Giant GH-secreting pituitary adenomas: management of rare and aggressive pituitary tumors

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Abstract

Objectives: Patients with acromegaly usually harbor macroadenomas measuring between 10 and 30 mm in maximal diameter. Giant (adenoma size ≥40 mm) GH-secreting pituitary tumors are rarely encountered and the aim of this study is to analyze different methods for managing them.

Design and methods: We have identified 34 patients (15 men and 19 females) with giant adenomas among 762 subjects (4.5%) with acromegaly in our records, and characterized their clinical characteristics and response to treatment.

Results: Mean age at diagnosis was 34.9 ± 12.5 years (range, 16–67 years). Mean adenoma size was 49.4 ± 9.4 mm (range, 40–80 mm); 30 adenomas showed cavernous sinus invasion and 32 had suprasellar extension. Twenty-nine (85%) patients had visual field defects. Mean baseline IGF1 was 3.4 ± 1.8 ULN. All patients except one underwent pituitary surgery (one to three procedures), but none achieved hormonal remission following first surgery. Among the 28 subjects with visual disturbances, 14 recovered post-operatively and 13 improved. Treatment with somatostatin analogs was given to all patients after surgical failure. Six achieved remission, nine others were partially controlled (IGF1 < 1.5 ULN; 3/9 when combined with cabergoline), and 17 did not respond (two were lost). Nine patients were treated with pegvisomant, alone (n = 4) or in combination with somatostatin analogs (n = 5); five are in remission and two are partially controlled. Pasireotide-LAR achieved hormonal remission in one of the six patients. Currently, after a mean follow-up period of 8.9 years, 17 patients are in biochemical remission, eight are partially controlled, and seven are uncontrolled (two were lost to follow-up).

Conclusions: Giant GH-secreting adenomas are invasive, uncontrolled by surgery, and respond poorly to medical treatment. Aggressive multimodal therapy is critical for their management, enhancing control rate and biochemical remission.

Introduction

Acromegaly is a rare condition that usually results from a growth hormone (GH)-secreting pituitary adenoma (1). Most of these tumors (75%) are macroadenomas (>10 mm in maximal diameter), whereas 25% are microadenomas (≤10 mm). The majority of GH-secreting tumors measure between 10 and 30 mm, while very large tumors (≥40 mm) are rarely encountered (2). These giant tumors may include atypical adenomas, but usually they consist of benign tumors with no different histological characteristics compared with smaller adenomas (3, 4). However, sparsely granulated GH-secreting adenomas tend to be larger and more aggressive compared with densely granulated tumors, responding less to medical treatment with somatostatin analogs (5).

Giant GH-secreting adenomas usually present as invasive tumors with extrasellar extension, chiasmal
compression, cavernous sinus invasion, and occasionally involve the clivus, the temporal lobe, the hypothalamus, and other cranial structures. These large tumors tend to prevail in young adults, usually 20–30 years old. Albeit aggressive, these tumors are mostly benign, rarely developing into malignant pituitary carcinomas (6). Giant tumors are usually unsuitable for complete removal, thus surgery alone is not expected to achieve disease control or hormonal remission in almost all cases (2).

Owing to the rarity of giant GH-secreting pituitary tumors, information regarding their management is very sparse in the literature; hence, we have summarized a multicenter unique experience in the management of these aggressive and challenging pituitary tumors.

**Patients and methods**

We have identified 34 patients with giant adenomas among 762 subjects (4.5%) with acromegaly diagnosed, treated, and followed between 1989 and 2014 in four different pituitary outpatient clinics in academic centers from Israel, Brazil, and USA. This collaborative, retrospective study included patients with acromegaly presenting with giant (adenoma size \( \geq 40 \) mm) GH-secreting pituitary tumors. The study was approved and conducted according to the local ethical institutional review boards.

Information on clinical presentation, laboratory tests including hormonal profile, pituitary imaging, and visual field assessment, at presentation and during follow-up period, were obtained from clinical records. Response to different treatment modalities and clinical improvement were also reviewed.

