Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Español de Acromegalia, REA)

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Abstract

Objective: To undertake a multicentre epidemiological study reflecting acromegaly in Spain.

Design: Voluntary reporting of data on patients with acromegaly to an online database, by the managing physician.

Methods: Data on demographics, diagnosis, estimated date of initial symptoms and diagnosis, pituitary imaging, visual fields, GH and IGF-I concentrations (requested locally), medical, radiotherapy and neurosurgical treatments, morbidity and mortality were collected.

Results: Data were included for 1219 patients (60.8% women) with a mean age at diagnosis of 45 years (S.D. 14 years). Reporting was maximal in 1997 (2.1 cases per million inhabitants (c.p.m.) per year); prevalence was globally 36 c.p.m., but varied between 15.7 and 75.8 c.p.m. in different regions. Of 1196 pituitary tumours, most were macroadenomas (73%); 81% of these patients underwent surgery, 45% received radiotherapy and 65% were given medical treatment (somatostatin analogues in 68.3% and dopamine agonists in 31.4%). Cures (GH values (basal or after an oral glucose tolerance test) <2 ng/ml, normal IGF-I, or both) were observed in 40.3% after surgery and 28.2% after radiotherapy. Hypertension (39.1%), diabetes mellitus (37.6%), hypopituitarism (25.7%), goitre (22.4%), carpal tunnel syndrome (18.7%) and sleep apnoea (13.2%) were reported as most frequent morbidities; 6.8% of the patients had cancer (breast in 3.1% of the women and colon in 1.2% of the cohort). Fifty-six patients died at a mean age of 60 years (S.D. 14 years), most commonly of a cardiovascular cause (39.4%); mortality was greater in patients given radiotherapy (hazard ratio 2.29; 95% confidence interval 1.03 to 5.08; P = 0.026), and in those in whom GH and IGF-I concentrations were never normal (P < 0.001).

Conclusions: This acromegaly registry offers a realistic overview of the epidemiological characteristics, treatment outcome and morbidity of acromegaly in Spain. As active disease and treatment with radiotherapy are associated with an increase in mortality, efforts to control the disease early are desirable.

Introduction

Acromegaly is a rare disease, with an estimated prevalence of around 69 cases per million inhabitants (c.p.m.) (1–5); this precludes the possibility of obtaining, from single reference centres, relevant data on disease incidence, prevalence, morbidity and mortality, and the comparison of different therapeutic options and outcome. Some of these limitations may be overcome by analysing national acromegaly registries; however, these registers, which depend on the voluntary reporting of cases by all the endocrinologists involved, also
have the limitation that it is not known how complete they really are.

The Spanish Acromegaly Registry (Registro Español de Acromegalia, REA) was set up in 1997 by the Spanish Society of Endocrinology and Nutrition, aimed at registering incident cases of acromegaly and as many cases as possible retrospectively, to analyse the incidence, prevalence, morbidity, mortality and treatment of this disease in Spain.

The aim of this report is to present a multicentre epidemiological study, larger than any previous studies in this country, of pituitary growth hormone (GH) hypersecretion in Spain, to determine clinical characteristics, treatment outcome, morbidity and mortality from which conclusions relevant to clinical practice may be drawn.

