Original article

The Liege Acromegaly Survey (LAS): A new software tool for the study of acromegaly

Le Liège Acromegaly Survey (LAS) : un nouveau logiciel pour l’étude des données des patients acromégales

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Abstract

Acromegaly is a chronic rare disease associated with negative pathological effects on multiple systems and organs. We designed a new informatics tool to study data from patients with acromegaly, the Liege Acromegaly Survey (LAS). This relational database permits the inclusion of anonymous historical and prospective data on patients and includes pathophysiology, clinical features, responses to therapy and long term outcomes of acromegaly. We deployed the LAS in a validation study at a single center in order to study the characteristics of patients with acromegaly diagnosed at our center from 1970–2011. A total of 290 patients with acromegaly were included (147 males and 143 females). There was a linear relationship between age at diagnosis and the date of diagnosis, indicating that older patients are being diagnosed with acromegaly more frequently. A majority of patients with a macroadenoma were significantly younger than patients with microadenomas (77.5%) and the median diameter was 14 mm. Patients with macroadenomas were significantly younger than patients with microadenomas (P = 0.01). GH values at diagnosis decreased with the age of the patients (P = 0.01) and there was a correlation between GH values and tumor size at diagnosis (P = 0.02). No correlation existed between insulin-like growth factor 1 (IGF-1) levels and tumor characteristics. The prevalence of diabetes was 21.4% in this population and 41.0% had hypertension. The presence of hypertension and diabetes were significantly associated with one another (P < 0.001). There was a linear relation between initial GH and IGF-1 levels at diagnosis and those obtained during SSA analog treatment and the lowest GH and IGF-1 values following SSA therapy were obtained in older patients (GH: P < 0.001; IGF-1: P < 0.001). The LAS is a new relational database that is feasible to use in the clinical research setting and permits ready pooling of anonymous patient data from multiple study sites to undertake robust statistical analyses of clinical and therapeutic characteristics.

Résumé

L’acromégalie est une maladie chronique rare associée à une morbidité touchant de multiples systèmes et organes. Nous avons conçu un nouvel outil informatique pour étudier les données des patients acromégales : le Liège Acromegaly Survey (LAS). Cette base de données relationnelle permet l’inclusion de données historiques et prospectives des patients et inclut la clinique, la physiopathologie, les réponses aux thérapies et les résultats à long terme. Nous avons déployé le LAS au cours d’une étude de faisabilité dans un centre unique afin d’étudier les caractéristiques des patients acromégales diagnostiqués à Liège de 1970 à 2011. Au total, 290 patients atteints d’acromégalie ont été inclus (147 M, 143 F). Il existait une relation linéaire entre l’âge au diagnostic et la date du diagnostic, montrant que l’acromégalie est de nos jours diagnostiquée plus souvent chez des personnes âgées. Dans la majorité des cas, la tumeur était un macroadénome (77,5 %) et le diamètre médian était de 14 mm. Les patients avec un macroadénome étaient significativement plus jeunes que les patients avec un microadenome (p = 0.01). Les concentrations d’hormone de croissance au diagnostic diminuaient avec l’âge des patients (p = 0.01) et étaient corrélées avec la taille de la tumeur (p = 0.02). Nous n’avons pas trouvé de corrélation entre les concentrations d’IGF-1 et la taille de la tumeur. La prévalence du diabète était de 21,4 % dans cette population et 41 % présentaient une hypertension artérielle. Diabète et hypertension semblaient corréler significativement (p < 0.001). Il existait une relation linéaire significative entre les valeurs initiales d’hormone de croissance et d’IGF-1 et les valeurs obtenues sous analogues de somatostatine.