**GH and insulin-like growth factor 1 evaluation**

Serum GH and insulin-like growth factor 1 (IGF1) levels were measured in the morning following overnight fasting, using chemiluminescent immunometric assays (Immulite 2000; Siemens, Flanders, NJ, USA) in most patients. GH has a sensitivity of 0.05 ng/ml. The intra-assay coefficient of variation (CV) for GH concentration of 3.7 ng/ml was 4.6%; the corresponding inter-assay CV was 5.7%. The intra- and inter-assay CV values for IGF1 concentration of 380 ng/ml are 2.9 and 7.4% respectively. IGF1 in Brazil was measured using Immulite 2000, or by RIA following ethanol extraction (Diagnostic Systems Laboratories, Webster, TX, USA). GH and IGF1 measurements in patients treated with pasireotide-LAR within the PAOLA study were assessed in a central laboratory (Quest Diagnostics, Madison, NJ, USA) using the Immulite 2000. IGF1 levels are presented based on the upper limit of normal range (ULN; the IGF1 value divided by the sex- and age-specific upper normal limit), comparing values among the different assays and along the years.

**Hormonal control**

Hormonal control was based on achieving mean or random GH levels \( \leq 2.5 \) ng/ml and normal IGF1 for sex and age. Remission in patients treated with pegvisomant was based on normal IGF1 levels. Patients were considered partially controlled when IGF1 achieved following treatment was below \( 1.5 \times \) ULN.

**Radiological assessment**

Tumor size and extension beyond the pituitary sella at presentation and during follow-up were assessed by magnetic resonance imaging (MRI). The irregular and asymmetrical shape of most tumors resulted in an imprecise calculation of its volume. Therefore, a preoperative maximal diameter \( \geq 40 \) mm was used to define a giant GH-secreting adenoma. In order to assess tumor shrinkage, MRI was performed 3–6 months following primary treatment.

**Histological studies**

Resected adenoma specimens were immunostained for GH, prolactin (PRL), adrenocorticotropin, thyrotropin (TSH), as well as luteinizing hormone beta (LHβ) and follicle-stimulating hormone beta (FSHβ).

**Statistical analysis**

Descriptive analysis was performed and results are expressed as mean \( \pm \) S.D.

**Results**

**Patients’ characteristics at presentation**

The study cohort included 34 patients (15 males and 19 females) with giant adenomas identified among 762 subjects (4.5%) with acromegaly in our records. Mean age at diagnosis was 34.9 \( \pm \) 12.5 years (range, 16–67 years) (Table 1). Initial complaints leading to diagnosis included acromegalic features in 21 patients, headaches in 19 patients, and visual deterioration in 15 subjects. One patient had nasal bleeding and another was incidentally discovered. Mean adenoma size at presentation was 49.4 \( \pm \) 9.4 mm (range, 40–80 mm). Twelve patients presented
with tumors ≥ 50 mm (Table 2). Cavernous sinus invasion was detected in 30 out of 34 adenomas and 32 had suprasellar extension. Twenty-nine patients (85%) had significant visual field defects, mostly bitemporal hemianopsia. Thirteen patients had random GH levels > 40 ng/ml at presentation. Maximal GH was 1261 ng/ml, measured in a female with a 56×47 mm giant tumor (patient 17, Table 2). Mean baseline IGF1 was 3.4±1.8×ULN for age. Eight patients presented with PRL-co-secretion (Table 2) and one with TSH co-secretion (patient 4), but GH was the dominant hormone secreted in all cases. Eight other patients without hyperprolactinemia or with only marginal serum PRL elevation showed PRL expression in the immunostained pituitary adenoma specimens. Data regarding pituitary cell proliferation rate (Ki-67 index) are missing for most tumors.

Five female patients were older than 45 years when diagnosed. Among the other women, all but one presented with amenorrhea, while 79% of males had hypogonadism. Twelve patients had central hypothyroidism and eight presented with secondary hypocortisolism. The clinical data of the patients are summarized in Tables 1 and 2. Figure 1 shows MRI studies of four giant adenomas at presentation (patients 1, 2, 17, and 20).

## Table 1 Baseline characteristics of 34 patients with giant GH-secreting adenomas.

<table>
<thead>
<tr>
<th>n</th>
<th>34/762 patients in our cohort (4.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±s.d.</td>
<td>34.9±12.5 years (range, 16–67 years)</td>
</tr>
<tr>
<td>F/M</td>
<td>19/15</td>
</tr>
<tr>
<td>Adenoma size, mean±s.d.</td>
<td>49.4±9.4 mm (range, 40–80 mm)</td>
</tr>
<tr>
<td>IGF1, mean±s.d.</td>
<td>3.4±1.8×ULN</td>
</tr>
<tr>
<td>Visual field defects</td>
<td>29/34</td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>30/34</td>
</tr>
<tr>
<td>Hormone co-secretion</td>
<td>PRL – 8; TSH – 1</td>
</tr>
<tr>
<td>Mean follow-up period</td>
<td>8.9±4.7 years</td>
</tr>
</tbody>
</table>

