CLINICAL STUDY

Long-term outcome in patients with acromegaly: analysis of 1344 patients from the German Acromegaly Register

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Abstract

Background: Acromegaly is a rare disease with significant morbidity and increased mortality. Epidemiological data about therapeutic outcome under ‘real life’ conditions are scarce.

Objective: To describe biochemical long-term outcome of acromegaly patients in Germany.

Design and methods: Retrospective data analysis from 1344 patients followed in 42 centers of the German Acromegaly Register. Patients’ data were collected 8.6 (range 0–52.6) years after diagnosis. Controlled disease was defined by an IGF1 within the center-specific reference range.

Results: Nine hundred and seventeen patients showed a normalized IGF1 (157 (range 25–443) ng/ml). In patients with a diagnosis dated back >2 years (n=1013), IGF1 was normalized in 76.9%. Of the patients, 19.5% had an elevated IGF1 and a random GH R 1 ng/ml, 89% of the patients had at least one surgical intervention, 22% underwent radiotherapy, and 43% received medical treatment. After surgery 38.8% of the patients were controlled without any further therapy. The control rates were higher in surgical centers with a higher caseload (P=0.034). Of the patients with adjunctive radiotherapy 34.8% had a normal IGF1 8.86 (0–44.9) years post irradiation, 65.2% of the medically treated patients were controlled, and 47.2% of the patients with an elevated IGF1 received no medical therapy.

Conclusion: The majority of acromegaly patients were controlled according to their IGF1 status. Long-term outcome could be improved by exploiting medical treatment options especially in patients who are not controlled by surgery and/or radiotherapy.

Introduction

Acromegaly is caused by excessive GH secretion from benign pituitary tumors in the vast majority of cases (1). GH excess and excessive production of insulin-like growth factor 1 (IGF1) is associated with increased morbidity, impaired quality of life, and reduced life expectancy (1). However, when GH-excess is controlled and/or IGF1 levels are normalized, the clinical symptoms and comorbidities improve (1, 2) and mortality risk can be markedly reduced toward that of the normal population (3, 4). The aim of therapy is normalization of GH and IGF1 levels (1, 2).

According to current consensus guidelines, transsphenoidal surgery is the treatment of choice as it is at the present time the only option to cure the disease (5). Normalization of IGF1 can be expected in 75–95% of patients with a microadenoma, if the operation is performed by an experienced neurosurgeon (5, 6, 7, 8, 9). Control rates, however, are substantially lower in patients with macroadenomas (40–69%) even in experienced centers (7). If surgery is contraindicated or if disease activity persists postoperatively, medical treatment is the most common second line approach (5). Somatostatin analogs (SSAs), dopamine agonists (DAs), and a GH receptor antagonist (GHRA) are currently available for pharmacological treatment. They are either used in monotherapy or in various combinations. Radiotherapy is another therapeutic option that should generally be considered as third line therapy (5). Normalization of IGF1 has been reported in up to 60% of cases 10–15 years after conformal fractionated radiotherapy (10, 11, 12). For single-dose radiosurgery, 5-year remission rates range from 29–60% according to the literature (13, 14, 15). Concerns about long-term safety, however, are the main limitation to a more widespread use in acromegaly (5). Taken together, disease control should be achievable by currently available treatment options in the vast majority of acromegalic patients. Information about
control or cure rates, however, comes from expert centers or randomized clinical trials that may not reflect treatment reality under ‘real-life’ conditions in day-to-day care.

As acromegaly is a rare disease, epidemiological data with regard to treatment strategies and long-term outcome are scarce. Several national data registries collecting data of patients with acromegaly have been initiated to observe ‘real-life’ long-term outcome (12, 16, 17, 18, 19, 20, 21, 22, 23, 24). Patients' outcome is not only affected by the efficacy of individual treatment options but also by the organization and funding of national health care systems. The system in Germany is pluralistic and the care of acromegalic patients is distributed over many academic and non-academic hospital settings as well as private practices. The aim of the current analysis of the German Acromegaly Register was to describe the biochemical outcome of acromegaly under the ‘real-life’ conditions of the national health care system. These data are a prerequisite for further improvements in the treatment and cost-effective management of acromegaly and are the basis to establish the most effective treatment plans.

