Clinical and metabolic characteristics of acromegalic patients with high IGF1/normal GH levels during somatostatin analog treatment

Maria Matta¹, Vanina Bongard², Solange Grunenwald¹, Jean-Christophe Maiza¹, Antoine Bennet¹ and Philippe Caron¹
¹Departments of Endocrinology and Metabolic diseases and ²Epidemiology, Pôle Cardio-vasculaire et Métabolique, CHU Rangueil-Larrey, 24 Chemin de Pourvouville, TSA 30030, 31059 Toulouse Cedex 9, France
(Correspondence should be addressed to P Caron; Email: caron.p@chu-toulouse.fr)

Abstract

Context: Divergence between GH and IGF1 values are often reported in treated acromegalic patients, but the mechanisms of this discrepancy have not been completely explored.

Objective: To evaluate the frequency of divergence between GH and IGF1 values and identify the role of clinical and metabolic factors in treated patients with acromegaly, according to the latest criteria of Cure published in July 2010.

Design: Retrospective study of patients’ records between October 2002 and March 2008. Patients were grouped according to their mean GH and IGF1 values as ‘controlled’ (normal GH and IGF1), ‘divergent’ (high IGF1 and normal GH) and ‘uncontrolled’ (high GH and IGF1), and compared with respect to their clinical characteristics and metabolic markers.

Results: Patients (n=104) were grouped as ‘controlled’ (n=20), ‘divergent’ (n=43) and ‘uncontrolled’ (n=41). More patients in the divergent group (93%) and uncontrolled group (98%) were treated with somatostatin analogs than in the controlled group (65%; P=0.001 for the comparison of the three groups). Patients in the divergent group had higher fasting blood glucose (0.94 g/l (interquartile range: 0.83–1.17)) and systolic blood pressure (130 mmHg (120–140) compared with the controlled group (0.84 g/l (0.80–0.92); P=0.017) and 120 mmHg (interquartile range: 110–130; P=0.029).

In patients with divergent IGF1/GH levels, fasting glucose and GH were both strongly associated with IGF1.

Conclusion: Totally 41% of treated acromegalic patients had a high IGF1 and normal GH level. In these divergent patients treated with somatostatin analogs, these clinical and metabolic parameters might either play a causal role or be a marker for disease activity.

European Journal of Endocrinology 164 885–889

Introduction

Monitoring both GH and insulin-like growth factor 1 (IGF1) levels in patients with acromegaly is currently recommended to guide therapy decisions and long-term management (1, 2). Normalization of both hormones is required to improve morbidity and reduce mortality in patients with acromegaly (3, 4). Many studies underlined the frequency of divergent values of GH and IGF1 (5, 6), but the mechanisms underlying this divergence are still not understood. In this study, we documented the frequency of divergent GH and IGF1 values in patients with acromegaly attending our clinic over 5 years, and examined the biochemical features and clinical characteristics of these patients.

Patients and methods

All patients with acromegaly regularly attending the Endocrinology department of the University Hospital of Toulouse, France between October 2002 and March 2008 were included.

Data concerning history and duration of acromegaly, treatment and related complications, history of diabetes mellitus, sleep apnea syndrome, and pituitary insufficiency were collected. Fasting blood glucose was recorded in 98 patients. HbA1c levels were estimated in 62 patients and lipid profiles in 96 patients. Blood pressure and body mass index (BMI) were recorded in 92 and 101 patients, respectively.

Of the patients treated with somatuline autogel 45, 19 and 36% received 120, 90 and 60 mg every 28 days,
respectively, and those treated with octreotide LAR, 70 and 30% received monthly 30 and 20 mg respectively. Patients treated with slow-release formulations of somatostatin analogs had an assessment of GH and IGF1 levels the day before injection.

At each visit, serum GH level was calculated as the average of six GH samples, taken at 30 min intervals between 0900 and 1200 h. Before 2003, GH assays were performed using a radioimmunometric technique (Cisbio international, Schering, Bagnols sur Cèze, France). The detection limit was 0.02 µg/l, and the intra- and inter-assay coefficients of variation (CVs) were 2.1 and 4.5%, respectively. From 2003, GH assays were performed using a chemiluminescence technique (Nichols Institute Diagnostics, San Clemente, CA, USA). The detection limit of this assay was 0.02 µg/l, and the intra- and inter-assay CVs were 3.7 and 6.2%, respectively. The reference preparation of GH assay was 2nd IS 98/574, and 3 ml/l correspond to 1 µg/l. The rate of correlation between these two methods is as follows: $r=0.9269$ with a regression formula $y=0.9127x-0.4601$, obtained from a linear regression analysis of the data.