**Pituitary surgery and radiotherapy**

All patients but one underwent pituitary surgery, 32 underwent transsphenoidal surgery and seven trancranial procedures, 13 underwent two to three consecutive procedures, and some had sellar operations by different approaches. Thirty-one patients underwent surgery as their first treatment approach for acromegaly. None achieved hormonal remission post-operatively. However, two out of 12 subjects are in hormonal remission following repeated surgery. Only seven patients had more than 50% reduction in pre-operative IGF1 levels following the primary surgery. However, among the 28 subjects with pre-operative visual disturbances, 14 patients recovered, 13 improved their vision, and, in one patient, vision remained unchanged after surgery. Significant post-operative complications included cerebrospinal fluid (CSF) leak in eight patients, bacterial meningitis in two, and one patient had permanent diabetes insipidus.

Radiotherapy was given to 12 patients, including radiosurgery in two subjects. Radiotherapy was always used after surgical and/or medical treatment failure. Most patients received radiotherapy due to a large post-operative adenoma remnant. Among the patients treated with radiotherapy, only one patient achieved GH/IGF1 control 1 year following radiosurgery.

**Medical treatment**

Medical treatment with somatostatin analogs (octreotide-LAR, n=30; lanreotide-Autogel, n=7) was given to most patients after surgical failure. Some patients were treated with both analogs during different periods. One patient received primary therapy with octreotide-LAR before surgery. Remission was noticed in six (five treated with octreotide-LAR 30 mg and one with lanreotide-Autogel 90 mg). Nine others were partially controlled (IGF1 <1.5×ULN), while treated with octreotide-LAR (3/9 when combined with cabergoline, 3.5 mg/week); and 17 did not respond (two were lost to follow-up) (Fig. 2). Mean treatment duration with octreotide-LAR was 5.6±3.8 years (median, 6 years), and 3.5±3 (median, 3 years) with lanreotide-Autogel. Cabergoline as a primary treatment (before surgery or somatostatin analog) was initiated in two patients who did not respond. Cabergoline (3.5 mg/week) when added to nine patients, uncontrolled while on octreotide-LAR, brought three patients (33%) into partial control (IGF1 <1.5×ULN) (Fig. 2).

Nine patients were treated with pegvisomant (not yet available in the public health system in Brazil), either alone (n=4), or in combination with octreotide-LAR or lanreotide-Autogel (n=5), for a mean period of 3.3±1.8 years (median, 4 years). Remission was achieved in five subjects (combination treatment in four), partial control (IGF1 <1.5×ULN) was noticed in additional two subjects (one female patient is now in remission following the addition of contraceptive pills to her regimen, patient 5, Table 2), one patient responded poorly to pegvisomant (30 mg/day) treatment, and one discontinued treatment due to intolerance.

Six of the patients in our cohort were treated with pasireotide-LAR 60 mg/4 weeks within the multicenter...
PAOLA phase III study for patients with inadequately controlled acromegaly, despite receiving high-dose somatostatin analogs (Novartis Pharma AG) (7). Five patients had baseline IGF1 >2×ULN before pasireotide administration, and, in one patient, it was measured between 1.5 and 2×ULN. After a mean treatment period of 3.3±0.3 years (median, 3.5 years), one of these patients (one of six patients; 17%) was in remission with pasireotide-LAR 60 mg, two others were partially controlled (IGF1 >1.5×ULN), and the other three were uncontrolled. Pasireotide-LAR has been previously given to medically naïve patients with active acromegaly within the CSOM230C2305 phase III study (Novartis) (8).

Currently, after a mean follow-up period of 8.9±4.7 years (median, 9 years; range, 1.5–19 years), 17 patients are in biochemical remission, eight are partially controlled, and seven remained uncontrolled. Two patients were lost to follow-up. Last follow-up mean maximal diameter of adenoma remnants assessed by MRI is 21.6±10.6 mm (Table 2). These results were achieved after exposure to multiple treatment modalities including surgery, radiotherapy, and medical therapies with somatostatin analogs, cabergoline, and pegvisomant (mean, 3.8 modalities/patient). Patients in remission (n=17) achieved biochemical (IGF1) control with repeated surgery (n=2), radiosurgery (n=1), somatostatin analogs (octreotide and lanreotide) (n=6), pasireotide (n=1), pegvisomant (n=1), somatostatin analog with pegvisomant (n=4), pegvisomant with estrogen (n=1), and somatostatin analog with estrogen (n=1).