Patients and methods

The intended aim was to register all patients diagnosed as suffering from acromegaly in Spain since 1997. Both prospectively and retrospectively (which comprised 90.3% of the cases); in this latter case, a minimum of available data were required to be included. A specific committee of endocrinologists designed the initial database and periodically analysed the available data. Sponsorship was provided by an unrestricted grant from Novartis Pharma, Barcelona, Spain. Patients were included voluntarily by the managing Spanish physician, who obtained an access password to enter the online web page database. The reporting physician was able to update follow-up data periodically; 70% of the patients have at least one update after inclusion into the database. During the first 2 years and if the physician had no access to the online forms, patients’ data were reported on completed printed forms by hand and sent to the central database company (RDES, SL), where the data were introduced manually into the registry. GH and insulin-like growth factor (IGF)-I measurements were those ordered locally by each physician and reported from the case notes. The following were collected: patients’ demographics, diagnosis (acromegaly, gigantism or ectopic growth hormone-releasing hormone [GHRH] secretion), estimated date of initial symptoms and diagnosis, pituitary imaging (magnetic resonance imaging or computed tomography scan with date and result), tumour size and extension, empty sella or other specified findings initially or tumour remains, postoperative changes or other findings after treatment, visual fields, hormonal data (initial or follow-up GH, basal and after oral glucose tolerance test [OGTT]), IGF-I concentration and an indication of whether it was normal or not with respect to the local reference values), and details on treatment: periods of medical treatment (dopaminergic drugs or somatostatin analogues), date, method and dose of radiotherapy, dates and routes of surgical treatment(s), morbidity related to the disease itself or to the treatment (gallstones, osteoarthrosis, obstructive sleep apnoea, visual defects, goitre, headache, hypopituitarism, diabetes mellitus or glucose intolerance, carpal tunnel syndrome, high blood pressure, neoplasms with specification of their nature, or others, with an indication of the year of appearance), and mortality (date, cause and whether it was a direct or indirect notification). No detailed diagnostic criteria were given for the different co-morbidities, which were reported on a checklist by the reporting physician.

Patients gave signed informed consent for their data to be included in the database. Data were entered on an SQL Server v6.5 and the web was programmed on Active Server Pages. Each investigator only has access to their own patients, and the security measures of the system do not allow unauthorized access by third parties, in accordance with the Spanish data protection laws. An endocrinologist is the database manager; they, together with the central database handling firm, are the only persons who have access to the complete database. Data are analysed periodically by the database manager using SAS 8.2 software on an SQL database. Possible inconsistencies and missing data are identified and queries sent to the reporting investigators for completion.

Cure

When the database was established in 1997, criteria for cure were considered to be: GH after OGTT < 2 ng/ml (µg/l) and normal age- and sex-matched IGF-I concentrations; however, if a patient met only one of these criteria (and the other was missing), or a basal GH < 2 ng/ml was reported, they were also included in the cured group. These criteria were maintained as initially agreed, although they have been modified since (6). It should also be remembered that GH and IGF-I assays have changed over the years; more recent determinations using more sensitive immuno-radiometric assays are difficult to compare with older polyclonal radioimmunoassays. Furthermore, conversion factors between SI units and metric measurements for GH have also changed over the years (1 ng/ml used to be deemed equivalent to 2 mIU/l in the 1980’s, but more recently this has changed to 2.6 or 3 mIU/l). Each reporting physician indicated if GH and IGF-I were normal or not according to these criteria and the local reference values.

Statistics

Results are expressed as mean ± 2 S.D. in the case of normally distributed data, and as median plus range in non-normally distributed data. The Weibull model for survival data, obtained using the stepwise method, was used to analyse the deaths; the statistical hazard ratio is given for variables included in this model. Differences between proportions are presented as the 95% confidence interval (CI) (7). A P value < 0.05
was considered statistically significant. In order to identify features related to survival after radiotherapy, a multivariate analysis was used. A Weibull model for survival data was obtained that included only patients treated with radiotherapy; in this case the backward method was used to identify significant differences.

All the statistical analyses were carried out using the statistical package SAS v8.2.

Results

Population

By January 2004, 1219 patients were included in the analysis: 478 (39.2%) men and 741 (60.8%) women, with a mean age at diagnosis of 45 years (S.D. 14 years) (Table 1).

Prevalence and incidence

The prevalence of GH hypersecretion was 33.7 c.p.m., based on the last population census in Spain (8). However, large differences between the regions were identified: there were three Autonomous Communities (Aragón, Asturias and La Rioja), which in total represent 2.5 million inhabitants, in which there were no reported cases; excluding these areas, the prevalence was 36 c.p.m. Reporting was maximal in the year after the database was set up (2.1 new c.p.m. in 1997), whereas the patients’ estimates of the year in which symptoms began was around 5 years before diagnosis.

