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"Micromegaly": an update on the prevalence of acromegaly with apparently normal GH secretion in the modern era

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Abstract
Purpose Approximately 25 % of cases of clinically active acromegaly cases treated in our academic center between 1996 and 2000, were diagnosed in patients who had elevated plasma IGF-1 levels, but apparently "normal" 24-h mean plasma GH levels. The current study served to update the data for patients with acromegaly referred to our facility, after increasing awareness of this "normal" GH subpopulation throughout the medical community.
Methods A retrospective chart review was conducted on 157 patients with acromegaly who underwent resection of a confirmed somatotroph pituitary adenoma at the University of Michigan Health System between the dates of 1 Jan 2001 to 23 Sept 2015.
Results Overall prevalence of acromegalic patients with "normal" GH levels, defined as GH <4.7 ng/mL, was 31 %. Over time, the percentage of patients with "normal" GH at diagnosis did not decline: 26 % from 2001 to 2005, 19 % from 2006 to 2010, and 47 % from 2011 to 2015. Mean pituitary tumor size was 1.8 ± 0.1 cm for the group with elevated GH, and 1.2 ± 0.1 cm for the group with "normal" GH ($p < 0.001$). Percent microadenomas was higher in a group with "normal" GH as compared to those with elevated GH (48 vs. 12 %, $p < 0.001$), and tumors >2 cm in the maximal diameter were encountered more frequently in the group with elevated GH (43 vs. 14 %, $p < 0.001$).
Conclusions Our data show that a substantial percentage of patients with clinical acromegaly have "normal" GH, and therefore strengthens the growing body of evidence which supports the leading role of IGF-1 levels in diagnostic evaluation. At the present time, questions about the natural course of "micromegaly" and treatment benefits compared to the subpopulation with elevated GH levels remain unanswered, but research continues to build on our understanding of the heterogeneous population of individuals.

Keywords Acromegaly · Pituitary tumor · Insulin-like growth factor 1 · Growth hormone

Introduction

Acromegaly is caused by pathologically-increased growth hormone (GH) secretion from a pituitary somatotroph adenoma. Left untreated, it is associated with increased morbidity and mortality. Historically, the diagnosis of acromegaly was difficult, with prolonged delay from the presentation of initial signs and symptoms to diagnosis and treatment. Over the past several decades, technology has advanced with the introduction of more accurate imaging modalities and improvements in biochemical assays, and as a result, the diagnosis of acromegaly is now being made in patients with progressively more subtle clinical manifestations of the disease.

In 2002, we described a series of 16 newly diagnosed patients with clinically active acromegaly, elevated plasma insulin-like growth factor 1 (IGF-1) levels but normal 24-h mean plasma GH levels, who had histochemically

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documented somatotropinomas and who experienced resolution of their symptoms following pituitary adenoma resection [1]. These patients represented 25 % of cases of acromegaly seen at our facility between 1996 and 2000. At that time, it was suspected that this number might not be accurate due to the low utilization of IGF-1 measurements and the rejection of acromegaly as a diagnosis when only GH-based criteria were used by community physicians, i.e. the ascertainment bias. The current study served to update the data for patients with acromegaly referred to our facility after the original study had been completed.

Methods

Study subjects

The study cohort consisted of 157 patients with newly-diagnosed and untreated acromegaly who underwent resection of their pituitary adenoma at the University of Michigan Health System between the dates of 1 Jan 2001 to 23 Sept 2015, and who had at least one GH and one IGF-1 measurement prior to surgery. All patients had immunohistochemical confirmation of a GH-secreting pituitary adenoma. Patients who had previously undergone unsuccessful pituitary surgery, radiation therapy or who were being treated medically were excluded.

Study design

Approval was obtained from the Institutional Review Board of the University of Michigan Health System. A retrospective chart review was conducted and pertinent biochemical and radiographic data was collected, including demographic information, date of surgery, all pre-operative GH and IGF-1 levels, and maximal tumor dimension. To assess for trends over time, patients were divided into groups based on date of surgery in 5-year intervals: 2001–2005, 2006–2010, and 2011–2015.

