness of patients with acromegaly and a paradoxical GH increase to oral glucose load

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## Abstract

*Objectives:* We aimed to investigate the clinical, biochemical, histological and radiological characteristics as well as the response to somatostatin analogs (SSA) in a large cohort of acromegaly patients with a paradoxical GH response (PR) to oral glucose tolerance test (OGTT).
*Design:* Retrospective study.
*Methods:* Of 110 patients with acromegaly included in our study, 30 (PR+; 27%) had a paradoxical GH increase of more than 25% relative to basal GH levels during OGTT.
*Results:* At diagnosis, PR+ patients were older than PR− patients (52 ± 16 years vs 44 ± 14 years, $P < 0.05$) and had smaller pituitary tumors (40% microadenomas vs 19%, $P < 0.05$), which were less often invasive (17% vs 35%, $P < 0.05$), overall more secreting (insulin-like growth factor-1 (IGF-1)/tumoral surface: 2.35 ULN/cm$^2$ (0.28–9.06) vs 1.08 (0.17–7.87), $P = 0.011$), and more often hypointense on T2-weighted MRI (92% vs 48%, $P = 0.001$). While the rate of remission after surgery was similar in the two groups (69%), a better response to SSA treatment was observed in PR+ patients, either before (IGF-1 reduction of > 50% after 3–6 months in 77% vs 49%, $P = 0.023$) or after surgery (normalization of IGF-1 in 100% vs 44%, $P = 0.011$).
*Conclusions:* Our study demonstrates that in acromegaly, a paradoxical GH increase during OGTT is associated with particular features of somatotroph adenomas and with a better prognosis in terms of response to SSA.

*European Journal of Endocrinology*
(2021) **185**, 313–321

European Journal of Endocrinology

## Introduction

The lack of growth hormone (GH) suppression after an oral glucose tolerance test (OGTT) is still considered the gold standard for the diagnosis of acromegaly. With the widespread use of ultrasensitive GH assays, the GH nadir during OGTT has been revised in recent years and a cut-off of 0.3–0.4 µg/L is now proposed by many experts (1, 2, 3, 4). Furthermore, the time course of GH concentration after oral glucose load is variable in acromegaly as hormone levels may drop, remain stable or rise paradoxically. Indeed, about one-third of acromegaly patients have a paradoxical GH increase during OGTT (5). This phenomenon was first described by Beck *et al.* in 1966 (6) and later confirmed by many other studies (7, 8, 9, 10, 11, 12, 13).

The mechanisms of this paradoxical GH rise in response to oral glucose are not yet completely understood, but a role of a glucose-dependent insulinotropic polypeptide (GIP) has been strongly suggested (5, 14). GIP is a peptide secreted by the endocrine K cells of the duodenum during feeding, which stimulates the adenylate cyclase pathway through binding to its receptors (GIPR). A paradoxical

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-21-0324

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GH response (PR) was reported after injection of GIP in two patients with acromegaly (15). Another study has demonstrated the ectopic expression of GIPR in the somatotroph adenomas of ten patients, all presenting a PR during OGTT (16). Moreover, the loss of this PR when glucose is administered intravenously supports the hypothesis of the involvement of a gastrointestinal hormone (15).

Few studies have examined so far whether this PR during OGTT is associated with specific clinical features, tumor characteristics or response to therapy in patients with acromegaly (12, 13). The aims of our study were to analyze the clinical, biochemical, histological and radiological characteristics as well as the treatment responsiveness of patients with a PR to glucose (PR+) and to compare them with patients without such a response (PR−).

## Patients and methods

### Patients

We retrospectively analyzed the medical records of 163 patients who had been diagnosed and treated for acromegaly in our institution between 1980 and 2019. Fifty-three patients had to be excluded for the following reasons: the lack of OGTT data at diagnosis (48 patients including 11 with overt diabetes), ectopic secretion of growth hormone-releasing hormone (GHRH) (3 patients) or McCune−-Albright syndrome (2 patients). According to the current criteria of the American Diabetes Association, diabetes mellitus was diagnosed when fasting plasma glucose was ≥ 126 mg/dL or when the 2 h post-OGTT glucose was ≥ 200 mg/dL (17, 18). In the end, the number of patients included in our study was 110.