Subjects and methods

The German Acromegaly Register is a nationwide register established in 2003 by the Pituitary Disease Study Group on behalf of the German Endocrine Society. The register performs an epidemiological, retrospective study on the diagnosis, treatment, and follow-up of patients with acromegaly in Germany. Details about the structure, database, and data collection have been published previously (19, 25, 26). Written informed consent has been obtained from the patients included in the present survey. The protocol of the register has been approved by the Ethics Committee of the Charité-Universitätsmedizin Berlin, Germany, and by the Berlin commissioner for data protection and freedom of information.

Patient selection and outcome definition

Patients, who had at least one recorded visit and data entry into the database within the last 3 years, were selected from the database of 3081 patients enrolled in the German Acromegaly Register at the time of the analysis in 2010/11. Disease control was assumed, if the locally measured IGF1 levels were below the upper limit of normal of the center-specific, age-, and gender-adjusted reference range. Patients with an IGF1 below the reference range, e.g. caused by treatment associated GH-deficiency, were also regarded as controlled. Active disease was defined as an IGF1 value above the center-specific reference range. In Germany, regular nationwide interlaboratory comparison testings are mandatory for clinical laboratories to participate in patients’ care, which assures a high-quality standard. IGF1 is a sensitive measure of integrated GH production and closely correlates with clinical, metabolic, and endocrine markers of disease activity. Normalization of IGF1 is associated with reduced morbidity and normal life expectancy (3, 4, 27). Furthermore, in patients who are treated with the GHRA pegvisomant, normalization of IGF1 is the only marker of disease control (27, 28). The most recent criteria for disease control in acromegaly, in addition to normalization of IGF1, also require a random GH < 1 ng/dl using an ultrasensitive GH assay (28). Random GH values as either single determinations or as the first value of a profile or an oral glucose tolerance test are also documented in the register although in fewer patients. Since commercial GH-assays show a high interassay variability, the use of a given threshold for all centers to define disease control could therefore be misleading (29, 30). As many centers guide their long-term treatment decisions especially in medically treated patients on IGF1 levels and in order to uniform the outcome definition for all treatment modalities, we used IGF1 normalization as the outcome parameter to define disease control in this nationwide retrospective analysis.

Statistical analysis

Statistical analyses were performed using SigmaPlot version 11, Systat Software (Erkrath, Germany). Results are given as mean ± S.D. (normally distributed data) or median plus range (non-normally distributed data). The Shapiro–Wilk test was used to test for normal distribution. Comparisons between datasets were done by the Mann–Whitney U test or the Kruskal–Wallis test. Significance was considered at P < 0.05.

Results

Patients

The study cohort included 1344 patients, of which 775 were females (57.6%) and 569 males (42.3%), with a median age of 47 (range 15–86) and of 41 (range 9–78) years respectively at diagnosis (P < 0.001). For 64 patients, the age at initial diagnosis was not available (42 women, 22 men). A pituitary macroadenoma was documented in 683 patients, 139 patients had a microadenoma, and in 22 patients no tumor could be delineated on imaging studies. In 500 patients no information about tumor size was available. All patients had a documented follow-up visit within the last 3 years and were treated in 42 centers participating in the German Acromegaly Register (19 university hospitals, 11 community hospitals, and 12 endocrine practices). Median age at the time of the survey was 58 (range 19–89) for female and 53 (range 9–85) years for male patients (P < 0.001). Patients’ data were collected 8.6
(range 0–52.6) years after the initial diagnosis. In 1068 patients, the diagnosis of acromegaly was made more than 2 years before the survey, whereas 211 patients were diagnosed within 2 years of data acquisition including 19 newly diagnosed cases.