At each visit, IGF1 level was assessed from a serum sample. Before 2003, the IGF1 assay used a radioimmunometric technique (Diagnostic System Laboratories, Webster, TX, USA). The detection limit was 0.8 µg/l; the intra- and inter-assay CVs were 1.5 and 3.7%, respectively. From 2003, the IGF1 assay used a chemiluminescence technique (Nichols Institute Diagnostics). The detection limit was 6 g/l; the intra- and inter-assay CVs were 5.2 and 5.7%, respectively. The rate of correlation between these two methods is as follows: $r=0.8819$ with a regression formula $y=0.882x-19.84$, obtained from a linear regression analysis of the data.

Patients were divided into three groups based on their GH and IGF1 levels according to the latest Acromegaly Consensus Group meeting on criteria for cure of Acromegaly (2) defined as ‘controlled’ (GH <1 ng/ml and normalized for age and sex IGF1), ‘uncontrolled’ (high IGF1 and GH levels), or ‘divergent’ (elevated IGF1 and normal GH level). These groups were compared according to their clinical characteristics and metabolic markers.

Statistical analyses were performed using SAS Software (version 9.1, SAS Institute, Cary, NC, USA). Categorical data are summarized as percentages and continuous variables are presented as medians with interquartile ranges. Categorial variables were compared between the three groups (controlled, divergent, and uncontrolled) using the $\chi^2$ test (Fishers’s exact test in case of small numbers). Continuous variables were compared with the non-parametric Wilcoxon test.

Parameters associated with IGF1 variability were assessed in the three groups using a multiple linear regression model. IGF1 was expressed as a percentage increase compared with the upper limit of the normal (ULN) range given by the laboratory.

### Results

One hundred and eight patients with acromegaly were included. Three patients with high GH and normal IGF1 levels and one patient treated with pegvisomant were excluded from the analysis. Data from 104 patients were analysed: 20 (19%) were considered controlled, 41 (40%) patients were uncontrolled, and 43 (41%) were divergent.

No significant difference was found between groups regarding sex ratio, BMI, GH and IGF1 levels at diagnosis, sleep apnea syndrome or radiotherapy. Comparisons between these three groups are given in Table 1. The divergent group was characterized by significantly lower levels of IGF1 and GH compared with the uncontrolled group. The median increase in IGF1 level compared with the upper normal limit (UNL) was 26% in divergent patients (interquartile range: 5–58) versus 88% (interquartile range: 57–143) in uncontrolled subjects ($P<0.0001$), whereas median GH levels were 0.70 ng/ml (interquartile range: 0.40–0.95) and 2.50 ng/ml (interquartile range: 1.50–4.76) in divergent and uncontrolled patients, respectively ($P<0.0001$). No other significant difference was observed between divergent and uncontrolled patients, except for total cholesterol level which was higher in divergent patients ($P=0.018$).

In comparison with controlled subjects, divergent patients were significantly older ($P=0.040$), with higher systolic blood pressure ($P=0.029$) and fasting blood glucose ($P=0.017$), exhibited more frequently diabetes ($P=0.026$) and less frequently pituitary insufficiency ($P=0.028$), were more often treated with SMS analogs ($P=0.008$), and less frequently undergone surgery ($P=0.024$).

In a multiple linear regression analysis assessing parameters associated with IGF1 variability, fasting blood glucose and GH were strongly associated with IGF1 in divergent patients, after adjustment for age (Table 2). Age, GH and fasting blood glucose explained 32% of IGF1 variability. Fasting blood glucose was no longer associated with IGF1 among uncontrolled patients but a significant relationship was observed with BMI (Table 2). None of the parameters studied was found to be associated with IGF1 variability in the controlled patients (Table 2).