In all patients, OGTT was performed at diagnosis by oral administration of 75 g glucose after an overnight fast, without any treatment with somatostatin analogs (SSA) or antidiabetic medications. In the absence of a universal consensus, a PR was defined as an increase greater than 25% at any time point of the test, compared to the basal fasting GH concentration. IGF-1 and prolactin values were also measured and expressed as the upper limit of normal (ULN) for age and gender, in order to account for assay variability over time.

Our study was approved by the Ethics Committee of Saint Luc University Hospital. As it was a retrospective study, the patient's informed consent was not requested.

### Methods

Serum GH concentrations were measured using an RIA until September 1999, the Nichols Advantage GH immunoassay from October 1999 to April 2006, the Siemens DPC Immulite assay between April 2006 and April 2008 (all these assays using the GH WHO RP 80/505 standard), and the Beckman DXI GH assay (using standard WHO RP 98/574) from April 2008 until today. Serum IGF-I concentrations were measured using an RIA until February 2000, the Nichols Advantage IGF-I assay until July 2006, the Siemens DPC Immulite IGF-I assay between August 2006 and March 2009 and the Liaison Diasorin IGF-I assay from March 2009 until today, as reported previously (18).

Radiological characteristics of the pituitary tumor were carefully reviewed by one author (D M) on the diagnostic MRI which was available for 82 patients, while in the remaining patients, data were retrieved from the protocol written by the neuroradiologist at the time of diagnosis. Tumors were classified as micro- or macro-adenomas if the maximum diameter was < 10 or ≥ 10 mm, respectively. An approximated coronal pituitary tumor area was calculated by the simplified circle formula ($\pi/4 \times$ tumor height $\times$ tumor width). Pituitary adenomas were considered invasive if they extended into the cavernous or sphenoid sinus, following the criteria previously described (19). The T2-weighted tumoral pattern was evaluated by calculating the ratio of the mean T2 intensity of the adenoma to the mean T2 intensity of the gray matter in the temporal cortex, both measured in a representative 50–100 $mm^2$ circle area on a coronal view (20). Tumors were arbitrarily classified as hypointense (ratio ≤ 0.90), isointense (ratio between 0.91 and 1.09) or hyperintense (ratio ≥ 1.10). In the final analyses, T2 iso- and hyperintense adenomas were considered together as they likely represent a similar clinicopathological entity different from hypointense GH-secreting tumors (21, 22).

The proliferative pattern of the tumor was available in 59 cases and defined according to the classification of Trouillas *et al.* (23). Somatotroph adenomas were considered as proliferative if at least two of the three following criteria were present: number of mitoses > 2/10 at a high power field (HPF), Ki67 index ≥ 3% and/or positive p53 detection, according to previously reported procedures (19). Finally, when the information was available ($n$= 32), we also classified the adenomas according to their pattern of GH-containing secretory granules at immunohistochemistry showing either strong and diffuse immunoreactivity for GH throughout the cytoplasm of a majority of adenoma cells (densely granulated adenomas)

or a weaker and more focal GH labeling (sparsely granulated somatotroph adenomas). Immunoreactivity for cytokeratin was also used to help differentiating the two immunophenotypes.

The response to SSA was assessed both preoperatively and postoperatively but using different criteria given differences in treatment duration and titration. A high dose of SSA was arbitrarily defined as an octreotide dose > 20 mg/4 weeks, a lanreotide dose > 90 mg/4 weeks or a pasireotide dose > 20 mg/4 weeks. Before surgery, patients were classified as responders if their insulin-like growth factor (IGF-1) level dropped by at least 50% within the 3–6 months of short pre-surgical treatment. After surgery, the patients were defined as good responders if they had a normal IGF-1 under a low/medium dose of SSA (defined as an octreotide or pasireotide dose ≤ 20 mg/4 weeks or as a lanreotide dose ≤ 90 mg/4 weeks), without any other concomitant treatment (dopamine agonist or pegvisomant) or prior radiotherapy.