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1. Introduction

The modern methods for the management of acromegaly have evolved over the past 30 years. Multiple therapeutic modalities have been developed and their efficacy and safety profiles are well documented [1]. Neurosurgical techniques have been refined from the first trans-sphenoidal operations to the new endoscopic techniques, while medical therapies now involve a range of options from somatostatin analogs (SSA) to growth hormone (GH) receptor antagonists [2,3]. Radiotherapy has itself also undergone significant development from early forms to techniques like the gamma-knife used today [2,3].

Studies on acromegaly have generally focused on individual aspects of the disease and despite continued interest in its pathology, relatively few comprehensive studies of multiple aspects of patients’ presentation and evolution have been published. One of the reasons for this is that acromegaly is a chronic disease that affects multiple organs and patients are often treated using multimodal therapy, which means that in order to capture an informative and comprehensive overview of long-term clinical evolution, detailed studies of acromegaly require the collection and analysis of large numbers of data-points. Moreover, as acromegaly is a relatively rare disease [4], long-term studies must be undertaken to recruit sufficient patient numbers to allow meaningful analyses. Most comprehensive studies of acromegaly populations to date have used registry-based approaches [5,6] and are often multicenter in nature [7–17]. Most of these studies were case-file oriented registers and reported relatively few individual data points per patient meaning that in some instances the conclusions have been drawn based on small subsets of the total theoretical number of patients included. The current literature shows a relative paucity of comprehensive data-collection approaches that use an underlying informatics structure that permits robust relational query-based analyses. To address this issue and to investigate the long-term evolution of a large number of patients in a comprehensive way, we designed, developed and deployed a new relational database, the Liege Acromegaly Survey (LAS) database, for the analysis of data collected from the population of patients with acromegaly that have been followed in our center over the last 30 years.

2. Methods

2.1. Study design

The study population comprised all patients with acromegaly that had been treated at the Centre Hospitalier Universitaire de Liège between 1970 and 2011. The LAS database was built in order to achieve two goals: to provide a comprehensive description of the clinical, pathological, diagnostic and therapeutic characteristics of this group of patients with acromegaly and to explore the relationships among disease characteristics and outcomes in this patient group over time. To achieve this goal, a preparatory phase was undertaken in which a full listing of variables to be included under headings of demographics, clinical characteristics, radiological measurements, pathological features, treatments and outcomes was developed from a review of patients charts. In parallel, a comprehensive list of potential questions to be addressed by the database was drafted by the investigators. This is a necessary step in the development of a relational database in order to assess fitness for purpose and to ensure that all potential relations among multiple data items could be assessed validly for undertaking statistical analysis. All items identified underwent scrutiny to determine which data variables will be included in the final program. The presence or absence of these data variables was then assessed in standard records and the final set of headings was defined (Supplementary data, Table 1). Thereafter, the database was constructed to allow organization of the included variables and to have an internal program structure that permitted optimal multiparametric data extraction. For example, these design decisions included how to organize the internal storage of GH values in mU/L within the database. Due to an inclusion period spanning more than three decades, different assays were used in our center. Due to differences in early GH calibrations, hormone levels expressed as ng/ml are not comparable across time. As GH values in mU/L are more consistent across time, the LAS database design automatically converts GH levels measured in ng/ml based on the assay used at each time-point and stores them in mU/L. Measures in mU/L were stored without conversion.

Evaluation at last follow-up was done on the last available data which could span different phases of patients’ follow-up: post-surgical evaluation for patients who were followed after surgery by an endocrinologist elsewhere, last data of patients under primary or presurgical medical treatment, last routine examination in patients routinely visiting the department, or last data available for deceased or lost to follow-up patients. We also limited this analysis to patients for whom insulin-like growth factor 1 (IGF-1) levels were available (some of the oldest patients had only GH measurements).

Data were recorded using a database server (MySQL community server, Uppsala, Sweden). A bespoke data acquisition interface (Medmine.com, Liege, Belgium) was designed to facilitate data entry and to maintain a complete separation of data and human interfaces.