Biochemical measurements

For samples analyzed at the University of Michigan, GH was measured by immunometric sandwich assay (from 2001 to 2003 using the DPC Immulite 1000 human Growth Hormone platform, and from 2004 to 2015 using the DPC Immulite 2000 human Growth Hormone platform; Siemens Medical Solutions USA, Inc., Malvern, PA, USA). IGF-1 was measured from 2001 to 2005 by immunoradiometric assay (ACTIVE Non-Extraction IGF-1 IRMA DSL-2800 kit; Diagnostics System Laboratories, Webster, TX, USA) and from 2006 to 2015 by solid-phase, enzyme-labeled chemiluminescent immunometric assay (DPC Immulite 2000 IGF-1, Siemens Medical Solutions USA, Inc., Malvern, PA, US). Plasma GH was conventionally considered elevated if the mean of all available preoperative values exceeded 4.7 ng/ml based on our old criteria [1]. Plasma IGF-1 was considered to be elevated if it exceeded the upper range of normal age/gender adjusted values provided by the manufacturer.

Statistical analysis

Statistical analysis was performed by Excel 2011 (Microsoft Corporation) using unpaired Student's *t* test or Chi-square test as appropriate. Values are shown as mean ± S.E.M., unless otherwise specified. $P < 0.05$ was considered statistically significant.

Results

Demographic information (See Tables 1, 2)

Of the total 157 patients with acromegaly evaluated in this study, 108 had elevated GH levels ≥4.7 ng/mL at diagnosis, and 49 had "normal" GH levels <4.7 ng/mL. The mean age at the time of surgery was 44 ± 1.4 years for the group with elevated GH, vs 52 ± 2 years for the group with normal GH ($p < 0.05$). Gender distribution was approximately equal, with 52 % of patients with elevated GH and 47 % of those with "normal" GH being males. (Table 1) Over time, the percentage of patients with elevated IGF-1 and "normal" GH at diagnosis was 26 % from 2001 to 2005, 19 % from 2006 to 2010, and 47 % from 2011 to 2015. Overall prevalence of patients with "normal" GH levels over a 15 years period was 31 % (Table 2).

Hormone levels (See Table 1)

The mean number of pre-operative GH measurements was 2.5 ± 0.2 for the group with elevated GH, vs 3.3 ± 0.4 for the group with "normal" GH. Mean GH level was 28 ± 3.5 ng/mL and mean IGF-1 1070 ± 38 ng/mL (364 ± 13 % ULN) for patients with elevated GH. Mean GH was 2.4 ± 0.2 ng/mL and mean IGF-1 654 ± 40 ng/mL (253 ± 16 % ULN) for those with "normal" GH.

Tumor size

The mean largest dimension of pituitary tumors was 1.8 ± 0.1 cm for the group with elevated GH, of which 12 % were microadenomas and 88 % were macroadenomas. The mean largest dimension was 1.2 ± 0.1 cm for the group with "normal" GH, of which 48 % were

Table 1 Demographic information, hormonal data, and tumor size for patients with acromegaly who underwent surgery between 2001 and 2015, distributed by elevated versus "normal" mean GH levels

	Acromegaly with elevated GH	Acromegaly with "normal" GH
Number (n)	108	49
Age at surgery (years)	44 ± 1.4	52 ± 2*
Percent male (%)	52	47
Number of GH measurements (n)	2.5 ± 0.2	3.3 ± 0.4
GH (ng/mL)	28 ± 3.5	2.4 ± 0.2*
IGF-1 (ng/mL)	1070 ± 38	654 ± 40*
IGF-1 percent ULN (%)	364 ± 13	253 ± 16*
Tumor size (cm)	1.8 ± 0.1	1.2 ± 0.1*
% Microadenomas	12	48*
% Macroadenomas ≥ 2 cm	43	14*

Data represented as mean ± S.E.M. unless otherwise specified

* $p < 0.05$

Table 2 Distribution of cases of patients with acromegaly who had "normal" GH who underwent surgery between 2001 and 2015, in 5-year intervals

Date range	Total cases of acromegaly (n)	Patients with "normal" GH (n)	Patients with "normal" GH (%)
2001–2005	42	11	26
2006–2010	58	11	19
2011–2015	57	27	47
Total	157	49	31

microadenomas and 52 % macroadenomas (Table 1). Of all macroadenomas, 21 % were associated with "normal" GH levels, and 79 % with elevated GH. Large tumors ≥2 cm in diameter were seen in 43 % of the group with elevated GH, and only 14 % of the group with "normal" GH (Table 1). Of microadenomas, 64 % were associated with" normal" GH and 36 % with elevated GH ($p < 0.01$ for all the above comparisons).

