Failure to achieve disease control in acromegaly: cause analysis by a registry-based survey

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Abstract

Context: Disease control is a prime target in acromegaly treatment. This should be achievable in the vast majority of patients by available treatment options. For unknown reasons, however, a significant number of patients do not achieve disease control.

Objective: To investigate reasons for failure to achieve disease control in long-standing acromegaly.

Design and methods: Survey based on the German Acromegaly Registry database (1755 patients in 57 centres). Questionnaires were sent to 47 centres treating 178 patients with elevated disease markers (IGF1 and GH) at the last documented database visit out of 1528 patients with a diagnosis dated back ≥ 2 years. Thirty-three centres returned anonymised information for 120 patients (recall rate 67.4%).

Results: Median age of the 120 patients (58 females) was 57 years (range 17–84). Ninety-four patients had at least one operation, 29 had received radiotherapy and 71 had been previously treated medically. Comorbidities were reported in 67 patients. In 61 patients, disease activity had been controlled since the last documented database visit, while 59 patients still had biochemically active disease. Reasons were patients' denial to escalate therapy (23.3%), non-compliance (20.6%), fluctuating insulin-like growth factor 1 (IGF-1) and growth hormone (GH) levels with normal values at previous visits (23.3%) and modifications in pharmacotherapy (15.1%). Therapy resistance (9.6%), drug side effects (4.1%) and economic considerations (4.1%) were rare reasons.

Conclusions: Main reasons for long-standing active acromegaly were patients' lack of motivation to agree to therapeutic recommendations and non-compliance with medical therapy. Development of patient education programmes could improve long-term control and thus prognosis of acromegalic patients.

Introduction

Acromegaly is caused by excessive growth hormone (GH) secretion from benign pituitary tumours in the vast majority of cases (1). The disease is associated with increased morbidity, impaired quality of life and a reduced life expectancy (1). However, when GH excess is controlled and/or insulin-like growth factor 1 (IGF1) levels are normalised, the clinical symptoms and comorbidities improve (1, 2) and mortality risk can be markedly reduced towards that of the normal population (3). Thus, a major aim of therapy is normalisation of GH and IGF1 levels according to current consensus guidelines (4, 5, 6). As many patients cannot be cured by surgery alone (7, 8) and as disease recurrence may occur, patients require lifelong surveillance and disease management (2, 4, 9).

The German Acromegaly Registry is one of the largest registries for acromegalic patients (8, 10). According to

a recently published analysis (8), ~20% of the documented patients were uncontrolled referring to the latest consensus guidelines (5, 6). Available treatment options, however, should allow disease control in the vast majority of patients.

Background information about the reasons for uncontrolled acromegaly is missing. We therefore investigated the causes of uncontrolled disease activity in long-standing acromegaly by a registry-based survey.

Subjects and methods

This was a registry-based survey to elucidate the causes for uncontrolled disease activity in long-standing acromegaly. Details about the structure, data collection and the database of the German Acromegaly Registry have been published (8, 10). Selection of the study cohort is shown in Fig. 1. At the time of the study in 2013, 1755

Figure 1
Selection of the study cohort.