Therapy
During the course of their disease, 1200 patients (89.3%) had at least one surgical intervention and 298 patients (22.2%) had received radiotherapy, mostly as an adjunctive therapy after surgery \((n=276)\). At the last follow-up, 573 patients (42.6%) were treated medically: 407 patients (30.3%) received SSAs, 140 patients (10.4%) DAs, and 122 patients (9.1%) were under a medication with the GHRA pegvisomant. Ninety patients were treated with various drug combinations. The different drug therapies used in medically treated patients are depicted in Fig. 1. In the 1068 patients with long-standing disease (diagnosis more than 2 years), 971 patients (90.9%) had at least one operation: 84 (7.9%) patients had no surgery and were treated medically and/or had received radiotherapy \((n=20)\). In 13 patients (1.2%) no therapy was documented. In the 211 patients with a more recent diagnosis of acromegaly \(( \leq 2 \text{ years})\), 173 already had an operation. Amongst the 38 patients without surgery, there were 19 newly diagnosed cases and 21 patients received medical therapy. None of these 38 patients had radiotherapy.

Biochemical outcome
At the last follow-up visit, IGF1 levels were available in 1275 of the 1344 patients. In 917 patients IGF1 was reported to be normalized with a median of 157 (range 25–443) \(\text{ng/ml}\), while in 358 patients IGF1 was elevated (median 349 (range 156–1195) \(\text{ng/ml}\), \(P<0.001\)). In the 1013 patients in whom diagnosis of acromegaly was made \(\geq 2\) years before the survey, 76.9\% \((n=779)\) were reported to have a normal IGF1. By contrast, in the 199 patients who were diagnosed \(\leq 2\) years before the survey, only 47.2\% of the patients had a normal IGF1.

Surgery and biochemical outcome
Transsphenoidal surgery was the standard operation in the vast majority of cases \((n=925)\). 50 patients were operated via the transcranial route, and in 225 patients the type of surgery was not documented. IGF1 was available for 1138 of the 1200 patients that had at least one operation. The time of the last follow-up visit was 9.07 (range 0–51.5) years post surgery. At the last follow-up visit, and 442 patients (38.8\%) had a normal IGF1 just by surgical interventions without adjunctive radiotherapy or medical treatment. The neurosurgical site of the first operation was documented in 947 patients and comprised 76 different neurosurgical units in Germany. In 252 patients, this information was lacking. In neurosurgical units with \(\leq 10\) documented surgical cases of the survey cohort, IGF1 was normalized in 28.9\% of the patients. In neurosurgical centers, however, with 11–29 or \(\geq 30\) cases, IGF1 normalization was significantly higher \((P=0.034)\) although the scatter was considerable (Table 1, Fig. 2). In the patient group with unknown surgical site, IGF1 normalization was reached in 28.6\% of the patients.

Radiotherapy and biochemical outcome
Post surgery 276 patients received adjuvant radiotherapy. In 267 patients, an IGF1 was documented at the time of the survey, which was on average 8.9 (range 0–44.9) years post irradiation. Ninety-three patients (34.8\%) had a normal IGF1 without further medical treatment. In patients who were treated by radiotherapy more than 10 years before the survey \((n=55, 16.5\%)\)
Three hundred and fifty-eight patients had an elevated IGF1 at their last follow-up. The distribution of IGF1 values in these patients stratified by disease duration is shown in Fig. 3. Most patients with long-standing disease had borderline or moderately elevated IGF1 (median 320 (range 156–971) ng/ml, n = 235), while patients with a more recent or new diagnosis (≤2 years) had higher IGF1 levels (median 464 (range 186–1195) ng/ml, n = 105) as could be expected.

A more detailed analysis revealed that 169 patients (47.2%) received no drug therapy. In these 169 patients, median IGF1 was 387.5 (range 167–1195) ng/ml, whereas IGF1 was 325 (range 156–1111) ng/ml (P < 0.001) in the 189 patients who were treated either with single or combined drug therapy. The proportion of patients that received no drug therapy despite an elevated IGF1 was higher in patients who were diagnosed within ≤2 years (66.7%; IGF1 597 ± 295 ng/ml, n = 90) compared with the patients with a long-standing history (38.5%; IGF1 386 ± 164 ng/ml, n = 70, P < 0.001). The medical treatment regimens used in the patients with an elevated IGF1 are depicted in Fig. 4. The median doses for patients treated by drug monotherapy were for depot octreotide 30 (range 7.5–40) mg every 28 days (n = 78), for depot lanreotide 90 (range 40–120) mg every 28 days (n = 10), for cabergoline 1.88 (range 0.25–4.0) mg/week (n = 22), for bromocriptine 10 (range 7.5–15.0) mg/day (n = 3), and for pegvisomant 20 (range 10–40) mg/day (n = 22). With the exception of octreotide LAR (P < 0.001), the doses used in the uncontrolled patients were not different from those used in patients who were medically controlled. There were no differences in the drug doses between patients with a long-standing (>2 years) or a more recent (≤2 years) diagnosis of acromegaly.
agonist; GHRA, GH receptor antagonist.

