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ORIGINAL

Subclinical acromegaly: to treat or not to treat?

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Abstract. Patients with acromegaly usually present with the classical signs of acromegaly, whereas patients without the specific signs or symptoms are rarely diagnosed. This unique entity can be named "subclinical acromegaly". This was a retrospective study. Our study group consisted of 6 patients (4 females) with incidentally diagnosed acromegaly, most following head MRI for unrelated reasons and without the specific signs of acromegaly. Mean age at diagnosis was 48.8 ± 19.2 years. Baseline IGF-1 ranged between 1.3–2.0 × upper limit of normal (ULN). MRI depicted a pituitary microadenoma in 5 patients, and one patient presented with a 12 mm intra-sellar macroadenoma. Mean calculated SAGIT clinical score was 4.8. Three patients underwent trans-sphenoidal resection; two achieved hormonal remission and one improved but did not normalize IGF-1 following surgery. Four patients (including one following surgery) were given somatostatin analogs, and three normalized IGF-1. Several patients improved clinically following treatment, reporting improvement in snoring, hypertension, or weight loss, and pituitary adenoma decreased in size in 2 patients that responded to medical treatment. We report a series of 6 patients with very mild and subclinical acromegaly. It is uncertain whether all such patients will gain clinical benefit from treatment, but most experienced clinical improvement due to treatment.

Key words: Acromegaly, Adenoma, Insulin-like growth factor-1 (IGF-1), Subclinical

ACROMEGALY is a rare condition caused by a growth hormone (GH)-secreting pituitary adenoma leading to elevated GH and insulin-like growth factor-1 (IGF-1) levels [1]. Uncontrolled acromegaly is associated with high morbidity and mortality rates [2]. Patients usually present with characteristic coarse facial changes, hands and feet swelling, macroglossia, snoring and sleep apnea, carpal tunnel syndrome, headache, sweating and new-onset diabetes mellitus. However, signs and symptoms develop slowly, 4–8 years prior to the diagnosis of acromegaly [3]. Nevertheless, when finally diagnosed, almost all patients have some classical signs of acromegaly, and successful treatment with GH and IGF-1 suppression to normal usually leads to clinical improvement. This may also restore mortality rates to those of the healthy population [2]. It is assumed that patients with severe clinical and biochemical acromegaly may benefit more from successful treatment (surgical and/or medical) than patients with milder forms of acromegaly. However, this was not studied, and all subjects with confirmed acromegaly are routinely advised and referred for specific treatment to normalize hormonal hypersecretion, as IGF-1 normalization is believed to reflect disease control, improves co-morbidities and reduces mortality [4].

The SAGIT instrument was designed and developed by leading acromegaly experts to assist clinicians to define the stage of acromegaly and response to treatment and to help in making therapeutic decisions. The SAGIT clinical score was designed for use after initial diagnosis and during patient follow-up and comprises five sections that assess key features of acromegaly: signs and symptoms (S), associated comorbidities (A), GH levels (G), IGF-1 levels (I), and the tumor profile (T) [5].

We have identified a group of six patients with mild biochemical acromegaly but without the specific signs or symptoms of acromegaly. All these patients were sent for pituitary surgery and/or medical therapy and improved clinically and biochemically.

Patients and Methods

Patients

The study group consisted of 6 patients (4 females) with incidentally diagnosed acromegaly and without the

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specific signs of acromegaly, presented at three endocrine outpatient clinics in Israel. We have named this entity "subclinical acromegaly", which was defined in the presence of all the following criteria:

1) Baseline age-adjusted IGF-1 ≥1.3-fold the upper limit of normal (ULN) and ≤2-fold the ULN.
2) Up to 1 sign or symptom of acromegaly (headache, sweating, joint symptoms, swelling)
3) Up to 2 associated comorbidities of acromegaly (diabetes, hypertension, sleep apnea, heart disease, hypopituitarism).
4) Evidence of a pituitary adenoma on imaging.

These criteria were used to differentiate cases of silent somatotroph adenomas, where IGF-1 levels are normal, and from cases of overt acromegaly, where patients may present with multiple features and/or significant elevation of GH and IGF-1 levels.

Patients did not present with the characteristic coarse facial changes, macroglossia or hands and feet enlargement. Baseline GH was below 1 ng/mL and/or suppressed to below 1 ng/mL following glucose load, in most cases. Magnetic-resonance imaging (MRI) depicted small pituitary microadenomas in most cases (Table 1). SAGIT instrument was used to exclude patients with coarse features of acromegaly, as those with >1 sign or symptom of acromegaly (headache, sweating, joint symptoms, or swelling) or >2 associated comorbidities (altered carbohydrate metabolism, hypertension, sleep apnea, heart disease, hypopituitarism, or active malignancy) were excluded.