Data on Belgian population were obtained from the Belgian government census estimations (SPF Économie. Direction générale Statistique et Information économique, http://economie.fgov.be/fr/spf/structure/Directions_generales/dgsie/) for 2010.

The project was approved by the Ethics Committee of the CHU de Liège.
2.2. Statistical analysis

Data were plotted and assessed for normal distribution. Since none of the variables showed a normal distribution, population spread was described using median and quartile ranges (25th and 75th percentiles) and graphs of population density. Density graphs were drawn by calculating the kernel density with Gaussian smoothing and individual points were then represented on the abscissa. Univariate data were also represented as boxplots, with the limits of the box showing the 25th and 75th percentiles, the central line representing the median and the whiskers 1.5 times the interquartile range of the data. For count variables, statistical comparisons used the Chi² test and for continuous variables, the Mann-Whitney test was used. Data were analyzed using the R software package [18] and graphics were generated using the Lattice package [19].

For comparisons with the general population in terms of demographic data (age, sex distribution, mortality) we used information on the characteristics of the population of Belgium from the government statistics office.

3. Results

3.1. Demographics

A total of 290 patients with acromegaly were included in the LAS (147 males and 143 females). The sex ratio did not differ from that of the general population in Belgium (Table 1, \( P = 0.61 \)). As seen in Fig. 1A, the age at diagnosis showed a bimodal, non-normal distribution. There was a linear relationship between age at diagnosis and the date of diagnosis, suggesting that as time progressed, older patients are being diagnosed with acromegaly more frequently (Fig. 1C and D). The median
duration of acromegaly symptoms before diagnosis was 6 years, but as seen in the duration before diagnosis plot (Fig. 1B), some irregularities can be seen due to approximation and rounding of duration as reported by patients from their memory when the onset of disease was more than 10 years before diagnosis.

3.2. Radiological characteristics

Radiological findings at diagnosis showed a majority presented with macroadenomas (77.5%) and the median diameter was 14 mm (Fig. 2A). Patients with macroadenomas were significantly younger than patients with microadenomas ($P < 0.01$) and there was a negative correlation between tumor size and age at diagnosis ($P < 0.001$, Fig. 2B).

3.3. Hormonal profiles

The description of GH levels is based on the lowest random pretreatment GH value at the time of diagnosis. A density plot demonstrated a non-normal distribution, as shown in Fig. 3A. The log(GH) plot had a closer correspondence with the theoretical normal distribution for central values, although there was a shift in the more extreme upper and lower range values (Fig. 3B). There was no sex difference in GH distribution at baseline and the characteristics of GH were virtually identical in both sexes (Fig. 3A). In the study population, GH values at diagnosis decreased with the age of the patients, older patients had lower GH ($P < 0.001$, Fig. 3C).

Linear regression analysis showed a significant correlation between GH values and tumor size at diagnosis ($P < 0.01$). In particular, the relationship between GH and tumor size at diagnosis became more apparent ($P < 0.001$) when tumors were divided into micro- and macroadenomas (Fig. 3D). GH secretion was also higher in radiologically invasive tumors, although this was not statistically significant ($P = 0.073$).

IGF-1 levels were expressed as a percentage of the upper limit of the normal range (ULN) for age and sex. As with GH there was a non-normal distribution of IGF-1 at diagnosis, but unlike the case for GH, the use of log(IGF-1) data did not improve the fit (Fig. 4A and B). There was no sex difference in IGF-1 values when expressed either as percentages of the upper limit of normal ($P = 0.57$, Table 2) or as absolute values (ng/ml) ($P = 0.53$, Table 3). When IGF-1 levels were expressed as absolute value (ng/ml), a linear decrease in values with age at diagnosis was observed. This trend was more apparent when patients were divided in four groups based on the age of diagnosis (Fig. 4C). When IGF-1 levels were expressed as percentage of upper values for age and sex, this relation disappeared (Fig. 4D). There was no general correlation between IGF-1 levels and tumor characteristics using linear regression irrespective of whether IGF-1 was expressed as percentage of

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**Table 1**

Sex ratio of Liege Acromegaly Survey (LAS) patients compared to the Belgian population (Estimation for 1/1/2010).