### Table 2  Baseline characteristics and response to treatment of each patient in the cohort.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Tumor size (mm)</th>
<th>Visual defect</th>
<th>IGF1/ULN</th>
<th>PRL (ng/ml)</th>
<th>Surgery</th>
<th>F/U (years)</th>
<th>Remission with</th>
<th>Current tumor size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>M</td>
<td>60</td>
<td>–</td>
<td>2.5</td>
<td>164a</td>
<td>TC, TSS</td>
<td>RS-10</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>50</td>
<td>+</td>
<td>2.5</td>
<td>65</td>
<td>TSS</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>M</td>
<td>45</td>
<td>+</td>
<td>2.5</td>
<td>32</td>
<td>TSS</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>F</td>
<td>41</td>
<td>+</td>
<td>NA</td>
<td>7</td>
<td>TSS</td>
<td>10</td>
<td>Pasireotide</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>F</td>
<td>45</td>
<td>–</td>
<td>4</td>
<td>6</td>
<td>TSS</td>
<td>FSR-1.1</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>M</td>
<td>40</td>
<td>–</td>
<td>4</td>
<td>54a</td>
<td>TSS, TC</td>
<td>3.5</td>
<td>Pasireotide</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>M</td>
<td>55</td>
<td>+</td>
<td>1.3</td>
<td>43</td>
<td>TSS, TC</td>
<td>9</td>
<td>Octreotide</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>M</td>
<td>43</td>
<td>–</td>
<td>2.3</td>
<td>475a</td>
<td>TSS</td>
<td>5</td>
<td>Octreotide + PEG</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>F</td>
<td>70</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>TSS</td>
<td>3.5</td>
<td>No follow-up</td>
</tr>
<tr>
<td>10</td>
<td>22</td>
<td>F</td>
<td>45</td>
<td>+</td>
<td>2.35</td>
<td>173a</td>
<td>TSS</td>
<td>16</td>
<td>Pasireotide + E2</td>
</tr>
<tr>
<td>11</td>
<td>25</td>
<td>M</td>
<td>40</td>
<td>–</td>
<td>2.6</td>
<td>28</td>
<td>TSS</td>
<td>FSR-11</td>
<td>19</td>
</tr>
</tbody>
</table>

*PRL co-secretion.

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Clinical Study

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Giant GH-secreting adenomas

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Acromegaly is a rare disorder usually caused by GH hypersecretion from a GH-producing pituitary adenoma. Most affected subjects harbor macroadenomas, but it is estimated that $\leq 5\%$ of these grow to very large sizes of $\geq 40$ mm in diameter to become gigantic tumors. As these adenomas are rare, only anecdotal case reports of patients diagnosed with giant GH-secreting pituitary adenomas were reported (9, 10, 11, 12), whereas no published cohorts devoted only to patients with very large somatotroph tumors are available in the literature. In a large consecutive series of 668 patients with acromegaly referred for pituitary surgery, only ten giant tumors were included (1.5\%) (2). We have identified and summarized a large series of 34 patients diagnosed with giant GH-secreting cell adenomas representing 4.5\% of the acromegalic patients in four large pituitary clinical centers. However, this may overestimate the true proportion of those aggressive tumors, as all participating pituitary clinics are tertiary centers. This unique cohort of rare GH-secreting tumors illustrates the difficulties encountered in achieving biochemical control of acromegaly and relieving tumor mass effects in these patients.

Transsphenoidal adenoma resection is the preferred first-line treatment modality for patients with acromegaly. Microadenomas and intrasellar macroadenomas are reported to have a relatively high remission rate, 60–80\% (2, 13, 14, 15, 16). With increasing adenoma size and invasiveness beyond the sellar boundaries, remission rate gradually decreases (2, 13, 17, 18) and reach almost 0\% for giant GH-secreting cell tumors (2), similarly to the surgical results observed for patients included in this study. Importantly, patients in our series were operated by well-experienced pituitary neurosurgeons, some with reported post-operative remission rate of $\approx 60\%$ for GH-secreting macroadenomas (13). However, patients with very large adenomas still can benefit from a pituitary operation that relieves chiasmal compression and can improve the subsequent response to medical treatment with somatostatin analogs after partial tumor debulking (19, 20, 21). Repeated surgery resulted in hormonal remission in two patients. Prior surgery also may decrease the radiation exposure to the optic pathways following tumor volume reduction if radiation is planned. However, after surgical failure, only one of the 12 patients with giant tumor, who were referred for radiotherapy, achieved hormonal remission. This is in contrast to the reported rate of 50–60\% of GH–IGF1 normalization following radiotherapy for smaller GH-secreting adenomas (22, 23). Thus, in the short term, pituitary surgery followed by radiotherapy is not efficacious as the only approach for these aggressive adenomas.