### Statistical analyses

Statistical analyses were performed with the IBM SPSS Statistics software version 25.0, using unpaired Student's *t*-tests for normally distributed continuous variables and Chi-squared tests for categorical variables. A *P*-value < 0.05 was considered statistically significant. Serum GH values were log-transformed before statistical comparisons.

## Results

### General characteristics of the patients

In our population of 110 acromegaly patients, there was a slight female predominance (53%) and the mean age at diagnosis was 46.4 years (Table 1). The median delay between the onset of the first clinical sign and the diagnosis was 5 years. In many patients (39%), the disease was revealed by morphological changes. At diagnosis, 43% of patients had a headache, 56% complained of sweating, 77% of acral overgrowth, 47% of asthenia and 53% of arthralgias. The median basal GH and IGF-1 concentrations at diagnosis were 2.8 × ULN and 2.44 × ULN, respectively, while one-third of the patients had hyperprolactinemia. A macroadenoma was found in 75% of the cases, and 30% of the tumors were invasive. Among cases with available histological data, the majority of adenomas were classified as densely granulated, and only 22 % were proliferative (Table 1).

**Table 1** Characteristics at diagnosis of all patients (*n* = 110), patients without paradoxical GH response (PR–: *n* =80) and patients with a PR to glucose load (PR+: *n* = 30). All values are shown as mean ± S.D. medians and interquartiles ranges or proportions. *P*-values apply to comparisons between PR– and PR+ patients.

| Characteristics | All patients (*n* = 110) | Patients PR– (*n* = 80) | Patients PR+ (*n* = 30) | *P*-value |
|---|---|---|---|---|
| Clinical | | | | |
| Age (years) | 46.4 ± 14.8 | 44.3 ± 13.9 | 52.0 ± 15.6 | **0.013** |
| Sex ratio (men/women) | 52/58 | 36/44 | 16/14 | NS |
| BMI (kg/m$^2$) | 28.0 ± 5.7 | 27.5 ± 5.1 | 29.3 ± 7.1 | NS |
| Biochemical | | | | |
| Basal GH (× ULN) | 2.8 (0.4–32.6) | 2.9 (0.5–23.7) | 2.7 (0.3–36.6) | NS |
| Basal IGF-1 (× ULN) | 2.44 ± 1.00 | 2.39 ± 1.02 | 2.67 ± 0.92 | NS |
| IGF-1/tumor surface (ULN/cm$^2$) | 1.30 (0.21–8.40) | 1.08 (0.17–7.87) | 2.35 (0.28–9.06) | **0.011** |
| Hyperprolactinemia (%) | 35/106 (33%) | 29/78 (37%) | 6/28 (21%) | NS |
| Prolactin (× ULN) | 0.77 (0.27–6.24) | 0.82 (0.27–5.69) | 0.64 (0.27–6.58) | NS |
| Glucose metabolism | | | | |
| HbA1c (%) | 5.8 ± 0.7 | 5.7 ± 0.7 | 5.9 ± 0.7 | NS |
| Fasting plasma glucose (mg/dL) | 99 ± 18 | 96 ± 15 | 108 ± 24 | **0.013** |
| Diabetes mellitus (%) | 14/110 (13%) | 5/80 (6%) | 9/30 (30%) | **0.005** |
| Radiological | | | | |
| Macro-/micro-adenoma | 83/27 | 65/15 | 18/12 | **0.022** |
| Tumor surface (cm$^2$) | 1.56 (0.18–8.21) | 1.92 (0.18–8.25) | 1.10 (0.16–5.91) | **0.036** |
| Cavernous sinus invasion (%) | 33/110 (30%) | 28/80 (35%) | 5/30 (17%) | **0.048** |
| Hypointensity T2 (%) | 50/82 (61%) | 28/58 (48%) | 22/24 (92%) | **<0.001** |
| Histological | | | | |
| Densely granulated (%) | 26/32 (81%) | 16/22 (73%) | 10/10 (100%) | NS |
| Proliferative tumor (%) | 13/59 (22%) | 12/46 (26%) | 1/13 (8%) | NS |
| Ki67 index | 2.0 ± 1.4 | 2.1 ± 1.5 | 1.5 ± 1.1 | NS |

NS, not significant; PR, paradoxical GH response during oral glucose tolerance test; ULN, upper limit of normal.