Aetiology

The most common cause of acromegaly was a pituitary tumour \((n = 1196): 842\) macroadenomas \((>10\ \text{mm in diameter})\) compared with 314 microadenomas; in 40 cases the tumour size was not recorded. In eight cases, GH hypersecretion was attributable to ectopic GHRH secretion; in the remaining 15 aetiology was not reported. Acromegaly was present in 97.3% of patients and pituitary gigantism in 2.2% of the reported cases. In six cases (0.5%) the clinical presentation was not specified. Three patients suffered from multiple endocrine neoplasia type 1.

Table 1 Number and percentage of acromegalic patients reported from each Spanish Autonomous Community (by January 2004), and prevalence calculated from the last available population census in Spain (dated 2001).

<table>
<thead>
<tr>
<th>Autonomous community</th>
<th>(n)</th>
<th>%</th>
<th>Prevalence 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andalusia</td>
<td>168</td>
<td>13.8</td>
<td>27.4</td>
</tr>
<tr>
<td>Balearic Isles</td>
<td>16</td>
<td>1.3</td>
<td>16.9</td>
</tr>
<tr>
<td>Community of Madrid</td>
<td>255</td>
<td>20.9</td>
<td>53.9</td>
</tr>
<tr>
<td>Community of Murcia</td>
<td>29</td>
<td>2.4</td>
<td>26.0</td>
</tr>
<tr>
<td>Community of Valencia</td>
<td>101</td>
<td>8.3</td>
<td>23.2</td>
</tr>
<tr>
<td>Canary Islands</td>
<td>33</td>
<td>2.7</td>
<td>15.7</td>
</tr>
<tr>
<td>Cantabria</td>
<td>33</td>
<td>2.7</td>
<td>56.5</td>
</tr>
<tr>
<td>Castilla-La Mancha</td>
<td>23</td>
<td>1.9</td>
<td>15.6</td>
</tr>
<tr>
<td>Castilla-León</td>
<td>87</td>
<td>7.1</td>
<td>37.8</td>
</tr>
<tr>
<td>Catalonia</td>
<td>270</td>
<td>22.2</td>
<td>46.6</td>
</tr>
<tr>
<td>Basque Country</td>
<td>85</td>
<td>7.0</td>
<td>75.8</td>
</tr>
<tr>
<td>Extremadura</td>
<td>17</td>
<td>1.4</td>
<td>16.6</td>
</tr>
<tr>
<td>Galicia</td>
<td>61</td>
<td>5.0</td>
<td>21.9</td>
</tr>
<tr>
<td>Navarre</td>
<td>41</td>
<td>3.4</td>
<td>66.2</td>
</tr>
<tr>
<td>Total</td>
<td>1219</td>
<td>100.0</td>
<td>33.7</td>
</tr>
<tr>
<td>Total *</td>
<td></td>
<td></td>
<td>36.2</td>
</tr>
</tbody>
</table>

* Excluding the Communities of Aragon, La Rioja and Asturias for which there were no reports.

Treatment

Eighty-one percent \((995\text{ of }1219)\) of the patients underwent surgery at least once, most commonly by the transsphenoidal route (Table 2). Only in the minority of patients who required a third \((n = 15)\) or even a fourth \((n = 4)\) operation was the transcranial route more frequently used. Forty-five percent of the patients included \((543)\) underwent radiotherapy, most commonly conventional \((n = 504; 92.7\%)\), with a few cases of fractionated stereotaxic radiotherapy \((n = 27; 5\%)\) or radiosurgery \((n = 9; 1.7\%)\); in three \((0.6\%)\) the irradiation technique was not specified. In 318 patients \((58.6\%)\), irradiation was performed before 1991, 221 patients \((40.7\%)\) underwent radiotherapy since 1992, and for four patients \((0.7\%)\) the date of radiotherapy was not reported. At the time of the latest report on the database, 153 \((28.2\%)\) of those who had undergone radiotherapy were considered cured. Time elapsed between radiotherapy and cure was up to 5 years in 18.1\% \((n = 90)\), up to 10 years in a further 5.8\% \((n = 29)\) patients, up to 15 years in another 4.4\% \((n = 22)\) and more than 20 years in 2.4\% \((n = 12)\).