<table>
<thead>
<tr>
<th></th>
<th>LAS</th>
<th>Belgium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>147</td>
<td>3,122,221</td>
</tr>
<tr>
<td>Females</td>
<td>143</td>
<td>527,684</td>
</tr>
<tr>
<td>Total</td>
<td>290</td>
<td>10,839,905</td>
</tr>
<tr>
<td>M/F</td>
<td>1</td>
<td>0.96</td>
</tr>
</tbody>
</table>

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**Table 2**

IGF-1 (% of UNL) at diagnosis based on sex.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>201.5</td>
<td>195.3</td>
<td>209.6</td>
</tr>
<tr>
<td>Min</td>
<td>37.5</td>
<td>37.5</td>
<td>39.1</td>
</tr>
<tr>
<td>25%</td>
<td>139.8</td>
<td>137.3</td>
<td>145.6</td>
</tr>
<tr>
<td>Median</td>
<td>205.8</td>
<td>199.6</td>
<td>215.9</td>
</tr>
<tr>
<td>75%</td>
<td>257.9</td>
<td>245.7</td>
<td>262.8</td>
</tr>
<tr>
<td>Max</td>
<td>394.7</td>
<td>394.7</td>
<td>368.8</td>
</tr>
<tr>
<td>n</td>
<td>120.0</td>
<td>66.0</td>
<td>54.0</td>
</tr>
</tbody>
</table>

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Fig. 2. Tumor size at diagnosis. A. Largest diameter. B. Tumor size and age.
Table 3
IGF-1 (ng/ml) at diagnosis based on sex.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>741.4</td>
<td>723.3</td>
<td>766.1</td>
</tr>
<tr>
<td>Min</td>
<td>102.0</td>
<td>102.0</td>
<td>253.0</td>
</tr>
<tr>
<td>25%</td>
<td>533.5</td>
<td>511.2</td>
<td>584.0</td>
</tr>
<tr>
<td>Median</td>
<td>724.0</td>
<td>723.0</td>
<td>748.0</td>
</tr>
<tr>
<td>75%</td>
<td>953.5</td>
<td>953.5</td>
<td>960.8</td>
</tr>
<tr>
<td>Max</td>
<td>1936.0</td>
<td>1439.0</td>
<td>1936.0</td>
</tr>
<tr>
<td>n</td>
<td>87.0</td>
<td>47.0</td>
<td>40.0</td>
</tr>
</tbody>
</table>

The Upper limit of normal (ULN) or in absolute values. There was a significant correlation \( P = 0.04 \) when IGF-1 levels were grouped based on micro/macroadenoma classification.

### 3.4. Glucose metabolism

At diagnosis of acromegaly 19/173 (11%) of patients with valid data were reported previously as having type II diabetes, while no patient had type I diabetes. When initial oral glucose tolerance test (OGTT) results for GH suppression were analyzed, a further 11 patients had glucose values higher than 200 mg/dL at the 120 minutes timepoint without having been previously diagnosed with diabetes (diabetes was therefore diagnosed at the same time as acromegaly in these patients). Using more stringent criteria of glucose values of more than 180 mg/dL at 120 minutes, a further of seven patients were identified. Including all of these subsets of patients, the prevalence of diabetes was 21.4% in this population. The distribution of HbA1c values in the whole population is presented in Fig. 5. Regression analysis for fasting glucose or glucose levels at 120 minutes versus GH and IGF-1 in non-diabetic patients did not show any correlation for GH but correlated with IGF-1 expressed as absolute value \( P = 0.03 \) and in percentage \( P = 0.02 \). There was no correlation between HbA1c values and GH values. In contrast, HbA1c values correlated significantly with IGF-1 levels among non-diabetic patients \( P = 0.04 \). Patients’ age at diagnosis, duration
of acromegaly before diagnosis, sex, presence of hypertension, IGF-1, random GH and GH values under OGTT were assessed as risk factors for diabetes in this acromegaly population. Of these, only increased age appeared as a significant risk factor ($P=0.01$).