patients treated at 57 centres were enrolled. The study was restricted to cases with a diagnosis of acromegaly ≥ 2 years before the last documented visit in the database ($n = 1554$). At the last documented follow-up visit, IGF1 was available in 1528 patients. In 295 patients without pegvisomant therapy, no random GH was available and, therefore, these patients were excluded (73 with an elevated IGF1 level). In 1042 patients without pegvisomant therapy, IGF1 and GH were documented and IGF1 was documented in 191 patients receiving pegvisomant. According to the criteria of cure from recent consensus guidelines (5, 6), 178 (14.4%) of the 1233 patients had uncontrolled disease (IGF1 levels elevated and random GH level was ≥ 1 ng/ml or IGF1 levels elevated in patients treated with the GH receptor antagonist (GHRA), pegvisomant). IGF1 was judged according to the centre-specific reference range. For each of the 178 patients, a questionnaire with the patient's ID was prepared and sent to the treating centre ($n = 47$). The questionnaire comprised information about sex, age, comorbidities (diabetes mellitus, hypertension, coronary artery disease (CAD) and sleep apnoea), previous and current therapies, and IGF1 and GH levels. If criteria for disease control were not fulfilled at the final visit to the centre, treating physicians had to give explanations as to why disease activity was uncontrolled. A choice of eight pre-formulated answers and a free text option were offered. The reasons provided were as follows: i) non-compliance, ii) patient's denial of therapy escalation, iii) side effects of therapeutic measures, iv) fluctuating and previously normal IGF1 and GH values, v) resistance to maximal therapy, vi) intentional treatment-free interval or change in therapy, vii) unfavourable benefit–cost analysis and viii) physician's unawareness of uncontrolled disease. Multiple answers were possible. To minimise reporting bias, questionnaires were anonymised by the participating centre.
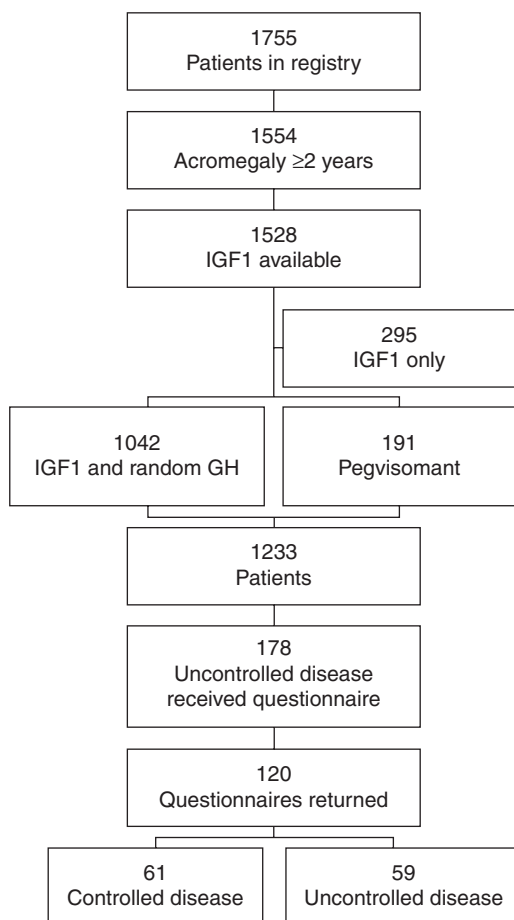
Results

Out of the 178 patients with uncontrolled acromegaly treated at 47 centres, the questionnaires for 120 patients (67.4%) treated in 33 centres were returned and could be analysed. The median age of the 120 patients was 57 years (range 17–84) and 58 of them were females (48.3%). During the course of their disease, 94 patients (78%) had at least one operation, 29 patients (24%) had received radiotherapy and 71 patients (59%) were treated medically in the past. Ten patients (8%) had received no prior treatment for acromegaly. Previous treatment of acromegaly is shown in Fig. 2A. Comorbidities were reported in
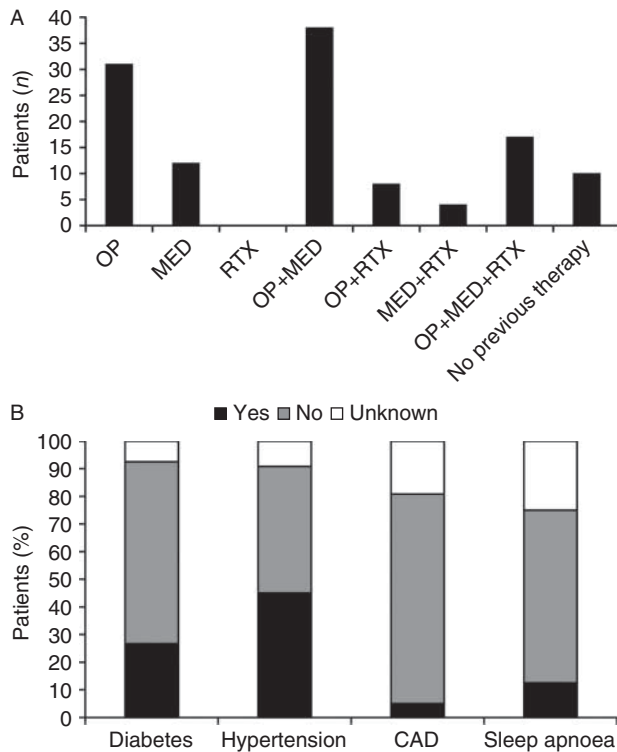
Figure 2