### Discussion

Monitoring patients with acromegaly requires measurement of both serum GH and IGF1 levels. Normal age- and sex-matched serum IGF1 level and GH concentration lower than 1 µg/l are the currently accepted criteria to define biochemical control in non-cured patients (2). Although the results of these two measurements are usually concordant, divergence between GH and IGF1 levels has been previously...
Table 1: Metabolic variables and other disease- or treatment-related factors in patients with acromegaly classified as controlled, divergent or uncontrolled. Results are presented as n (%) or median (IQ, interquartile range).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controlled (n=20)</th>
<th>Divergent (n=43)</th>
<th>Uncontrolled (n=41)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF1, % increase&lt;sup&gt;†&lt;/sup&gt;</td>
<td>–34 (–55; –11)</td>
<td>26 (5–58)</td>
<td>88 (57–143)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>0.70 (0.40–0.95)</td>
<td>Max (239)</td>
<td>2.50 (1.50–4.76)</td>
<td>&lt;0.0001</td>
<td>0.010</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>28.1 (25.0–31.3)</td>
<td>28.7 (24.5–31.6)</td>
<td>25.8 (24.8–28.3)</td>
<td>0.224</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86 (78–96)</td>
<td>79 (70–94)</td>
<td>71 (63–84)</td>
<td>0.024</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>28.1 (25.0–31.3)</td>
<td>28.7 (24.5–31.6)</td>
<td>25.8 (24.8–28.3)</td>
<td>0.224</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (n (%))</td>
<td>8 (40%)</td>
<td>20 (49%)</td>
<td>18 (44%)</td>
<td>0.068</td>
<td>0.024</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 (110–130)</td>
<td>120 (110–140)</td>
<td>120 (110–140)</td>
<td>0.086</td>
<td>0.029</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70 (60–80)</td>
<td>80 (70–80)</td>
<td>70 (70–80)</td>
<td>0.280</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (n (%))</td>
<td>2 (10%)</td>
<td>16 (37%)</td>
<td>13 (32%)</td>
<td>0.084</td>
<td>0.026</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting blood glucose (g/l)</td>
<td>0.84 (0.80–0.92)</td>
<td>0.94 (0.83–1.17)</td>
<td>1.03 (0.94–1.17)</td>
<td>0.001</td>
<td>0.017</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 (5.3–5.9)</td>
<td>5.8 (5.5–6.6)</td>
<td>6.0 (5.6–6.9)</td>
<td>0.068</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (g/l)</td>
<td>2.05 (2.00–2.16)</td>
<td>2.14 (1.83–2.43)</td>
<td>1.94 (1.73–2.11)</td>
<td>0.045</td>
<td>NS</td>
<td>0.018</td>
</tr>
<tr>
<td>Triglycerides (g/l)</td>
<td>0.91 (0.72–1.20)</td>
<td>1.12 (0.84–1.53)</td>
<td>0.99 (0.73–1.21)</td>
<td>0.110</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep apnea syndrome (n (%))</td>
<td>4 (20%)</td>
<td>13 (30%)</td>
<td>12 (29%)</td>
<td>0.679</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, non-significant. *Comparison of the three groups. †Percent increase compared to the upper limit of the normal range given by the laboratory (data were available for 99 patients).

Comparison of the three groups: comparison between divergent and controlled patients.

Comparison of the three groups: comparison between divergent and uncontrolled patients.

reported (5–7). Data from the AcroBel register showed that up to 35% of treated acromegalic patients exhibit discordant GH and IGF1 levels (7). Differences in the reported definitions of remission, the type of GH and IGF1 assays used and the lack of information about the timing of somatostatin analog injection in relation to GH and IGF1 measurement might have contributed to the conflicting results regarding the frequency of GH and IGF1 divergence (8).

In this study, the main profile of GH and IGF1 was a moderate increase in IGF1 with normal GH values (found in 41% of this cohort). Only three patients presented an increased GH level and normal IGF1. Radiotherapy treatment did not differ significantly between the three groups, as it is recognized that radiotherapy may result in achievement of seemingly normal mean GH but without necessarily achieving normal IGF1 secretory dynamics (9), resulting in a GH/IGF1 divergent profile. Patients with high IGF1 and normal GH values exhibited a poor metabolic profile with significantly higher fasting blood glucose and higher incidence of diabetes mellitus, and systolic blood pressure, as reported previously in the AcroBel study (7) and recently by Berg C and colleagues (10) in partially controlled acromegalic patients.