In non-diabetic patients, homeostatic model assessment insulin resistance (HOMA-IR) was calculated using initial OGTT data [20]. Basal GH, 120 min GH, IGF-1 (absolute value), IGF-1 (% upper limit of normal) and IGF-1/GH ratio [21] values did not correlate significantly with HOMA-IR. Multivariate analysis using GH and IGF-1 as principal components were also performed but did not show any significant correlation with HOMA-IR values. Among diabetic patients, a correlation was shown between HOMA-IR and GH ($P<0.001$) only. It should be noted that the HOMA-IR calculation was only performed in a minority of the diabetic patient subset as baseline insulin values were missing in many of that subgroup.

3.5. Hypertension

At diagnosis, 29.7% of patients had current hypertension based on measured blood pressure, but a total of 41.0% of patients had a previous diagnosis of hypertension at some time in the past. Patient age was a significant risk factor for hypertension ($P<0.001$). The presence of hypertension and diabetes were significantly associated with one another ($P<0.001$).

3.6. Treatment

Treatment in patients with acromegaly at the study center has relied almost exclusively on surgery and SSA over the last 20 years. Radiotherapy was used in a minority of cases, which peaked in the 1980s (24 cases) and fell rapidly with the introduction of long acting depot SSAs, such that since 1990 only 15 patients have received radiotherapy and only two since 2000.
Recent years have seen the availability of pegvisomant, but this is used in a small number of patients at this time \((n = 6)\). Data on radiotherapy and pegvisomant are very sparse, therefore, and statistical analysis of the dataset for outcome purposes is sub-optimal.

### 3.7. Medical treatment with somatostatin analogs (SSA)

Since the mid-1980s patients with acromegaly have, whenever possible, been pretreated with SSA for at least three months before surgery [22]. In the cohort, 156 patients were pretreated with SSA and in 85 patients valid pre- and post-treatment GH and IGF-I values were available (Fig. 6). GH and IGF-I were controlled in 59.3% and 58.8% of cases, respectively. There was a linear relation between initial GH and IGF-1 levels at diagnosis and those obtained during SSA analog treatment (GH: \(P < 0.001\); IGF-1: \(P < 0.001\); Fig. 7). In terms of patient age, the lowest GH and IGF-1 values following SSA therapy were obtained in the older patients (GH: \(P < 0.01\); IGF-1: \(P < 0.001\)). Interestingly, it was noted that patients that normalized their GH or IGF-1 values under SSA were significantly older than patients that maintained elevated IGF-1 values during SSA treatment (Fig. 8, GH: \(P < 0.01\), IGF-1: \(P < 0.001\)).

MRI examination results were available before and after at least three months of SSA treatment prior to surgery in 55 cases. Tumor shrinkage was described in 27 cases and one case of tumor growth was seen. The median decrease in tumor maximal diameter after SSA therapy was 9.1%. Sex or age at diagnosis did not predict tumor shrinkage with SSA.

### 3.8. Surgical treatment

The trans-sphenoidal approach was the main surgical route used and was performed in 91.6% of cases, while 5.9% of cases had repeated trans-sphenoidal surgery and 1.3% had a transfrontal and also a transfrontal approach. In 1.3% of cases a transfrontal approach alone was used. After surgery 89 patients were not cured and underwent medical treatment (median duration before for starting medical treatment after surgery: 12 months). Of those that had a hormonal assessment at least 3 months after surgery, 113 patients were not treated following surgery, however, some patients were followed up elsewhere (median duration for the last evaluation: 5.1 years).

