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Acromegalic patients lost to follow-up: a pilot study

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Abstract Approximately 50 % of all acromegalic patients will require lifelong medical treatment to normalize mortality rates and reduce morbidity. Thus, adherence to therapy is essential to achieve treatment goals. To date, no study has evaluated the frequency and reasons for loss to follow-up in the acromegalic population. The current study aimed at evaluating the frequency of acromegalic patient loss to follow-up in three reference centers and the reasons responsible for their low compliance with treatment. All of the files for the acromegalic patients in the three centers were reviewed. Those patients, who had not followed up with the hospital for more than a year, were contacted via phone and/or mail and invited to participate. Patients who agreed to participate were interviewed, and blood samples were collected. A total of 239 files were reviewed; from these 42 patients (17.6 %) were identified who were lost to follow-up. It was possible to contact 27 of these patients, 10 of whom did not attend the appointments for more than one time and 17 of whom agreed to participate in the study. Fifteen of these 17 patients had active disease (88.2 %), and all of the patients restarted treatment in the original centers. The main reason for loss to follow-up was an absence of symptoms. High-quality follow-up is important in acromegaly to successfully achieve the aims of the treatment. An active search for patients may allow the resumption of treatment in a significant proportion of these cases, contributing to reduced morbidity and mortality in this patient population.

Keywords Acromegaly · Compliance · Follow-up · Chronic disease

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Introduction

Acromegaly is a chronic endocrine disease associated with enhanced morbidity and mortality [1, 2]. Surgery is the treatment of choice for patients with enclosed microadenomas and macroadenomas. However, the majority of those harboring macroadenomas with extra-sellar extension are unlikely to be cured by surgery alone [3–5]. Medical treatment with somatostatin receptor ligands (SRLs) is the first treatment option in acromegalic patients, both for those in whom surgical cure is improbable and for those patients who are not cured by surgery. The treatment with SRLs is lifelong in nearly all patients [4].

Currently, the efficacy of treatment approaches is evaluated according to the cure criteria established by the 2010 Consensus [6]: (1) basal GH < 1.0 ng/mL, (2) nadir

GH during oral glucose tolerance test (OGTT) < 0.4 ng/mL and (3) normalized age-matched IGF-I. For patients being treated with SRLs, only basal GH and IGF-I are used [7].

The normalization of GH and IGF-I is associated with a reduction in mortality to the expected rates for a normal population [2]. As approximately 50 % of all patients will not be cured by surgery and thus require medical treatment, high-quality follow-up of these patients along with good compliance with the prescribed therapy are essential to achieving treatment goals.

To our knowledge, no study has evaluated the frequency of and reasons for loss to follow-up in reference centers for acromegaly treatment. Thus, the aim of this study was to evaluate the prevalence of acromegaly patients who failed to follow-up with treatment among a large sample of patients from three reference centers in the city of Rio de Janeiro, Brazil. In addition, we investigated the percentage of uncontrolled patients and the reasons behind their low compliance with treatment.

Subjects and methods

This study was approved by the Ethics Committee of the Clementino Fraga Filho University Hospital/Federal University of Rio de Janeiro (coordinator center), and it was also approved by the two other collector centers. All of patients signed informed consent forms before enrolling in the study.

Patients

All of the files for acromegalic patients who were diagnosed between 1994 and 2009 were reviewed. Patients who had not visited the hospital for more than a year were contacted via phone or mail and invited to participate in the study. All of the patients who agreed to sign an informed consent form were included in the study. The patients were interviewed, and blood samples were collected from them.

Interview

The patients were interviewed to determinate the main reason for their failure to follow up with treatment. Their answers were classified as follows:

- "I thought I was cured"
- "I do not feel sick"
- "I moved to another city"
- "I am being treated at another hospital"
- "I do not have time to attend my appointments"
- "I do not have money to come to the hospital"

Methods

Hormonal assessment

A fasting blood sample was collected from each patient on the day of the interview, and the patient's basal GH, IGF-I, glucose and glycosilated hemoglobin levels were measured. An oral glucose tolerance test (OGTT) was performed in non-diabetic patients who had a basal GH level higher than 0.4 ng/mL or an IGF-I level higher than that of age-matched normal subjects [6].