There are conflicting data regarding the relationship between IGF1 and the metabolic syndrome. A number of studies in non-acromegalic patients have suggested that increased levels of IGF1 occur in patients with obesity or type 2 diabetes (11, 12), but others have reported different results. In divergent patients: IGF1 (percentage of increase compared with UNL) = – 34.2 + 0.24 age (years) – 43.8 GH (ng/ml) + 81.9 fasting blood glucose (g/l).

Table 2: Parameters associated with IGF1 variability.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controlled group (n=18)</th>
<th>Divergent group (n=36)</th>
<th>Uncontrolled group (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>–136.3</td>
<td>–34.2</td>
<td>–72.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.66</td>
<td>0.24</td>
<td>0.92</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>0.41</td>
<td>0.24</td>
<td>0.004</td>
</tr>
<tr>
<td>Fasting blood glucose (g/l)</td>
<td>78.0</td>
<td>81.9</td>
<td>–75.3</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>0.09</td>
<td>0.32</td>
<td>0.621</td>
</tr>
</tbody>
</table>

In divergent patients: IGF1 (percentage of increase compared with UNL) = – 34.2 + 0.24 age (years) – 43.8 GH (ng/ml) + 81.9 fasting blood glucose (g/l).
shown a correlation between decreased IGF1 levels and some markers of the metabolic syndrome, e.g. insulin resistance (13), impaired glucose tolerance (14), and obesity (13, 15). Conversely, it is well established that during treatment of patients with acromegaly, IGF1 normalization not only reduces excess mortality rate and the clinical signs and symptoms of acromegaly, but also reduces morbidities such as insulin resistance, glucose intolerance, and cardiovascular disease (4).

Of interest is whether the increased IGF1 in the divergent group was a consequence of poor metabolic control or whether high IGF1 levels played a causal role in poor metabolic control. The role of IGF1 in glucose homeostasis and insulin sensitivity is not well understood. It seems that the initial rise in insulin levels observed in patients with pre-diabetes leads to a concomitant compensatory rise in IGF1 levels that subsequently decreases as hepatic insulin sensitivity decreases, eventually resulting in a relative IGF1 deficiency in patients with full-blown diabetes (16).

Considering this theory, we observed a significant and positive correlation between fasting blood glucose and IGF1 level in the divergent group.

It is important to note that the present study has several limitations; most data was collected retrospectively from patients’ charts, and information regarding other markers of the metabolic syndrome (e.g. waist to hip ratio, HDL cholesterol value and serum insulin levels) were not available.

In our cohort, uncontrolled and divergent patients were more often treated with somatostatin analogs compared with controlled group. The use of somatostatin analogs introduces an adjunctive variable, lowering insulin levels on one hand and increasing insulin sensitivity on the other, the result depending on the balance of the two actions in the individual patient. Thus the GH/IGF1 relationship is altered in patients under somatostatin analog treatment. Relevant effects of serum insulin levels on IGF1 secretion and on modulating their response to GH are well known (17). GH receptor (GHR) polymorphism also seems to have a relevant impact on the posttreatment GH/IGF1 relationship (18). In the absence of appropriate studies in acromegalic patients, we unfortunately cannot offer a conclusive proof of mechanism of IGF1/glycemia relationship at the physiological level.

In summary, 41% of treated patients with acromegaly had a high IGF1 and normal GH level. These patients also exhibited higher fasting blood glucose and systolic blood pressure – markers of metabolic syndrome. Should we consider this category of patients as having active disease and adjust medical treatment accordingly, switch them to a GH antagonist receptor (pegvisomant) to achieve a normal level of IGF1, or try to improve their metabolic profile? Epidemiological data are not currently available to guide this decision and management of such patients needs to be individualized.

Declaration of interest
P Caron has been a consultant for and received lecture fees from Novartis, Ipsen, and Pfizer. Other authors (M Matta, V Bongard, S Grunenwald, J-C Maiza, A Bennet) have nothing to declare.

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

Acknowledgements
The authors acknowledge editorial assistance from ESP Bioscience and Ipsen financial support for the editorial assistance.

References
8 Freda PU. Monitoring of acromegaly: what should be performed when GH and IGF-1 levels are discrepant? Clinical Endocrinology 2009 71 166–170. (doi:10.1111/j.1365-2265.2009.03556.x)


Received 18 March 2011
Accepted 6 April 2011