Previous treatment regimens (A) and comorbidities (B) in 120 patients, who were biochemically uncontrolled at the last documented database visit. OP, operation; MED, medical therapy; RTX, radiotherapy.

67 patients (56%) as depicted in Fig. 2B. Thirty-five patients (28%) had no comorbidities and, for 18 patients, information was incomplete or unknown. Thirty-five patients (28%) suffered from one comorbidity, 27 (20.8%) from two comorbidities, and five (5.8%) from three comorbidities, as shown in Fig. 2B.

In 61 patients (51%), the treating physicians reported that disease activity has been controlled since the last documented database visit as evidenced by IGF1 and random GH or IGF1 in pegvisomant-treated patients. However, 59 patients (49%) were still biochemically uncontrolled at the final visit to the centre. A histogram of the IGF1 values in uncontrolled patients is shown in Fig. 3. There were no differences between controlled and uncontrolled patients concerning the prevalence of comorbidities and the proportion of patients who were operated, had received radiotherapy or had been previously medically treated. At the final visit to the centre, 48 (81%) of the 59 uncontrolled patients were medically treated with somatostatin analogues (SSAs), dopamine

agonists, or pegvisomant either as monotherapy or in various combinations (Fig. 4). In patients with drug monotherapy ($n=30$), the median dose for depot octreotide was 20 (range 10–30) mg every 28 days ($n=9$), for depot lanreotide 120 (range 60–120) mg every 4 weeks ($n=6$), for cabergoline 1.5 (range 0.5–2.0) mg/week ($n=6$) and for pegvisomant 25 (range 10–42.5) mg/day ($n=9$). Eleven patients were on no medical treatment.

The reasons why therapy of acromegaly in the 59 uncontrolled patients had not been escalated are shown in Fig. 5. According to the treating physicians, the main reasons were the patients' denial to escalate or step-up therapy, and fluctuating IGF1 and GH levels with normal IGF1 and/or GH at previous visits. Non-compliance was another frequent cause of uncontrolled disease. In some patients, medical treatment had been temporarily paused because of pending pregnancy or to evaluate the effect of radiotherapy or surgery, or drug therapy has been recently switched and patients were in the phase of dose titration. Only seven patients were considered as non-responders. Three patients could not tolerate a step-up in medical treatment because of side effects. An unfavourable benefit–cost ratio as judged by the treating physician was another rare reason and none of the physicians reported that they accidentally overlooked the patient's uncontrolled disease state. All free-text comments could be allocated to one of the eight reasons mentioned earlier in this study.

Discussion

This is the first study investigating the reasons for failure of biochemical control in patients with long-standing acromegaly in a large nation-wide cohort. More than
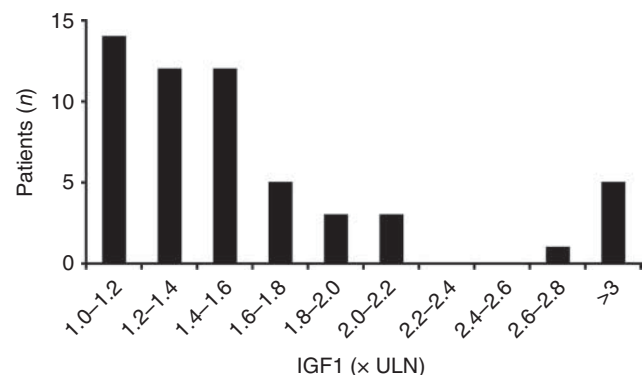
Figure 3