Plasma GH levels were measured using a chemiluminescence assay kit (IMMULITE; Diagnostic Products Corp. Inc., Los Angeles, CA, USA). The inter-and intra-assay coefficients of variation for this assay were 6.0 and 5.8 %, respectively. The International Reference Preparation of GH was 98/574. Plasma IGF-I levels were measured using an immunoradiometric assay kit (DSL, Webster, TX, USA). The inter-and intra-assay coefficients of variation for this assay were 2.6 and 4.5 %, respectively. The International Reference Preparation of IGF-I was 80/185.

The patients were considered to be uncontrolled if their basal GH level was higher than 1.0 ng/mL, if their nadir GH level after OGTT was higher than 0.4 ng/mL, or if their plasma IGF-I level was higher than that of age-matched normal subjects.

Statistical analysis

Statistical analyses were performed using SPSS version 16.0 for Windows (SPSS, Inc., Chicago, IL, USA). The results were reported as the mean (±SD). Student's t test was used to compare numerical variables. A Chi-squared test was used to compare categorical variables. p values<0.05 were considered statistically significant.

Results

Patients' files review

A total of 239 files from acromegalic patients were reviewed in the participating centers. A total of 42 patients (17.6 %) who were lost to follow-up were identified. An attempt was made to contact all of these patients.

Patients lost to follow-up

At the last evaluation before loss to follow-up, the IGF-I levels were normal in eight out of the 42 patients (19 %) without treatment, normal in six (14.3 %) with medical treatment and uncontrolled despite medical treatment in 28 patients (66.7 %). At that time, octreotide LAR as

monotherapy was the treatment modality in 23 out of the 42 patients (54.8 %), octreotide LAR with cabergoline was the treatment modality in nine of the patients (21.4 %), and cabergoline monotherapy was the treatment modality in two out of the 42 patients (4.8 %).

Out of the 42 patients, contact was not possible in 14 cases (33.3 %) due to inaccurate telephone and address information. Ten patients (23.8 %) were contacted but failed to attend more than one scheduled interview (total number of interviews ranging from 2 to 10). One of the patients (2.4 %) had died the year before from urinary sepsis. The remaining 17 patients (40.5 %) came to the interviews and were included in the study. The results are summarized in Fig. 1.

Disease status and reasons for noncompliance

Fifteen out of the 17 patients (88.2 %) had active acromegaly during the study evaluation. Thirteen patients had elevated GH and IGF-I levels, and two patients had elevated IGF-I levels with normal GH levels. The baseline GH and IGF-I levels at the last visit before loss to follow-up and at the time of the study are listed in Table 1. Four of the patients (23.5 %) were being treated at other centers (all of them had uncontrolled disease). Financial problems were the reason for the loss to follow-up in one of the patients (5.9 %); this patient was not being treated and had active disease. The remaining 12 patients (70.6 %) failed to attend their last outpatient clinic visit, and because they were not feeling sick, they stopped treatment. Ten out of these 12 patients had active disease at the time of the interview.

The median time without treatment was 2 years (ranging from 1 year and 4 days to 5 years). All 17 patients agreed to restart follow-up in the original centers. The four patients who were being followed in the other centers but still had active disease received different therapy when they returned to their original center. Treatment was restarted for the 11 patients who had disease symptoms and were not being treated. Octreotide LAR was started for 10 of the patients, and cabergoline was started for one patient.

Comparison between patients lost to follow-up and compliant patients

At the time of study, the mean age in the group of patients who were lost to follow-up and that of the group of compliant patients were 50.2 (±14.5) years and 50.4 (±11.7) years, respectively ($p = 0.434$). There were no differences with regard to sex, educational attainment or annual family income between the two groups. Considering the laboratory evaluation in the last visit before loss to follow-up, uncontrolled acromegaly was present in 47.0 and 76.5 % of the compliant patients and of the patients who were lost to follow-up, respectively ($p = 0.043$).