Regarding treatment, most of the patients (97/110, 88%) underwent a transsphenoidal surgery and three-quarters of them had received preoperative medical treatment with SSA, given for a median of 4 months. Fifty-eight percent of the patients were considered as responders, their IGF-1 levels returning to normal or decreasing by more than 50% during this short period. A global remission rate of 69% was observed after surgery, while a postoperative tumor residue was observed in 29%. However, some patients had a recurrence (16%) which occurred on average 2 years after the operation. In the end, 37/97 operated patients required postoperative treatment with SSA (Table 2). Figure 1 summarizes the different lines of therapy used in our cohort.

## Clinical and biological characteristics of patients with (PR+) and without paradoxical GH response (PR−)

A PR (≥ 25%) after glucose load was found in 30/110 patients (27%). The GH peak occurred after 120 min in half of the cases, at 60 min in 37% and at 30 min in 13% (Fig. 2). However, all patients but one would still have been classified as paradoxical responders if only the 120 min time point was considered (data not shown).

When comparing patients with and without PR, the same clinical features were found at diagnosis (sex ratio, BMI, hypertension, smoking), except age, the mean age being higher in the PR+ than in the PR− group (52 years vs 44 years, $P = 0.013$) (Table 1). The delay of diagnosis and the frequency and severity of symptoms were also comparable.

No significant difference was found in basal serum GH and IGF-1 levels between the two subgroups, but the relationship between basal fasting GH (expressed on a log scale) and IGF-1 concentration at diagnosis was different between both subgroups, with each baseline GH value corresponding to a higher IGF-1 concentration in the PR+ group compared to the PR− group (Fig. 3). In addition, when IGF-1 values were related to the tumoral surface, they were significantly higher in PR+ patients (2.35 ULN/cm2 vs 1.08 ULN/cm$^2$, $P = 0.011$), while such difference was not observed regarding fasting GH values expressed per unit of tumor surface (data not shown).

The median prolactin level at diagnosis and the prevalence of hyperprolactinemic patients were similar between the two groups. On the other hand, the fasting plasma glucose concentration and the rate of diabetes were higher in the cohort of PR+ patients than in PR− patients (108 mg/dL vs 96 mg/dL, $P = 0{,}013$; 30% vs 6%, $P = 0{,}005$, respectively).

## Radiological and histological findings of patients with (PR+) and without paradoxical GH response (PR−)

In the PR− group, the tumoral surface was significantly larger, the prevalence of macroadenomas was greater (81% vs

**Table 2** Treatment outcome in all patients and in patients without paradoxical GH response (PR−) and with a paradoxical response (PR+) to glucose load). All values are shown as mean ± s.d., medians and interquartiles ranges or proportions. *P*-values apply to comparisons between PR− and PR+ patients.

| | **All patients** (*n* = 110) | **Patients PR−** (*n* = 80) | **Patients PR+** (*n* = 30) | ***P*-value** |
|---|---|---|---|---|
| Preoperative SSA treatment | | | | |
| No. of patients on high SSA dose* | 17/71 (24%) | 12/49 (25%) | 5/22 (23%) | NS |
| GH under SSA (× ULN) | 0.91 (0.10–7.79) | 1.20 (0.19–10.83) | 0.33 (0.09–7.63) | **0.025** |
| GH under SSA/basal GH | 0.39 (0.04–1.43) | 0.40 (0.06–1.55) | 0.22 (0.01–1.24) | NS |
| IGF-1 under SSA (× ULN) | 1.47 ± 0.83 | 1.57 ± 0.90 | 1.26 ± 0.61 | NS |
| IGF-1 under SSA/basal IGF-1 | 0.56 ± 0.27 | 0.59 ± 0.25 | 0.46 ± 0.21 | **0.035** |
| SSA responders | 41/71 (58%) | 24/49 (49%) | 17/22 (77%) | **0.023** |
| Surgery | | | | |
| No. of patients operated | 97/110 (88%) | 75/80 (94%) | 22/30 (73%) | **0.006** |
| Remission after surgery | 67/97 (69%) | 52/75 (69%) | 15/22 (68%) | NS |
| Visible postoperative residue at MRI | 28/97 (29%) | 21/75 (28%) | 7/22 (32%) | NS |
| Recurrence | 11/67 (16%) | 7/52 (13%) | 4/15 (27%) | NS |
| Postoperative SSA treatment | | | | |
| No. of patients on high SSA dose* | 11/25 (44%) | 11/18 (61%) | 0/7 (0%) | **0.006** |
| IGF-1 under SSA (× ULN) | 1.11 ± 0.68 | 1.22 ± 0.63 | 0.68 ± 0.24 | **0.002** |
| SSA responders | 15/25 (60%) | 8/18 (44%) | 7/7 (100%) | **0.011** |