Figure 4 Medical treatment regimens in patients with elevated IGF1 subdivided by the disease duration. Black columns, patients with long-standing disease (>2 years; n=234). Of these patients, 190 had at least one operation with or without adjunctive radiotherapy, seven had received radiotherapy without surgery, and 38 were treated medically only. Gray columns, patients diagnosed within ≤2 years of data acquisition (n=105). Of these patients, 73 had at least one operation with or without adjunctive radiotherapy and 32 were treated medically only. SSA, somatostatin analog; DA, dopamine agonist; GHRA, GH receptor antagonist.

In order to further explore the reasons for not treating or for not stepping up medical treatment, we assessed random GH in patients with elevated IGF1. Random GH was available in 300 (83.8%) of the 358 patients and was lower than 1.0 ng/ml (2.5 ng/ml) in 63 (136) patients. As depicted in Table 2, the proportion of patients with a random GH <1 or 2.5 ng/ml as well as the GH-levels was similar in patients with or without medical therapy. Considering only patients as clearly uncontrolled with both an elevated IGF1 and random GH, then this would apply to 19.5% (GH ≥ 1 ng/ml) or 13.5% (GH ≥ 2.5 ng/ml) of the cases.

Discussion

The aim of the present analysis was to describe the biochemical outcome of patients with acromegaly under the conditions of the health care system in Germany. In the present retrospective survey, 1344 patients from the German Acromegaly Register were included. Based on a population of about 80 million and a disease prevalence of about 40–60 cases/million (31, 32), this cohort represents ~30–40% of all acromegalic patients in Germany. The proportion of patients treated either in university or non-university hospitals or in private endocrine practices was similar to previous reports from the German Register (25, 26). We assume that this is a representative picture of endocrine specialist care for patients with acromegaly in Germany. Patients, however, treated only by their general practitioners are disregarded because of the selection criteria for participating centers. According to two recall studies performed at two neurosurgical centers in Germany, this group of patients might be as large as 25% of surgically treated patients (33).

In the current analysis, there was a female predominance which is consistent with previous reports from this (25, 26) and other registers (Table 3). Women with acromegaly were significantly older than men at diagnosis which is again in accordance with the literature (31). About 80% of the patients with a documented tumor size had a macroadenoma at diagnosis further indicating that the cohort analyzed was representative for the disease (Table 3).

The latest criteria for disease control are an IGF1 level in the adjusted normal range and a random GH level <1 ng/ml measured by an ultrasensitive GH assay (28). In this study, disease control was primarily defined by IGF1 as described in the Subjects and methods section. For financial and logistic reasons, a centralized measurement of IGF1 on a nationwide and continuous basis is not feasible in the current setting of the German Acromegaly Register. Local measurement of IGF1 and center-specific evaluation appears appropriate in an epidemiologic study, as this approach controls for some of the well-known variations between IGF1 assays (34, 35) and as decisions to adjust treatment strategies in daily routine are based on locally available IGF1. As normalization of IGF1 is associated with an improvement in clinical symptoms and comorbidities and markedly reduces the mortality risk (2, 3, 4, 27), some centers guide their treatment decisions mainly, if not exclusively, on IGF1 levels. This may explain why random GH was only available for 81% of the patients at the last follow-up (IGF1 95%). Furthermore, the pulsatile nature of GH secretion may persist in controlled acromegaly and thus random GH could lead to misclassifications (27). In about 20–30% of the patients, discordance of GH and IGF1 has been

Table 2 Random GH in patients with elevated IGF1 with or without medical therapy stratified by two different thresholds for random GH (1 and 2.5 ng/ml).