In a subset of patients, surgery, although not curative, allowed the removal of a significant amount of adenomatous tissue, namely tumor debulking. When patients were thereafter treated with SSA, lower IGF-1 levels were achieved compared to presurgical SSA treatment (\(P = 0.04\), Fig. 9). The median further reduction in IGF-1 compared to best presurgical values was 40.1% after debulking. In this group there was no correlation...
between patients' age and IGF-1 levels achieved under SSA ($P = 0.98$).

3.9. Characteristics at last follow-up

At last visit, the acromegalic population was older than the general Belgian population. A total of 198 patients out of 245 had undergone surgery. Based on IGF-1 values, 177 patients were controlled. The uncontrolled patients include those who were on presurgical treatment and some patients that were lost from follow-up. Limiting the selection to those who had undergone surgery and those whose last visit occurred the last 5 years, the number of uncontrolled patients fell to 16 individuals (percentage of controlled patients: 92%).

Patients that were controlled at last visit were numerically but not significantly older at the time of diagnosis than uncontrolled patients (median age at diagnosis = 48 vs. 44 years, respectively, $P = 0.48$) and had smaller tumor diameter at diagnosis (median = 13 vs. 15 mm, respectively, $P = 0.08$). Initial GH values were significantly lower in the controlled group versus the uncontrolled group (median = 7.5 vs. 11 ng/ml, respectively; $P = 0.02$), although there was no difference between the groups in terms of IGF-1 levels at diagnosis.

3.10. Mortality

Among the study population we confirmed death in 27 patients. The median age of death was 69.85 years as compared to a median age of 74.0 years for Belgian population. Reported causes of death were cancer (10 cases, 37% vs. 27% in Belgium) cardiovascular (four cases, 15% vs. 33% in Belgium), infection
(three cases, 11% vs. 2% in Belgium) and respiratory disease (one case, 4% vs. 11% in Belgium).

4. Discussion

The LAS presents data from patients followed in a single center by the same team of endocrinologists and neurosurgeons. This study spanning more than four decades provides an interesting perspective on acromegaly patients, their responses to treatment over time and the abilities of a relational database to combine data points for statistical analyses.

The study provides a number of results that suggest trends in diagnosis and disease characteristics in acromegaly over time. The acromegalic population appears generally older at last follow-up than the overall Belgian population. An interesting trend appears when looking at the age at diagnosis over the past few decades. It appears that the age at diagnosis is increasing and older patients are more commonly being diagnosed. A possible explanation could be a better awareness and diagnosis of acromegaly in older patients with time, with the related implication that acromegaly was probably under-diagnosed in the past due to relatively lower disease severity in older patients. Under diagnosis may be related to differences in tumor characteristics and hormonal secretion between young and old patients [23], and the older patients in the current study tended to have smaller tumors and lower somatotrope axis hypersecretion than younger patients.

Despite advances in diagnostics and efforts to increase disease awareness, disease duration before diagnosis remains difficult to assess accurately. In our center the clinical practice is to approximate the onset of disease as closely as possible using the patient anamnesis in combination with photographs and family recollections. Different centers report duration for diagnosis from 3.2 to 10 years [24–26]. In our database, the duration of the disease before diagnosis is not clear-cut. Initially there is a regular curve with a median value of 6 years. This is probably explained by a number of practical factors, including more rapid changes being more clinically noticeable in terms of date of onset, easier recall or recent events, or the success of efforts to improve the diagnosis of acromegaly via local educational efforts with general practitioners. An interesting pattern emerges when the disease duration before diagnosis was more than 10 years. As seen in Fig. 1, the density plot shows a crest every 5 years, which is likely to be due to an artifact caused by subjective rounding by the clinician, patient or family or the use of official photographs from identity cards that are updated approximately every five years.