*A high SSA dose was arbitrarily defined as an octreotide dose > 20 mg/4 weeks, a lanreotide dose > 90 mg/4 weeks or a pasireotide dose > 20 mg/4 weeks.
NS, not significant; PR, paradoxical GH response during oral glucose tolerance test; SSA, somatostatin analog; ULN, upper limit of normal.

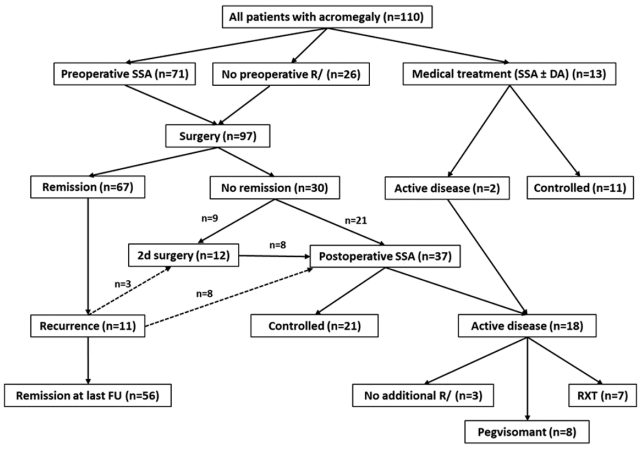


**Figure 1**
Summary of the different treatment lines used in our cohort of 110 patients.

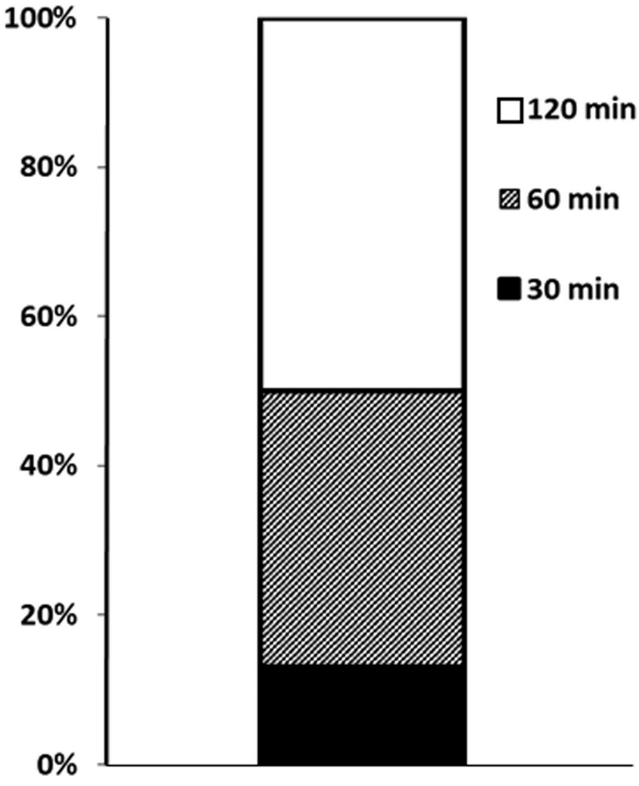


**Figure 2**
Time of the growth hormone peak during oral glucose tolerance test (OGTT) in the patients with a paradoxical GH response (PR+) to glucose load.