Discussion

We show here that in the current era of better awareness of acromegaly by community physicians, and wide availability of MRI and reliable GH and IGF-1 assays, the proportion of patients with clinically-apparent acromegaly and high IGF-1 concentrations, but with apparently "normal" GH levels, comprises almost a third of the total number of patients with this disease. This has significant epidemiological and clinical implications. The definition of GH "normalcy" in this study differs from our previous one [1] in which mean 24-h GH values were derived from serial venous sampling every 10 min in a controlled research environment. In the current survey, we used only a limited number of random GH measurements. However, as we have shown in the past [2], in a group analysis, even a single, random GH value strongly correlates with the true 24-h mean GH ($r = 0.93$, $p < 0.0001$). Thus, while less accurate on an individual basis, even small numbers of random GH measurements are sufficiently robust to describe the prevailing GH milieu in patients with acromegaly. On the other hand, the current study reflects the mode of GH testing done by community physicians, and thus is more applicable from the practical point of view than a complicated research protocol performed in a Clinical Research Center of an academic institution. Similarly, the use of different assays recreates the situation encountered by community physicians relying on their hospital or outside laboratories.

Thus, our current report reflects the "real life" situation of diagnosis of acromegaly in a community setting.

Over the years, diagnostic criteria for acromegaly have changed dramatically, and the numbers of patients diagnosed with this disease have increased in parallel. Older studies have estimated an incidence of about 3–4 cases per million patient-years [3–5], but the newest data found it to be 11 cases per million patient-years [6]. This has been attributed to the familiarity of physicians with that

diagnosis and refinement of diagnostic tools. As the best illustration of this trend, in 1926, Davidoff described a series of 100 surgical cases of acromegaly in which 93 % had enlargement of the sella turcica on x-ray and 62 % had visual disturbances due to compression of the optic chiasm, reflecting the proportion of patient with a very large tumor size at presentation [7]. The presence of visual field deficits decreased to 27 % between 1951 and 1975, a result of dissemination of information and awareness of the disease, and as GH assays as well as computerized tomography became widely available, it further dropped to 15.4 % between 1976 and 1996 [8]. In the late 1970s, it was discovered that plasma IGF-1 concentrations are more strongly correlated with the manifestations of acromegaly than GH concentrations [9] and MRI instruments became widely available in the late 1990s. These new refinements of our diagnostic armamentarium introduced yet additional means of biochemical and radiological diagnosis in patients with milder disease and smaller tumors, so that the prevalence of large adenomas compromising vision between 1982 and 2006 decreased to only 5.2 % [10]. However despite availability of commercial IGF-1 assays, random plasma GH and GH nadir following glucose administration continued to be the gold standards for diagnosis of acromegaly for quite some time in the general medical community. As has been described previously [1], there is a subset of patients with acromegaly, confirmed on pathological examination of resected pituitary adenomas, who have seemingly normal pre-operative mean GH levels and even GH suppression by glucose but elevated IGF-1. In 2002, we found that this subset of patients made up 25 % of newly diagnosed patients with acromegaly referred to our institution, but hypothesized that due to ascertainment bias, whereby patient with "normal" random and/or glucose-suppressed GH were considered not having acromegaly and not referred to a specialized center, the true proportion of such patients in the general population might be even higher [1]. We show here that in the era of almost universal use of IGF-1 measurement as a diagnostic criterion, the numbers of such patients are $\sim$30 % of all patients with acromegaly. It can be inferred that over the past decade, awareness of this normal GH subpopulation has spread, thus eliminating, or at least minimizing, ascertainment bias. Interestingly, this updated analysis has demonstrated that the proportion of patients with acromegaly who have "normal" mean serum GH levels does not appear to have fallen over time. While it looked as though the prevalence might have remained stable or even decreasing in the eight years immediately following our original publication, over the most recent 5 year period it reached almost 50 %. Thus, increased familiarity with this subpopulation and use of IGF-1 as a diagnostic tool is leading to identification of more patients with the disease, who previously would have been overlooked when the diagnosis was based strictly on GH criteria. This would explain the data by Burton et al. [6] who used US administrative claims data from 2008 to 2012.