The medical records were reviewed for clinical characteristics, signs and symptoms, laboratory tests, treatment approach, and response to treatment. Pituitary adenoma size at presentation and during follow-up was assessed by MRI. The study was approved by the Rabin-Beilinson Institutional Review Board.

Patients were treated by experienced endocrinologists specializing in the field of pituitary diseases. Decision on specific treatment for each patient was achieved following multi-disciplinary discussions and discussion with the patient. Patients were treated with either cabergoline or somatostatin analog or were referred for pituitary surgery.

GH and IGF-1 and other hormonal assays

Serum GH and IGF-1 levels were measured in the morning following an overnight fast, using chemiluminescent immunometric assays (Immulite 2000; Siemens) in most patients. The GH assay has a sensitivity of 0.05 ng/mL an intra-assay coefficient of variation (CV) of 4.6% for a GH concentration of 3.7 ng/mL and an inter-assay CV of 5.7%. The intra- and inter-assay CVs for an IGF-1concentration of 380 ng/mL are 2.9% and 7.4%, respectively. Baseline IGF-1 measurements were repeated 2–3 times. Some patients had their IGF-1 levels measured by the Liaison chemiluminescence immunoassay (DiaSorin, Italy). IGF-1 levels are presented as fold-increase of the ULN (mean IGF-1 value divided by the sex- and age-specific upper normal limit), comparing values along the follow-up of each patient.

Total testosterone, TSH, FT4, and cortisol levels were determined by a variety of commercially available immunoassays, according to the site of follow-up treatment. For each patient, all hormonal measurements were performed in the same laboratory, using the same hormonal assays.

Table 1 Baseline characteristics of patients, treatments and response to treatment

No	M/F	Age	Symptoms	Incidental	Basal GH	Glucose Suppressed GH	IGF-1 × ULN	Adenoma size (mm)	TSS/ pathology/ remission	Medical treatment	Follow-up (months)	Clinical response	Hormonal remission —IGF-1 × ULN	Adenoma shrinkage
1	M	35	ED	Hyper PRL	0.7	NA	2.0	4	Yes/GH-PRL, KI67-2-3%/no	Lan/Oct	24	Weight loss	1.12	N/A
2	F	69	Headache	MRI for headache	2.9	NA	1.53	12	Yes/GH, KI67-2%/yes	No	24	N/R	0.86	6
3	F	43	Foot enlargement	MRI for TIA	0.8	0.17	1.33	4	No	Lan	48	Facial improvement	0.64	2.5
4	F	68	None	MRI for meningioma	1–2	0.86	1.89	6	No	Cab/Lan	90	N/R	0.51	2.5
5	M	57	Snoring, DM, HTN	HTN	0.6	0.52	1.85	8	No	Cab/Lan	50	Snoring, HTN	0.9	N/A
6	F	21	Amenorrhea	Amenorrhea, normal PRL	6.8	5	1.38	4	Yes/GH, KI67 <1%/yes	No	21	Normal menstruation	0.5	Normal MRI

Cab, cabergoline; DM, diabetes mellitus; ED, erectile dysfunction; HTN, hypertension; N/A, not available; N/R, not relevant; Oct, Octreotide-LAR; PRL, prolactin; Lan, Somatuline autogel; TIA, transient ischemic attack.

Statistical analysis

We summarized the data descriptively. Categorical variables are presented as numbers; continuous variables as means and standard deviations, or with ranges.

Results

Patients' characteristics at presentation

The study cohort included four women and two men with suspected subclinical acromegaly. Mean age at diagnosis was 48.8 ± 19.2 years (range, 21–69) (Table 1). All patients were incidentally diagnosed, or following head MRI for unrelated reasons, including headache, transient ischemic attack, amenorrhea, and following meningioma surgery (Table 1). None of the patients presented with the classical signs of acromegaly. However, one patient reported on mild enlargement of foot size, and one suffered of snoring (Table 1). One male patient was diagnosed following complains of erectile dysfunction and a female patient was diagnosed because of amenorrhea. According to SAGIT instrument, 4 of 6 patients had no signs or symptoms of acromegaly (Table 2), and two had a single feature associated with acromegaly. Most patients (5/6) had no associated co-morbidities, whereas one patient (patient 5) had two associated co-morbidities (Table 1 and 2). The mean SAGIT score for signs & symptoms was only 0.33 as for comorbidities (Table 2). According to SAGIT instrument the total score at diagnosis for the patients in our study group ranged between 4–7 (mean, 4.8), compared with the maximal possible score of 22 (Table 2).