<table>
<thead>
<tr>
<th>GH &lt; 1 ng/ml</th>
<th>GH ≥ 1 ng/ml</th>
<th>GH &lt; 2.5 ng/ml</th>
<th>GH ≥ 2.5 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>With medical therapy (n=143)</td>
<td>31 (21.7%)</td>
<td>112 (78.3%)</td>
<td>68 (47.5%)</td>
</tr>
<tr>
<td>Median GH (range)</td>
<td>0.65 (0.20–0.98)</td>
<td>3.75 (1.0–108)</td>
<td>1.09 (0.20–2.40)</td>
</tr>
<tr>
<td>Without medical therapy (n=157)</td>
<td>32 (20.4%)</td>
<td>125 (79.6%)</td>
<td>68 (43.3%)</td>
</tr>
<tr>
<td>Median GH (range)</td>
<td>0.52 (0.06–0.98)</td>
<td>3.90 (1.0–145)</td>
<td>1.0 (0.00–2.31)</td>
</tr>
</tbody>
</table>
described after treatment (36, 37, 38). In most cases, GH is normal and IGF1 is elevated, but in some cases it is just the opposite (36, 39). So far there is no clear evidence that the mortality risk is increased in patients with discordant GH and IGF1 levels and there is no consensus as to whether these patients require treatment (28). Therefore, we may rather underestimate than overestimate the proportion of patients with a ‘safe’ GH status by just using IGF1 as the criterion for disease activity.

Of the patients with available IGF1, 72% were controlled. This percentage increased to 77% in the patients with long-standing disease (>2 years), while patients with a more recent diagnosis (≤2 years) were controlled in only 47% of cases as expected. This is similar to a very recent analysis from Spain (24) and to data from Finland, where diagnostic procedures and treatment are centralized in five university hospitals (18). By contrast, comparable cure rates from the Belgian registry were considerably lower, even if only the cases with normal IGF1 were considered (20). In the Belgian survey, however, classification was done by centralized measurement of IGF1, which allows a more standardized evaluation of disease control over different centers (20).

**Surgery**

Surgery is currently the only option to cure the disease, and if this goal can be attained, surgery is by far the most cost-effective treatment. According to current as well as previous guidelines, transsphenoidal surgery is the treatment of first choice (5, 40). Approximately 90% of our cohort underwent surgery at least once, mostly by the transsphenoidal route. This percentage is in the range of that reported from the Spanish registry (81%) (16), but higher than those reported from the Belgian cohort (68%) (20) or the UK National Acromegaly Register (68.7%) (41). At the time of the survey, 38.8% of the operated patients had a normal IGF1 without further treatment. This is less than the postoperative IGF1 normalization rate of 67.2% reported previously from the same register (19). While the latter analysis was performed after a median of 9.8 months post surgery, IGF1 in the present study was evaluated after 9 years, which also comprises patients with disease recurrence and thus better reflects the long-term surgical success rates. Furthermore, the number of patients in this study was more than twice as high as in the previous analysis. This ‘long-term’ surgical control rate is similar to the one published from AcroBel (20), but less than the 70% reported from Spain (16). In any case, surgical success rates were lower than those published from experienced neurosurgical centers which range between 42 and 82% (7). However, criteria for disease control and observation periods differ, which hampers comparisons between studies (Table 3).
In 939 patients, the neurosurgical unit of the first operation was documented. In these patients, operations were performed in 76 different surgical centers. The number of patients from the present cohort treated by these centers ranged from 1 to 110. Experience is a well accepted and important determinant of surgical success and the number of operations might be used as a surrogate parameter (9, 41, 42). Although the documented cases in the register do not necessarily reflect the total number of pituitary operations performed by each center, there was a significant trend of higher cure rates in centers with more cases. Nevertheless, the scatter of surgical success rates was considerable even in the large centers with a median control rate of ~50%. To further improve the postsurgical outcome on a nationwide perspective, it appears therefore reasonable to concentrate surgery of acromegaly patients in the hands of a smaller number of specialized centers. Such a strategy substantially improved the surgical results in the UK (41).