Histogram of IGF1 values in patients who were biochemically uncontrolled at the final visit to the centre. n, number of patients; × ULN, times upper limit of normal.
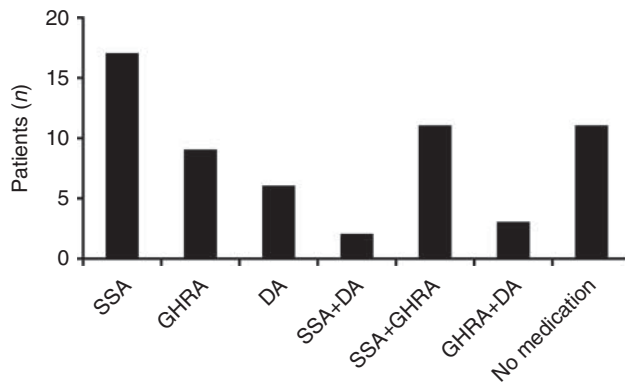
Figure 4

Medical treatment regimens in patients who were biochemically uncontrolled at the final visit to the centre. SSA, somatostatin analogue; GHRA, GH receptor antagonist (pegvisomant); DA, dopamine agonist; *n*, number of patients.

two-thirds of the 47 centres participated and returned information for almost 70% of the patients who had complete data and were by definition biochemically uncontrolled at the last documented visit in the central database. Uncontrolled disease was defined by an elevated IGF1 level and a random GH level ≥1 ng/ml in patients without pegvisomant therapy. We therefore had to leave out a group of 295 patients from the survey cohort due to missing GH, among them 73 with an elevated IGF1 level. Discordance between IGF1 and GH may occur in up to 30% of patients with most of the cases having an elevated IGF1 and a normal GH level (4, 5, 6). There is no consensus as to whether patients with discordant GH and IGF1 should be regarded as uncontrolled and whether they require treatment (4, 5, 6). Thus, there is some degree of uncertainty about the true rate of uncontrolled long-term acromegaly in the study cohort. This, together with missing information about patients, whose questionnaires had not been returned, may potentially introduce some bias. However, even in the unlikely event that all 73 patients with an elevated IGF1 level but without available GH values were definitely uncontrolled, we obtained information for ∼50% of all uncontrolled cases in the registry. Thus, despite this limitation, our assessment appears to be representative and sufficient to derive valid conclusions (11, 12).

In the 120 patients with returned information, previous treatment of acromegaly was similar to recently published data for the total Registry cohort (8). As could be expected, the majority had received a combination of various treatment regimens during the course of their

disease. Comorbidities were reported in many patients. Although most common, hypertension and diabetes mellitus were less frequent than those in another observational study of patients with uncontrolled and long-standing acromegaly (13). A difference in the age range of the two cohorts might be one explanation as young patients were also included in the present cohort. Remarkably, however, in almost one-third of the patients, physicians reported no comorbidities, which indicate that not all patients equally suffer from uncontrolled and long-standing acromegaly. This might be one factor influencing therapeutic decisions by both patients and physicians especially in cases of borderline biochemical control.

Since the last documented visit in the central database, about half of the patients had achieved biochemical control according to the information provided by the centres. This suggests that the biochemical control rate within the Registry substantially improved since the last published analysis (8). One reason might be a quality initiative targeted to participating centres and endocrinologists in Germany, which had been launched by the German Acromegaly Registry ∼12 months before the present survey.