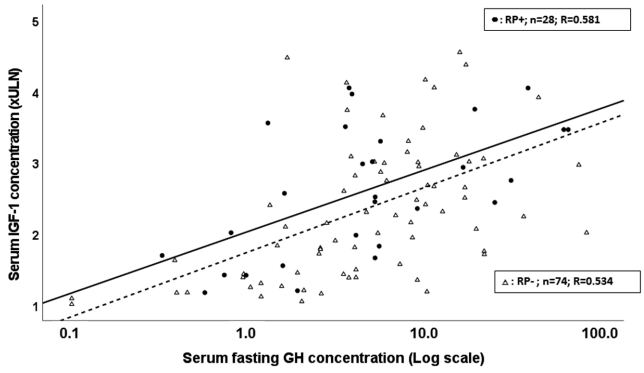


**Figure 3**
Relationship between basal fasting growth hormone (GH) and insulin-like growth factor (IGF-1) concentration at diagnosis in patients with and without a paradoxical GH response (PR+ and PR−) to oral glucose tolerance test (OGTT).

60%, $P = 0.022$), and tumors were two-fold more frequently invasive (Table 1). On the other hand, a significantly greater proportion of T2-weighted hypointense adenomas was found in PR+ patients (92% vs 48%, $P < 0.001$). In this PR+ group, all the pituitary tumors with available pathology reports were classified as densely granulated while 6/22 adenomas were sparsely granulated in the PR− patients. The proportion of proliferative adenomas was much lower in the PR+ than in the PR− group (8% vs 26%). However, this difference was not significant, likely because of the low number of patients with histological data.

## Treatment responses in patients with (PR+) and without paradoxical GH response (PR−)

The number of patients receiving preoperative SSA was similar between the two groups. A lower GH level under SSA (0.33 vs 1.20 × ULN), a greater decrease in IGF-1 (−54% vs −41%), and a higher prevalence of good SSA responders (77% vs 49%, $P < 0.05$) were observed before surgery in the group of PR+ patients.

A greater proportion of PR− patients had undergone surgery (94%) compared to PR+ patients (73%). After surgery, similar postoperative GH and IGF-1 concentrations were observed in the two groups, as well as similar remission rates, the prevalence of a postoperative tumor residue, and recurrence rates (Table 2).

To evaluate the response to SSA after surgery, we only analyzed data from the 25 patients operated and treated thereafter only with SSA, that is, without any other concomitant (dopamine agonist or pegvisomant) and without prior treatment with radiotherapy. A majority

of PR– patients (11/18) but none of the PR+ patients were treated with high SSA doses (61% vs 0%, $P = 0.006$). Despite these lower SSA doses, the IGF-1 levels in the PR+ patients were significantly lower and the number of good responders (having normal IGF-1 under low/medium doses of SSA) was higher than in PR– patients (100% vs 44%, $P = 0.011$). In fact, all PR+ patients were finally controlled by a treatment including surgery ± SSA at low doses, while in the PR– group, 10% received pegvisomant and 9% underwent radiotherapy.

## Discussion

A paradoxical GH increase during OGTT was first described in 1966 (6) and since then has been reported in about one-quarter to one-third of patients with acromegaly, depending on different criteria used to define such response among studies, regarding both the magnitude of GH increase and the timing of GH peak (8, 9, 10, 12, 13). In our study, considering a PR as an increase in GH greater than 25% relative to the pretest value and at any time during OGTT, we found a proportion of 27% of PR+ patients.

Two recent studies on this issue defined the GH PR as a 20 and 30% increase, respectively (12, 13). To the best of our knowledge, these two studies are the only ones that aimed to compare the clinical, biological, histological and/or radiological characteristics as well as the treatment responsiveness of acromegaly patients with or without a PR to an oral glucose load. The first study published by Scaroni *et al.* included a large but heterogeneous cohort of 496 patients managed in four different Italian centers (12). The second one published by Mukai *et al.* included a smaller group of 63 patients followed in the same hospital (13). Our own study concerns a monocentric cohort of 110 patients with acromegaly thoroughly investigated and managed using similar protocols. We compared our results to those of these two studies (Table 3). As reported by Scaroni *et al.* (12) but not by Mukai *et al.* (13), we found that PR+ patients were older (by around 8 years) than PR– patients, while the sex ratio was roughly equivalent between the groups in the three studies.