Baseline GH was below 1 ng/mL in 3 patients and in 3 it was suppressed by glucose load to below 1 ng/mL. One patient with baseline GH of 6.8 ng/mL failed to suppress GH following glucose tolerance test. Patients had 2–4 consecutive measurements of serum IGF-1 (mean, 3 measurements) before decision on treatment for acromegaly. Mean IGF-1 level for each patient is shown in Table 1. Mean baseline IGF-1 for these patients was 1.67 × ULN (range, 1.3–2.0 × ULN). All patients had intact pituitary function.

MRI depicted a pituitary microadenoma in 5 patients, and one patient presented with a 12 mm intra-sellar macroadenoma.

Surgical treatment

Three patients underwent trans-sphenoidal resection for a pituitary adenoma. Pathology report revealed GH-expressing adenoma, with Ki-67 proliferation index of 1–3%. Two female patients achieved hormonal (IGF-1) remission (Table 1; patients 2, 6), and one man (patient 1) improved but did not normalize IGF-1 levels following surgery.

Medical treatment

Medical treatment with cabergoline was given to two patients but it did not show any beneficial effect on IGF-1 levels. Four patients (including two patients that did not respond to cabergoline and one that did not achieve remission following surgery) started with monthly injections of somatostatin analogs (somatuline autogel). Three out of these four patients achieved hormonal remission with somatostatin analog treatment, and the other one suppressed but did not normalize the elevated IGF-1 (Fig. 1). Two patients treated with somatuline autogel developed adverse effects, one had severe gastrointestinal symptoms, was switched to octreotide-LAR and improved (patient 1), and the other (patient 3) underwent cholecystectomy due to cholecystitis.

Clinical response

Several patients improved clinically due to somatostatin analog treatment (Table 1). One (patient 3) noticed a favorable change of her hands and facial look, although she did not present with a characteristic appearance. In another (patient 5) there was improvement in snoring and blood pressure control. In addition, one patient experienced weight loss (patient 1), and a female resumed

Table 2 SAGIT instrument score (5) for patients in our cohort

Patient No	S Signs & Symptoms	A Associated Comorbidities	G GH	I IGF-1 × ULN	T Tumor size (mm)	Total SAGIT Score
1	0	0	0	3	1	4
2	1	0	2	2	2	7
3	1	0	0	2	1	4
4	0	0	1	2	1	4
5	0	2	0	2	1	5
6	0	0	2	2	1	5
Mean score	0.33	0.33	0.83	2.17	1.17	**4.83**

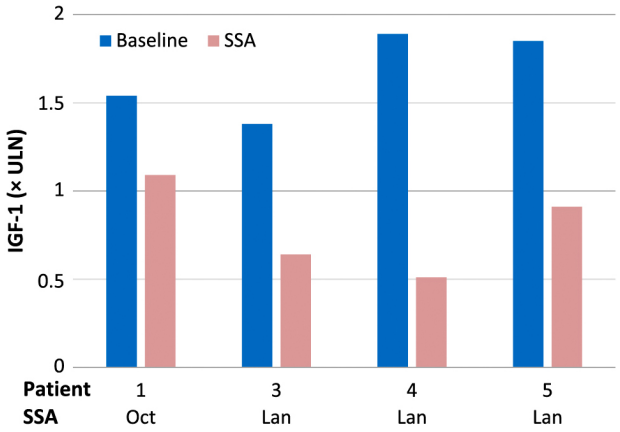

Fig. 1 IGF-1 levels before and while treated with somatostatin analogs (SSA) in 4 patients. Patients 3, 4, 5 were treated with somatuline autogel (Lan), and patient 1 was switched to octreotide LAR (Oct)

normal menstruation following pituitary surgery (patient 6). Pituitary adenoma decreased in size in 2 patients that responded to lanreotide treatment by suppressing and achieving normal IGF-1 with injections given every 8 weeks. One of these patients (patient 3) also improved clinically.