However, 59 patients (49%) were still biochemically uncontrolled at the time of the final visit to the centre. Most of these patients were treated with drug monotherapy and 11 patients received no medical treatment. This suggests that escalation of medical therapy by starting, up-titrating or switching medication or by commencing drug combination therapy should principally allow disease control in the majority of patients according to current guidelines (5, 6). For whatever reason
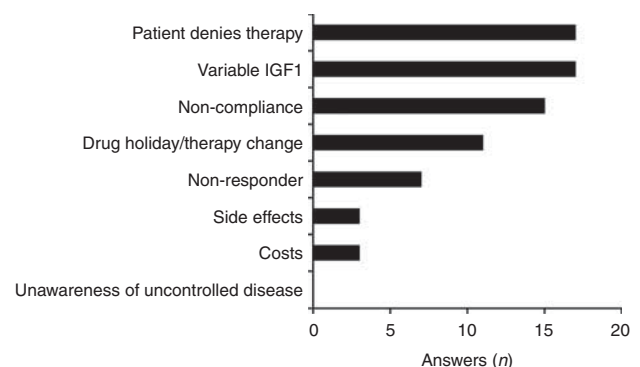

Figure 5

Reasons for uncontrolled acromegaly at the final visit to the centre in 59 patients as reported by treating physicians. Multiple mentions were possible.

medical therapy has not been intensified, the issue is clearly important and should be addressed in physicians' education. Consistently, treating physicians regarded true therapy resistance as a relatively rare reason for failure to achieve disease control. Drug side effects were also a rare cause. Medical treatment with SSAs or the GHRA pegvisomant is expensive, but economic considerations were only of minor importance for therapeutic decisions. The latter point may reflect the situation in Germany, where all treatment options are covered by health insurance. In other countries, however, restricted availability of expensive drug treatment may be a relevant limitation to achieve disease control.

In many uncontrolled patients, disease activity at this cross-sectional presentation was only moderate according to IGF1. With the well-known challenges of IGF1 and also GH assays (14, 15, 16, 17), it is of no surprise that a considerable number of patients had, at previous visits, an IGF1 or GH level within the target range respectively. Obviously, fluctuating IGF1 or GH values due to inter-assay variations are a major reason as to why a substantial number of patients were cross-sectionally categorised as uncontrolled and yet received no medical therapy or seemingly inadequate low-dose drug monotherapy. Thus, the present data emphasise again the need for reliable assay technology to monitor and guide therapeutic decisions for optimal long-term disease management.

Quite a number of patients had elevated biochemical disease markers because medical therapy had been intentionally paused to evaluate the effect of radiotherapy or surgery, or because drug therapy has been recently switched and patients were in the phase of dose titration. Similar to patients with fluctuating IGF1 and/or GH values, these patients may not suffer from long-term uncontrolled acromegaly as suggested by the cross-sectional approach.

The most common reasons for apparently long-standing active disease were the patient's denial to intensify or escalate the therapeutic strategy and non-compliance with medical therapy. Reluctance about the need for therapy and non-compliance are not unique to acromegalic patients but can be observed in many chronic endocrine and non-endocrine diseases (18, 19, 20). A low burden of disease due to the absence of symptoms and comorbidities and/or patients' lack of knowledge about the disease and its course may underlie the reported lack of motivation to agree to therapeutic recommendations or to comply with medical therapy.

Taking together, in this registry-based survey, frequently reported reasons for uncontrolled disease at cross-sectional presentation were patients' lack of motivation to agree to therapeutic recommendations (23.3%) or to comply with medical therapy (20.6%), methodological challenges with fluctuating IGF1 and/or GH (23.3%) and changes or modifications in therapy (15.1%). Therapy resistance (9.6%), drug side effects (4.1%) and economic considerations (4.1%) were rare causes. It can be assumed that apparently active disease due to methodological challenges or adjustments in therapy at cross-sectional presentation may not necessarily reflect long-term uncontrolled acromegaly. Therefore, it appears that patient-based reasons were the predominant cause for true long-standing active acromegaly. Thus, further exploration of the patients' adherence barriers, the development of specific education programmes and involvement of patient support groups could improve the long-term control rate and thus prognosis of patients with acromegaly.

Author contribution statement

C Schöfl, M Grussendorf, J Honegger, A Tönjes, D Thyroke-Gronostay and J Schopohl designed the survey and contributed to the interpretation of the data. Statistical analysis was performed by B Mayr. The manuscript was written by C Schöfl and all authors read, discussed and approved the final manuscript.

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