The treatment modalities were not different between the groups. In the compliant group, the treatment modalities included cabergoline as monotherapy in 6.0 % of the patients, octreotide LAR as monotherapy in 51.0 % of the patients, octreotide LAR with cabergoline in 21.8 % of the patients, pegvisomant in 5.5 % of the patients and no drug therapy in 15.7 % of the patients. (these patients had been recently diagnosed or had been cured by surgery and/or radiotherapy). There was no difference in treatment duration between the two groups.

Discussion

Acromegaly therapy has evolved in the last decades, and many treatment options have become available. Transsphenoidal surgery remains the procedure of choice for enclosed adenomas [3, 4]. However, the cure rate for

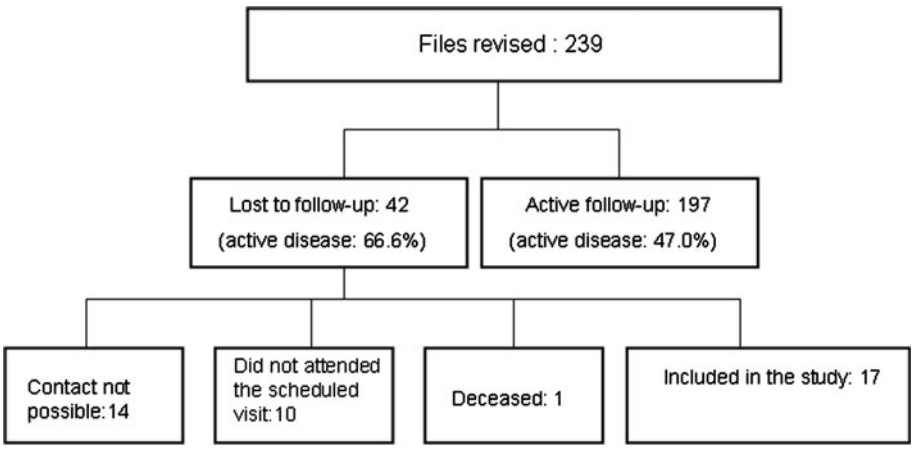

Fig. 1 Flowchart showing the total number of patients who were lost to follow-up and the results of the active search

Table 1 GH and IGF-I levels at the last patient visit before loss to follow-up and at the time of the study evaluation

Patient	GH levels at the LVLF (ng/mL)	IGF-I levels at the LVLF (%ULNR)	GH levels at the study visit (ng/mL)	IGF-I levels at the tudy visit (% ULNR)
1	11.3	385	17.5	386
2	20.4	240	32.0	308
3	4.5	183	7.4	185
4	12.4	203	19.7	264
5	3.1	320	3.4	423
6	0.7	49	0.9	197
7	0.3	81	0.2	78
8	1.0	52	0.7	56
9	11.4	95	5.4	265
10	4.6	138	4.8	145
11	1.9	196	2.2	206
12	9.0	257	2.1	155
13	10.4	411	11.9	424
14	3.2	370	2.5	355
15	4.4	186	5.2	131
16	2.4	203	2.2	204
17	0.9	50	0.8	205

GH growth hormone, *IGF-I* insulin-like growth factor type 1, *LVLF* last visit before loss to follow-up, *ULNR* upper limit of normal range

macroadenomas with extra-sellar extension, which occur in the majority of acromegaly cases, is less than 50 % of the total cases and can be as low as 10 % for giant adenomas [5]. Therefore, adjuvant therapy with drugs is necessary in a large number of patients.

Radiotherapy is reserved as a third-line treatment because of its potential risks and the availability of other effective medical treatments [3, 8, 9].

Somatostatin receptor ligands are currently the first choice of medical therapy for the treatment of acromegaly, and disease control using this drug class is achieved in approximately 30 % of patients in prospective clinical trials [3, 10–12]. Although two recently published studies report the possibility of an acromegaly cure after long-term SRLs treatment in selected patients [13, 14], SRLs therapy is usually a life-long treatment; the disease persists if the treatment is stopped, and rates of disease control are lower if adherence to therapy is low.