The depot somatostatin analogs, octreotide-LAR, and lanreotide-Autogel are considered as the preferred first-line pharmacological treatment for patients with active acromegaly (24, 25), either as a primary treatment (26, 27) or as an adjuvant therapy following unsuccessful pituitary surgery. Normalization of GH and IGF1 is achieved in 50–60\% of

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**Figure 1**
Coronal MRI T1-weighted sequence, gadolinium enhanced, of four patients with giant GH-secreting adenomas at presentation.

**Figure 2**
Number of patients with giant GH-secreting adenomas achieving biochemical control or partial control with different treatment modalities available for acromegaly. Cab, cabergoline; OCT, octreotide-LAR; LAN, lanreotide-Autogel.
patients treated as primary or secondary therapy. The efficacy rate may be improved by surgical debulking of large macroadenomas (19, 20, 21). Only six out of 32 patients in our cohort (19%), treated with the commercially available analogs octreotide-LAR or lanreotide-Autogel, achieved biochemical remission, whereas nine others were partially controlled. This remission rate is far below the rate considered appropriate for patients harboring GH-secreting macroadenomas (28). It has been shown that baseline or pretreatment GH levels inversely correlated with the chance to achieve GH and IGF1 control with somatostatin analogs, although absolute greater GH suppression is achieved when tumors with higher baseline GH are treated medically (29). Moreover, aggressive GH tumors show low p21 (CDKN1A) and SSTR2 expression that results in decreased responsiveness to medical treatment (30). This may explain why our patients with giant tumors and high GH and IGF1 secretion poorly responded to somatostatin analogs, although the response rate might be improved somehow after partial adenoma resection, or with the addition of cabergoline (31), as shown in three out of nine patients on octreotide-LAR monotherapy who became partially controlled when cabergoline was added as co-treatment. Importantly, six of our patients were referred to treatment with pasireotide-LAR, the second-generation multireceptor-targeted somatostatin analog, developed by Novartis Pharma AG and given as monthly injection, within a large multicenter phase III study (PAOLA) for patients with inadequately controlled acromegaly, previously treated with high-dose somatostatin analogs (7). One out of six (17%) achieved hormonal control and two others were partially responders. Pasireotide with its higher affinity for SST5 has shown superior efficacy in providing biochemical control over the first-generation somatostatin analogs both in medically naïve patients with acromegaly (8) and in patients with inadequately controlled acromegaly despite receiving somatostatin analogs (7). The response rate to pasireotide-LAR in our patients with giant adenomas (17%) was compatible with the 15 and 20% control rate reported in the PAOLA study for patients receiving the 40 and 60 mg monthly injections respectively (7). This novel analog has been approved recently in Europe and the USA for treating patients with inadequately controlled acromegaly.

Five of our patients (out of nine), who were not in biochemical remission, achieved IGF1 control when switched to pegvisomant treatment, either alone or as part of a combination treatment. However, as pegvisomant is not available in the public health system of Brazil, almost half of the patients included in the cohort were not suitable for this therapeutic option. As pegvisomant has no effect on tumor shrinkage, combination medical treatment may be beneficial in these patients to relieve tumor mass effects.

Other options in the therapeutic armamentarium for patients with aggressive tumors resistant to the currently available medical treatments include the alkylating agent temozolomide that may be effective for aggressive pituitary tumors and pituitary carcinomas (32, 33) resistant to the conventional treatments.

Our cohort of giant pituitary somatotroph adenomas emphasize the poor response these patients show to surgery, radiotherapy, or medical therapy. However, an aggressive multimodal management strategy has a reasonable likelihood to achieve disease control in these challenging patients.

Declaration of interest
I Shimon has received research grants, and consulting and lectureship fees from Novartis and Pfizer, and participated in the PAOLA study. M Fleseriu received research support to OHSU from Novartis, Pfizer, and Ipsen, and scientific consulting fees from Novartis and Pfizer. Y Greenman received research grant from Pfizer, and research grant, travel support, and speaker fees from Novartis. M D Bronstein is a speaker for Ipsen and Novartis, a member of steering committees for Chisima, Ilsen, and Novartis, and participated in the Paola study.

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