Discussion

We report herein a unique group of 6 adult patients with subclinical acromegaly diagnosed incidentally following head MRI performed for unrelated reasons in most cases. Patients presented without the characteristic facial appearance of acromegaly. Patients in our cohort mostly had low baseline or post-glucose load GH levels and relatively low IGF-1 levels (mean, 1.67 × ULN; range, 1.33–2.0 × ULN) compared to patients with active acromegaly. In line with these patients' features, MRI depicted pituitary microadenomas in five patients, and one had an intra-sellar macroadenoma. Thus, we coined the term *subclinical acromegaly* to describe patients with very mild disease that were discovered without the classical features of acromegaly and without significant biochemical abnormalities or the typical pituitary invasive macroadenomas reported in most patients with acromegaly.

Acromegaly has a spectrum of clinical and biochemical presentation. Most patients present with the classical full-blown acromegaly [3], others have normal GH levels but with the classical symptoms and signs of excess GH secretion, also known as micromegaly [6, 7]. At the other hand of the spectrum are silent somatotroph adenoma, characterized by adenomas that express but do not secrete GH, hence IGF-1 levels are within the normal range and patients do not have any clinical signs or symptoms associated with acromegaly [8]. The patients reported here presented with clinical and biochemical phenotype of GH excess, thus are not considered to have silent somatotropinomas, however, hormone levels and signs and symptoms were relatively mild and were not suggestive of classical overt acromegaly. Our definition of subclinical acromegaly is characterized by minimal clinical features and without significant biochemical abnormality or invasive tumor on imaging.

With the improvement of neuroimaging techniques and the increased availability of reliable IGF-1 assays over the last two decades, more patients with acromegaly and milder disease are diagnosed, occasionally with very mild symptoms and signs [9]. Possibly, some of these diagnosed patients may reflect early disease development with future possible clinical worsening if followed later without treatment, but others may remain with mild and subclinical disease.

We suggest determining the diagnosis of subclinical acromegaly in patients with limited signs and symptoms of acromegaly and associated comorbidities. The SAGIT instrument may be used to identify patients with subclinical acromegaly, as our definition was limited to those with one or no signs and symptoms of acromegaly and up to 2 associated comorbidities. Furthermore, in most patients, the biochemical and imaging abnormalities were also mild, as most patients were diagnosed with IGF-1 below 2 × ULN, nadir or random GH <1.0 ng/mL, and an intrasellar microadenoma.

Noteworthy, patients may present with mildly elevated IGF-1 levels repeatedly below 2 × ULN, that may reveal also a false positive error of the assay instead of an indication of active acromegaly. Thus, to confirm the diagnosis of acromegaly in some of these mild/marginal cases we looked for other clinical clues. Baseline or post OGTT GH levels are usually low in these unique patients, but almost all of them harbor a small pituitary microadenoma, albeit this may still suggest a pituitary incidentaloma and not necessarily a GH-secreting adenoma.

Of note, our trigger to investigate and assess for this entity was patient #3 in our cohort (Table 1), which presented with mild acromegaloid features, mildly elevated IGF-1 levels, but suppressed GH following OGTT. In our view, the external features and the clinical and biochemical response to treatment with somatostatin analogues supported the diagnosis of subclinical acromegaly, but in this case the diagnosis of acromegaly is not definite, as autonomous GH secretion was not definitely proved and pathological evidence for a GH-staining tumor was not available as the patient did not have surgery.

In our cohort all patients had direct or indirect clinical proof for the diagnosis of subclinical acromegaly at

presentation. Three patients underwent pituitary surgery with a histologically proven GH-secreting adenoma. Two other patients treated medically with somatostatin analog showed clinical improvement of their mild acromegaly and co-morbidities, and two subjects showed shrinkage of their pituitary microadenoma in response to medical treatment. Interestingly, remission following adenoma resection was achieved in two of three patients referred for surgery, and in three of the four patients treated with somatostatin analog (Fig. 1), similarly and even better compared to the remission rates achieved in patients with classical acromegaly. Two of the patients that responded to medical treatment achieved remission with a long interval (8 weeks) between lanreotide injections [10], in agreement with the mild baseline IGF-1 elevation. Hormonal remission in these two females was associated with clinical improvement and/or adenoma shrinkage.

It is uncertain whether the cost-benefit ratio of active treatment for these patients is in favor of treatment over surveillance. It is well established that elevated serum GH and IGF-1 are important factors contributing to the morbidity and increased mortality reported in patients with classical acromegaly, and hormonal normalization alleviates the morbidity and reduces mortality to the expected rates in the general population [11, 12]. Moreover, prolonged diagnostic delay that postpones treatment initiation is probably associated with increased morbidity and mortality [13]. However, the benefit of treatment is obviously high in patients with severe disease with very high GH and IGF-1 levels but becomes more limited when the disease is mild and subclinical. All patients in our series were offered specific treatment for acromegaly, either surgery or medical treatment, even though they presented with mild and subclinical disease. Two patients developed side effects during somatostatin analog treatment, including one with cholecystitis that resumed treatment following cholecystectomy.