At diagnosis, 77% of tumors were macroadenomas with a median maximum diameter of 14 mm. Comparing patients with microadenomas versus macroadenomas, those with bigger tumors at diagnosis appeared younger ($P<0.01$). GH levels at diagnosis, prior to treatment, show a statistical distribution that is clearly non-normal. This non-normal distribution strongly suggests that studies where GH levels are compared should use non-parametric tests for statistical analyses (e.g. Mann-Whitney, medians and quartiles). GH levels showed the same relation with patient age as tumor size: younger patients had higher GH levels. While there was some indication of a relation between tumor size and GH levels, this was not clear-cut as some patients had small adenomas with high GH levels, others presented with larger tumors with low GH secretion.

Therefore, looking at age at diagnosis, tumor size and GH levels, there appeared to be a tripartite relationship among these variables. Younger patients had bigger tumors with higher GH secretion where older acromegals had low GH and small tumors. It is not clear which one of these parameters is the causative factor and whether younger patients have more aggressive tumors. Alternatively young patients may “need” higher GH levels to develop clinical acromegaly which may explains why they have big tumors and high GH when they are diagnosed. Older patients may develop small non-aggressive adenomas that gradually lead to the development of acromegaly and are diagnosed very late. Also older patients may develop acromegaly with just a slightly elevated GH.

This finding has echoes in separate work we have performed on genetic causes of pituitary tumors, specifically familial isolated pituitary adenomas (FIPA) and the aryl hydrocarbon receptor interacting protein (AIP) gene [27–29]. Patients with FIPA and acromegaly have an early age at onset as compared with sporadic acromegaly patients. In particular those acromegaly patients with germline mutations in the AIP gene have an age at onset that is about 20 years before that of patients without AIP mutations. Furthermore, patients with AIP mutation related acromegaly characteristically have a high proportion of macroadenomas at diagnosis that secrete high levels of GH. Although in the current study we did not undertake clinical genetic study for AIP mutations, it is possible that AIP mutations that affect up to 4% of sporadic acromegaly cases may play a role in the relationship we noted between age and tumor size [29,30]. However as AIP mutations are present in a minority of unselected acromegaly patients such as the LAS, this specific factor is not the explanation for the apparent relationships
between tumor size, GH and age at diagnosis seen in the LAS.

A similar picture does not emerge for IGF-1 levels. When expressed as a percentage of the upper limit of normal, IGF-1 levels showed a weak correlation with GH \((P = 0.08)\) whereas absolute IGF-1 levels strongly correlated with GH \((P = 0.004)\). As a percentage of the upper limit of normal age and sex, IGF-1 showed a remarkable homogeneity as there appeared to be no difference in IGF-1 levels at diagnosis in relation to sex or patient age. This homogeneity could be explained by the “normalization” of IGF-1 when it is expressed as percentage of UNL since absolute values of IGF-1 decreased with patient age.

Cardiometabolic risk factors were highly prevalent in the acromegaly population in this study. The prevalence of diabetes in our population was 22.6%, close to what has been described in the French acromegaly registry to which our center also contributed data [7]. Hypertension was present in 29.7% of patients at time of diagnosis and correlated with the presence of diabetes. In non-diabetic patients, there was no correlation between glucose concentrations and GH whereas glucose correlated with IGF-1. HbA1c also correlated with IGF-1 levels. It was not possible to robustly compare diabetes markers with acromegaly markers in non-treated diabetic patients, but this subgroup was too small in the study population. Of the different diabetes risk factors, only patients’ age appeared as significant. Regarding the respective effects of GH and IGF-1 levels or of IGF-1/GH ratio on insulin resistance, we did not demonstrate the relation between HOMA-IR and either GH or IGF-1 in non-diabetic patients that was suggested previously [21]. However, a possible correlation may have been masked by the size of our population that did not allow the study of GH values compared to different IGF-1 levels nor to stratify sufficient numbers of valid patient data by patients’ age. Similarly, further study of the diabetic population was challenging due to the variety of different diabetes treatments being used (diet, metformin or sulfonylureas) and relatively small treatment-specific subgroups [7].