The two previous studies found comparable GH levels but higher IGF-1 at diagnosis in PR+ acromegaly patients (12, 13). In contrast, in our work, basal serum GH and IGF-1 concentrations were not significantly different between the two groups. However, when IGF-1 values were related to the tumor surface, these relative values were much higher in the PR+ subgroup than in the PR– subgroup, while this was not true for GH. In addition, the relationship between GH and IGF-1 was different between both groups, showing higher IGF-1 generation despite similar fasting GH concentration in PR+ patients. As IGF-1 is considered the best indicator of integrated GH secretion over 24 h, we may conclude that PR+ adenomas are secreting overall more GH than PR– tumors. The reasons for this are not fully elucidated but might reflect repeated higher increases of GH secretion after every meal containing carbohydrates in PR+ despite similar fasting GH levels.

**Table 3** Comparison of studies analyzing the characteristics and treatment responsiveness in acromegaly patients without paradoxical growth hormone response (PR–) and with paradoxical growth hormone response (PR+). All values are shown as mean, medians, or proportions. *P*-values apply to comparisons between PR– and PR+ patients.

| | **Scaroni *et al.*** (12) | | **Mukai *et al.*** (13) | | **Our series** | |
|---|---|---|---|---|---|---|
| | Patients PR– | Patients PR+ | Patients PR– | Patients PR+ | Patients PR– | Patients PR+ |
| Patients, *n* | 312 | 184 | 44 | 19 | 80 | 30 |
| Age (years) | 40.5 | 44.1** | 52 | 48 | 44.3 | 52.0* |
| Sex ratio (men/women) | 180/132 | 91/93 | 22/22 | 9/10 | 36/44 | 16/14 |
| Basal GH (µg/L) | 10.7 | 11.1 | 7.4 | 10.6 | 6.3 | 5.3 |
| Basal IGF-1 (× ULN) | 2.6 | 3.5** | SDS = 6.4 | SDS = 8.3* | 2.4 | 2.6 |
| Prolactine (µg/L) | 12.8 | 8.3** | NA | NA | 15.8 | 9.8 |
| Fasting plasma glucose (mg/dL) | NA | NA | 98 | 100 | 96 | 108* |
| Diabetes mellitus (%) | NA | NA | 27% | 21% | 6% | 30%** |
| Macro-/micro-adenoma | 258/54 | 148/36 | 34/10 | 16/3 | 65/15 | 18/12* |
| Cavernous sinus invasion (%) | 81/299 (27%) | 27/182 (15%)** | 7/44 (16%) | 1/19 (5%) | 28/80 (35%) | 5/30 (17%) * |
| Hypointensity T2 (%) | NA | NA | 15/44 (34%) | 14/19 (74%)* | 28/58 (48%) | 22/24 (92%)** |
| Densely granulated (%) | 17/32 (53%) | 10/11 (91%) | 20/32 (63%) | 12/14 (86%) | 16/22 (73%) | 10/10 (100%) |
| SSA responder | 52/104 (50%) | 48/63 (76%)** | NA | NA | 24/49 (49%) | 17/22 (77%) * |
| Postoperative remission | 93/145 (64%) | 54/80 (68%) | 21/42 (50%) | 8/18 (44%) | 52/75 (69%) | 15/22 (68%) |
| No. of patients controlled by SSA | 25/97 (26%) | 32/61 (52%)** | NA | NA | 8/18 (44%) | 7/7 (100%) * |

*$P$-value < 0.05; **$P$-value < 0.01.
NA, information not available; SDS, standard deviation score; SSA, somatostatin analog; ULN, upper limit of normal.

The median prolactin level and the proportion of patients with hyperprolactinemia tended to be lower in the PR+ group although these differences were not significant. Such a difference was also found in the study by Scaroni *et al.* (12). Hyperprolactinemia in acromegaly patients is explained either by co-secretion of GH and prolactin by the tumor or by pituitary stalk compression. Among patients with an increase in prolactin, we found a greater number of adenomas with this co-secretion in the PR− group than in the PR+ group. In addition, the tumors were smaller in PR+ patients and were, therefore, less likely to compress the pituitary stalk.