Is subclinical acromegaly a true entity? Certainly yes. We propose that there is a true continuum from silent to functioning somatotroph adenoma: (A) silent somatotroph tumor, characterized by hormonal positive (GH-expressing adenoma), but clinically and biochemically silent disease; (B) subclinical acromegaly, characterized by hormonal and biochemical positive disease, which is clinically silent or borderline; (C) full-blown acromegaly, characterized by hormonal, biochemical and clinically positive disease. Treating patients with subclinical acromegaly may potentially prevent progression to full-blown acromegaly, with the associated increased morbidity and mortality, as shown by the clinical improvement in several of the treated patients in our cohort. However, as data are limited, additional studies are required to determine the benefit of treating patients with subclinical acromegaly, and currently decision on treatment or surveillance only should be made on an individual basis.

In conclusion, we report here a series of 6 patients with very mild acromegaly and suggest using the term subclinical acromegaly for those that fulfill the criteria aforementioned. Early diagnosis and treatment of patients with subclinical acromegaly may be beneficial and can lead to clinical improvement. However, additional studies are needed to better assess the disease course and the benefits of treatment in this unique group of patients.

Declarations

Conflict of interest

All authors have nothing to disclose.

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Ethics approval

The study was approved by the Rabin-Beilinson Institutional Review Board.

Disclosure Statement

The authors have nothing to disclose.

References

1. Colao A, Grasso LFS, Giustina A, Melmed S, Chanson P, *et al.* (2019) Acromegaly. *Nat Rev Dis Primers* 5: 20.
2. Holdaway IM, Bolland MJ, Gamble GD (2008) A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *Eur J Endocrinol* 159: 89–95.
3. Caron P, Brue T, Raverot G, Tabarin A, Cailleux A, *et al.* (2019) Signs and symptoms of acromegaly at diagnosis: the physician's and the patient's perspectives in the ACRO-POLIS study. *Endocrine* 63: 120–129.
4. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, *et al.* (2018) A consensus statement on acromegaly therapeutic outcomes. *Nat Rev Endocrinol* 14: 552–561.
5. Giustina A, Bevan JS, Bronstein MD, Casanueva FF, Chanson P, *et al.* (2016) SAGIT®: clinician-reported

outcome instrument for managing acromegaly in clinical practice—development and results from a pilot study. *Pituitary* 19: 39–49.
6. Butz LB, Sullivan SE, Chandler WF, Barkan AL (2016) "Micromegaly": an update on the prevalence of acromegaly with apparently normal GH secretion in the modern era. *Pituitary* 19: 547–551.
7. Espinosa de Los Monteros AL, Sosa-Eroza E, Gonzalez B, Mendoza V, Mercado M (2018) Prevalence, clinical and biochemical spectrum, and treatment outcome of acromegaly with normal basal GH at diagnosis. *J Clin Endocrinol Metab* 103: 3919–3924.
8. Langlois F, Woltjer R, Cetas JS, Fleseriu M (2018) Silent somatotroph pituitary adenomas: an update. *Pituitary* 21: 194–202.
9. Wade AN, Baccon J, Grady MS, Judy KD, O'Rourke DM, *et al.* (2011) Clinically silent somatotroph adenomas are common. *Eur J Endocrinol* 165: 39–44.
10. Neggers SJ, Pronin V, Balcere I, Lee MK, Rozhinskaya L, *et al.* (2015) Lanreotide Autogel 120 mg at extended dosing intervals in patients with acromegaly biochemically controlled with octreotide LAR: the LEAD study. *Eur J Endocrinol* 173: 313–323.
11. Holdaway IM, Rajasoorya RC, Gamble GD (2004) Factors influencing mortality in acromegaly. *J Clin Endocrinol Metab* 89: 667–674.
12. Holdaway IM, Bolland MJ, Gamble GD (2008) A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *Eur J Endocrinol* 159: 89–95.
13. Esposito D, Ragnarsson O, Johannsson G, Olsson DS (2020) Prolonged diagnostic delay in acromegaly is associated with increased morbidity and mortality. *Eur J Endocrinol* 182: 523–531.