The diagnosis of acromegaly has been evolving over the past century, from the early years when only those patients with the most advanced signs and symptoms were identified, to the current state. Historically, mean plasma GH levels and GH suppression following oral glucose administration have been the mainstay of diagnosis, even though the latter has more recently been shown to have very limited utility in patients without obviously elevated GH levels [11]. Our data show that a substantial percentage of all patients with clinical disease and confirmed somatotroph adenoma have "normal" GH, and therefore strengthens the growing body of evidence which supports the leading role of IGF-1 levels in the diagnosis of acromegaly. It would be a mistake, however, to ignore GH measurements as part of a diagnostic/surveillance work-up, because GH and IGF-1 reflect different aspects of acromegaly: GH as a measure of secretory activity of the tumor vs. IGF-1 as a parameter of biochemical (and, likely, biological) activity of the disease.

Prior studies have shown [10], there does tend to be a correlation between tumor size and mean GH levels, which might conceivably suggest that a smaller tumor and "normal" GH will eventually progress into the elevated GH subpopulation as the tumors enlarges. If the "normal" GH subpopulation simply represents early acromegaly, one would also expect the mean age at the time of surgery to be lower for this group, however the opposite was seen here, with a trend towards older age at surgery in patients with "normal," as compared to those with elevated, GH ($p = 0.005$). In this regard, it is interesting to remember that the levels of 24-h mean GH concentrations in patients with acromegaly are inversely related to their age [12].

Wade et al. [13] presented data showing that a full third of patients with immunochemically-positive somatotropinomas were clinically-silent (i.e. had no symptoms and signs suggesting acromegaly upon examination by an experienced endocrinologist), but had in fact elevated plasma IGF-1 levels and therefore had active disease. While our patients presented with clinical manifestations of acromegaly of different severity and benefitted clinically from IGF-1 lowering surgery, those described by Wade et al. [13] pose a challenging question further complicating the issue. Does the subpopulation of patients with elevated IGF-1 and "normal" mean plasma GH simply represent acromegaly in its early stages, or is it a part of the spectrum from a clinically silent somatotroph adenoma to classical acromegaly? Do these patients have the same associated morbidity and mortality risks as the patients with obviously elevated GH levels? Should they be treated conservatively

with surveillance only, or aggressively with resection of their pituitary tumors? It was shown both in patients with acromegaly and healthy controls that plasma IGF-1 concentrations correlate better with basal GH secretion than with pulsatile or even total 24 h GH and that basal GH concentrations as low as 0. 2 ng/ml may be sufficient to raise plasma IGF-1 into an acromegalic range [14]. It has also been shown that the clinical manifestations of acromegaly correlate more closely with plasma IGF-1 than GH, and that normalization of IGF-1 is associated with resolution of symptoms [9, 15]. Furthermore, the persistence of elevated IGF-1 in patients with acromegaly following transsphenoidal surgery was associated with a higher mortality rate, regardless of GH levels [16]. As data point towards IGF-1, rather than GH, levels as the driver for the signs and symptoms of acromegly, it could also be inferred that the long-term outcomes in patients with acromegaly may actually be more closely related to IGF-1 levels. This opens yet another Pandora box: whereas all patients with normal IGF-1 levels in the above epidemiological studies had IGF-1 concentrations safely within the normal range, those with "elevated" IGF-1 encompassed a wide IGF-1 range, from only mildly elevated to frankly increased. Thus, the increased morbidity and mortality rates in the latter group might have been dictated by the patients with significantly increased IGF-1 concentrations. Is there a threshold for plasma IGF-1 concentration below which its further decline does not bring about clinical benefits but rather increases the risk/benefit ratio of therapeutic interventions? Damjanovic et al. [17] have presented provocative data suggesting that complete surgical normalization of GH and IGF-1 levels was no more effective than only partial decline of these parameters in terms of cardiac indices, body composition and insulin resistance.

Based on these findings, one might question whether it would be ethical to perform a randomized trial of long-term surveillance versus active intervention to clarify the fate of patients with "normal" GH or even those with no clinical manifestations but with pituitary tumors and elevated IGF-1, if they have even a theoretically increased risk of poor long-term outcomes. On the other hand, if these subpopulations do represent a clinical subtype with more benign course, aggressive treatments would be exposing them to unnecessary risks and contributing to rising healthcare costs. At the present time, these questions remain unanswered, but research continues to build on our understanding of the heterogeneous population of individuals with acromegaly.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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