Regarding glucose metabolism, PR+ patients had significantly higher plasma glucose concentrations in the fasting state and were more often diabetic than PR− subjects, while glucose levels during OGTT and HbA1c, though higher in the PR+ group, were not statistically different between the two groups. Mukai *et al.* also reported a higher frequency of glucose intolerance in PR+ patients (13), even though the rate of diabetes in their study was similar between both subgroups. These discordances between the two studies could be explained by differences in the population characteristics and in the criteria used to evaluate glucose metabolism, knowing that such criteria may evaluate different physiopathological aspects of glycemic regulation. In addition, we excluded from our study overtly diabetic patients who did not undergo glucose tolerance testing at the diagnosis of acromegaly.

Patients with a paradoxical GH increase after glucose load had smaller, less invasive and more often T2-weighted hypointense tumors than those without PR. All PR+ patients with available histology were also classified as densely granulated adenomas. The correlation between younger age at diagnosis, greater tumor size and more frequent cavernous sinus invasion has been previously described in acromegaly patients (24). Our study supports this observation and associates this phenotype with the absence of a paradoxical GH increase to OGTT. In addition, a T2-weighted hypointense signal of GH-secreting pituitary adenomas has been also associated with a similar phenotype and a densely granulated pattern (22, 25, 26, 27).

Although the majority of our patients underwent surgery, patients without a paradoxical GH increase were more frequently operated. Their larger tumor size and poorer response to SSA treatment might retrospectively explain this difference in treatment options. The GH response to OGTT, however, does not affect the neurosurgical outcome, as we observed similar rates of remission and recurrence between the two groups. This observation is intriguing, considering that tumors of PR+ patients were smaller and less invasive. Previous studies have also reported the same percentage of remission, based on the postoperative IGF-1 level (12, 13).

A better response to preoperative and postoperative SSA treatment was seen in PR+ patients compared to PR− acromegaly patients. After surgery, all PR+ patients were controlled with or without SSA, while it was not the case in the other group. Scaroni *et al.* and Mukai *et al.* have also found a better response to SSA treatment in patients with a PR to glucose load (12, 13). The mechanisms increasing SSA responsiveness in PR+ patients are not yet completely understood but may involve in part an additional inhibitory effect of SSA on GIP (28, 29), which likely mediates post-glucose GH secretion in these patients (5, 14, 15, 16). Moreover, as observed in our study, previous studies have demonstrated that a better response to SSA is usually observed in patients with a T2-hypointense GH adenoma (22) or with a densely granulated somatotrope adenoma (27). Furthermore, it has been shown that the concentration of somatostatin receptors subtype 2 is greater in densely granulated tumors (30, 31). These radiologic and pathological features seem thus to correspond, at least partly, to the same phenotype as the PR+ adenomas.

Our study has several limitations. Because of the retrospective nature of our work, all data were not available for all patients. However, the number of missing data was generally limited for the main parameters. The hormonal analyses have not been systematically performed in our institution and there was, therefore, some heterogeneity in laboratory assays. In addition, these assays have evolved over time. However, we corrected this limitation by expressing GH and IGF-1 relative to the ULN for each assay. Thirdly, we only included in our study patients who performed an OGTT. Therefore, a subset of patients with overt diabetes, a common complication of acromegaly, were excluded. Finally, we evaluated the biological response but not the radiological response to medical treatment.

In conclusion, in our large cohort of 110 acromegaly patients, we show a PR during OGTT in 27% of the cases. This paradoxical increase in GH reflects several significant characteristics of the tumor: PR+ patients are older, have smaller and less often invasive pituitary tumors, which also are more secreting (as reflected by IGF-1 levels related to basal GH or tumor surface). PR+ adenomas are more often hypointense on T2-weighted MR images and have more frequently a densely granulated pattern at histology. In addition, while the initial remission rate after a first surgery is similar and reasonably good in the two groups (69%), our study demonstrates a better response to SSA treatment in PR+ patients, whether before or after the surgery.

**Declaration of interest**
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

**Funding**
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 26 March 2021
Revised version received 21 May 2021
Accepted 3 June 2021