**Radiation**

Radiation therapy, although effective in controlling tumor growth and lowering GH-excess, has been recently viewed as a third-line treatment because of still unsolved long-term safety issues (5). In the present cohort, irradiation had been applied in 22% of cases almost exclusively as an adjunctive therapy after surgery. This is less than the numbers in the Belgian register and about half of those published from Spain or the UK (Table 3). A very recent publication from the Spanish Acromegaly Registry, however, documented a decline of the use of radiotherapy to 11.9% in patients diagnosed after 2000 (24). Overall, about 35% of the patients with adjunct radiotherapy had a normal IGF1 after a median follow-up period of 8.9 years. This response rate is somewhat less than those reported from other large cohorts with similar observation periods (12) but similar to the one from the Belgian registry (10, 20). Maximum response occurs 10–15 years after irradiation. In patients who had their radiotherapy more than 10 years before the survey, normalization of IGF1 was almost 90%, which is in line with data from the UK National Acromegaly Register (12).

**Medical treatment**

Almost 43% of the patients received medical treatment at the time of the survey. As reported from other registers, SSA were the most frequently used drugs (16, 20). Most patients were on drug monotherapy, which could achieve disease control in the majority of patients treated with the respective compounds ranging from 53 to 75%. Although there was an overall trend for higher drug doses in patients with uncontrolled disease, this was only statistically significant in patients treated with octreotide LAR. Thus, there is room for up-titrating medical therapy in the majority of patients with uncontrolled disease under ongoing medical treatment. A similar phenomenon has been reported from the observational registry of the GHRA pegvisomant (43). In order to further enhance the success rates of medical therapies, it is therefore important to understand the reasons for the failure of dose titration. One reason might be discordant biochemical information about disease activity as in 20% of patients with an elevated IGF1, random GH was below 1 ng/ml and in 43% it was below 2.5 ng/ml.

**Uncontrolled patients**

About 23% of the patients with long-standing disease had an elevated IGF1. Patients with a more recent diagnosis had an elevated IGF1 in more than 50% of the cases, which, however, also included patients with newly diagnosed acromegaly. Accordingly, the distribution of elevated IGF1 levels was shifted more toward the normal range in patients with long-standing disease. Despite elevated IGF1 levels, however, the majority did not receive any further treatment. The most recent guidelines for the management of acromegaly suggest making therapeutic decisions according to an individualized biochemical and clinical assessment (5). Additional therapy should be considered if IGF1 and GH are elevated, and clinical judgment should be used if IGF1 and GH measurements are discrepant (5). About 80% of the patients with an elevated IGF1 had a random GH ≥1 ng/ml, and 55% had a random GH ≥2.5 ng/ml. Thus, 19.5% (GH ≥1 ng/ml) or 13.5% (GH ≥2.5 ng/ml) of the patients were clearly untreated. The latter threshold for random GH (<2.5 ng/ml) has been used in a recent overview about the clinical, quality of life, and economic value of acromegaly disease control (2). Although there are many unanswered questions about the benefits regarding individual morbidities, health-related quality of life, and cost of controlled vs uncontrolled disease (2, 44, 45), there is no doubt about the overall advantage of disease control for long-term morbidity and mortality. Understanding the reasons for not treating or not up-titrating an ongoing medical therapy in clearly uncontrolled patients should be investigated in a future project in order to further improve the long-term outcome in acromegaly patients.

**Conclusions**

A retrospective database like the German Acromegaly Register clearly has limitations but reflects the real life outcome under routine conditions. The results provide important information about the management and outcome of acromegalic patients under the conditions of the health care system in Germany. Germany as the most populous country in Europe has a non-centralized...
healthcare system. The care of acromegalic patients is distributed over many academic and non-academic hospital settings, as well as private practices. We assume that the results of the present survey provide a representative picture of endocrine specialist care for patients with acromegaly in Germany. Overall, surgical success rates were moderate and could be enhanced by concentrating surgery of acromegalic patients in the hands of a smaller number of specialized centers. After applying the most recent criteria for disease control, 20% of the patients were still uncontrolled. Commencing or up-titrating ongoing drug therapy and fully exploiting medical treatment options, especially in patients not controlled by surgery, could further improve the long-term outcome of acromegalic patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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