Dopamine agonists (DAs) are less effective than SRLs; however, in patients with slightly elevated hormonal levels, good efficacy can be achieved [15, 16]. This drug class can be administered alone or in combination with SRLs [16, 17]. There have been only two reported cases of disease cure in acromegaly with long-term use of DAs [18]. Thus, similar to SRLs, DAs are a life-long treatment in the majority of cases.

GH receptor antagonist (pegvisomant) therapy is highly effective in normalizing IGF-I levels, with control rates between 60 and 90 % [19, 20]. However, because the drug has no effect on tumor, it is reserved for patients whose diseases is not controlled despite surgery and previous medical therapy with SRLs [3, 4]. Pegvisomant can be used alone or in combination with SRLs [21]. Because pegvisomant does not act on somatotropinomas, cure is not expected with this drug.

As mentioned previously, acromegaly is a chronic disease with many therapeutic options that are effective in normalizing GH and IGF-I levels and controlling tumor growth [3]. However, an acromegaly cure is only obtained in a small proportion of patients (those with enclosed tumors, operated on by experienced surgeons). Thus, patients require regular outpatient clinic visits (every 3–6 months depending on their disease status), and many treatment modifications may be needed. Therefore, as with any chronic disease, adherence to therapy is essential to reduce morbidity and mortality [22, 23].

In our study, the rate of patient loss to follow-up was higher than in some population studies [24, 25] but similar to that reported in others [26]. To our knowledge, no study to date has reported the reasons for loss to follow-up in the acromegalic population. We found that the most common cause was absence of symptoms or the presence of mild symptoms that were not improving with therapy. These are also the major causes for low adherence to therapy in other chronic diseases, such as arterial hypertension [27]. Although the patients in our study reported that they were not feeling sick, disease activity was observed in 10 out of the 12 patients (83.3 %). High GH and IGF-I levels are associated with chronic complications of acromegaly, such as left ventricular hypertrophy, heart failure, sleep apnea and arterial hypertension, as well as increased mortality [28].

There were no differences between the group of patients who were lost to follow-up and the group of compliant patients, with regard to their demographic characteristics and treatment duration and modality. However, there was a higher frequency of active acromegaly cases in the group that was lost to follow-up after the last hospital visit. It is possible that unsuccessful treatment was the reason the patients abandoned treatment, especially those who experienced mild symptoms or no symptoms despite having elevated hormonal levels. Thus, this group of patients should be followed very closely to prevent loss to follow-up.

As there are no studies that report reasons for low compliance in acromegaly cases, there are no descriptions of strategies to improve adherence to therapy. In a systematic review of the literature regarding interventions to enhance medical adherence in chronic medical conditions [29], both behavioral interventions (such as medication dose reductions) and information intervention (such as phone calls) were found to be effective. In our study, active patient follow-up via mail and phone allowed us to restart treatment in 40.5 % of the patients who were lost to follow-up, which certainly had an impact on morbidity or mortality. Thus, we encourage all centers to review patient files to identify patients who have been lost to follow-up and to actively search for these patients to restart therapy. This process may allow treatment resumption in a significant percentage of patients and contribute to reductions in the morbidity and mortality associated with acromegaly.

In conclusion, acromegaly is a chronic disease associated with enhanced morbidity and mortality when hormonal levels are not normalized. Because approximately 50 % of acromegalic patients will require long-term therapy, compliance with the treatment is essential to achieving treatment goals. As in many other chronic diseases, loss to follow-up is common, and an active search of these patients may allow the resumption of treatment in a significant proportion of cases.

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Conflict of interest MRG received grant support from Novartis Biociências S.A and Pfizer and speaker fees from Novartis Biociências, Pfizer and Ipsen. RNC is an employee of Novartis Biociências S.A in Brazil.

Ethical standards The authors declare that this study complies with the current laws of Brazil.

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