In our center, we have long advocated the use of SSA as a medical pretreatment in all acromegaly patients, whenever possible [22]. Hence the LAS population contains data on systematic pretreatment of patients with SSA for more than 25 years. SSA treatment given before surgery normalized IGF-1 levels in 58.8% of cases. A linear relation was found between patients’ age and the levels of IGF-1 achieved under SSA treatment. Patients normalizing their IGF-1 levels were older, although age did not seem to be related to initial values of IGF-1. On the other hand, an inverse relation was seen between the initial IGF-1 levels and the values obtained under SSA treatment.

The evaluation of pituitary adenoma size is challenging as measurement of tumor size in three dimensions and calculation of the volume is not always feasible or performed using similar mathematical models. Most tumors have irregular shapes, not adapted to an accurate mathematical volume calculation. Moreover, parametric volume calculation is prone to variation related to different measurement axes between two MRIs. In the current study, however, a number of MRI images have been analyzed by our radiologist or neurosurgeon. Using these valid data we described SSA-related tumor shrinkage in 49.1% of cases and tumor growth in 1.8%. Notably, the median shrinkage was actually very modest (9.1% of the maximal diameter). This may be explained by the fact that the LAS is a truly unselected population and that data in the literature on larger tumor shrinkage come from selected populations with known acute responses to SSA administration.

When we did our last evaluation (excluding the oldest patients for whom, IGF-1 assessments were not available), 237 patients had undergone surgery. The remaining patients were either under primary medical therapy, medical pretreatment or refused surgery. The majority of our patients that were operated upon had one single surgery by a trans-sphenoidal route (91.6%). After surgery, some patients were referred back to an outside endocrinologist and we did not receive follow-up data. Excluding these patients, 44.1% of patients were not cured and treated medically. While the median time to renewal of SSA treatment was 11 months, treatment could be started in some cases many years after surgery, drawing attention to the necessity of a long-term follow-up of these patients to detect late recurrence. When SSA treatment was reinstated after surgery, lower IGF-1 values were achieved compared to the presurgical SSA treatment. This observation is consistent with our original study on tumor debulking [31]. Contrasting with presurgical SSA response data, age did not influence IGF-1 normalization under SSA after surgery. Large initial tumor size and the age of patients at the time of initial diagnosis seemed to influence final outcome. Controlled patients had smaller tumors and were diagnosed later in life compared to uncontrolled patients. Initial GH but not IGF-1 levels were also lower in controlled patients.

When looking at the last follow-up data, a significant number of patients (27.8%) seemed insufficiently controlled. This impression is somehow misleading since it is based on raw numbers. Looking individually at these “uncontrolled” patients, some were in presurgical SSA treatment and could not be considered representative of true treatment escape. Some uncontrolled patients did not have an optimal follow-up period before treatment adaptations could be applied to them (either SSA dose titration or pegvisomant).

In conclusion, the LAS is a new tool for the study of acromegaly in the clinical setting, which permits the collection and aggregation of multiple sources of patient data into a single database. The design of the database behind the LAS was undertaken to maximize its ability to compare various separate data points for the purpose of investigating relationships among disparate but relevant disease characteristics. The LAS permits both retrospective compilation of historical data and the addition of prospective data that is gathered during normal clinical practice in real time. The current study initial study of patients in one center covers an approximately 40-years period of management by the same clinical team and permits the study of the evolution of treatment and patients over time, although subgroup studies are limited somewhat by population size.

As the design, refinement and deployment of the LAS in its home center has proven feasible and has provided useful clinical information, the database has been seeded to a selected number of centers across Europe in order to gather very large numbers of anonymous patient information in acromegaly. The future of
the LAS will potentially be to provide a more accurate picture of the variety of clinical features and management possibilities in patients with acromegaly in thousands of patients across multiple centers and countries.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ando.2012.05.001.

References