Medical treatment was used in 65\% of cases, most commonly somatostatin analogues \((n = 540; 68.3\%)\), followed by dopamine agonists \((n = 248; 31.4\%)\), especially in the patients treated before the early 1990s. Before 1990, just 199 patients \((25\%)\) received medical treatment, whereas since then the percentage has incresed to 75\% \((n = 584)\). The commercial availability of lanreotide since 1994, and soon after of octreotide-LAR, in Spain explain this increase, and probably also the decline in the use of radiotherapy.

Treatment outcome

Postoperative evaluations were available for 995 patients who underwent surgery; in 124 patients, the immediate postoperative outcome could not be determined because GH and IGF-1 values were not provided \((n = 112)\) or the date of the blood tests was missing \((n = 12)\), making it unclear whether they corresponded to a pre- or postoperative evaluation. Of the remaining 871 patients, 351 \((40.3\%)\) were considered cured and 520 \((59.7\%)\) uncured. The classification as cured was based on the classical criteria (post-OGTT GH <2 ng/ml and normal IGF-1 values) in 72.6\% of the
patients; 17.7% only had normal IGF-I (with no available GH values); in 3.7% basal GH or post-OGTT GH, or both, were <2 ng/ml but IGF-I values were unavailable; and in 2%, basal GH was <2 ng/ml with normal IGF-I. Cure rates differed considerably between the reporting hospitals (which were not necessarily where the patients had been operated on), being greatest (between 57.8 and 65.4%) in three large reference centres (responsible for 21.2% of the reported patients), but being 0% in some units.

Among non-operated patients, the number of cures was low (25/224, 11.2%: eight treated with drugs, 10 treated with radiotherapy alone, five treated with radiotherapy and drugs; for two, data were missing). Of these, insufficient GH/IGF-I information precluded classification as cured or not-cured; 105 of the not-cured patients received drugs alone, 37 received radiotherapy and drugs, 13 received radiotherapy alone, 8 received no treatment, and in 27 no data were available.

Morbidity

Associated morbidity is shown in Table 3. Hypertension, diabetes mellitus, hypopituitarism, goitre, carpal tunnel syndrome and sleep apnoea were most frequently reported. Ninety malignant neoplasms were identified (6.8% of patients), most commonly breast and colon cancer (Table 4). In five patients, at least two malignant tumours were detected during follow-up.

Comparison with those who were never exposed to somatostatin analogues, patients who were treated with these drugs had more diabetes mellitus (42% compared with 33.5%; 95% CI 2.7 to 14.3; P = 0.005), gallstones (15.5% compared with 4.1%; 95% CI 7.7 to 15.3; P < 0.001), sleep apnoea (16.3% compared with 10.5%; 95% CI 1.3 to 10.4; P = 0.013) and colon polyps (13.9% compared with 7.5%; 95% CI 0.5 to 12.4; P = 0.034).

Mortality

Fifty-six patients are known to have died, at a median age of 60 years (range 26–84 years). The most common cause of death was cardiovascular (Table 5). Of these, 32 (57.1%) had undergone radiotherapy, whereas 19 (33.9%) had not; for the remaining five, information on radiotherapy was missing. Patients who died had a twice greater probability of having been treated with radiotherapy than those who survived (hazard ratio of 2.29; 95% CI 1.03 to 5.08; P = 0.026). A multivariate analysis (which included tumour size, presence or not of diabetes, age when radiotherapy was administered, high blood pressure, attainment of normal IGF-I concentration after treatment, presence or not of associated cancer or cardiovascular disease, and time elapsed between diagnosis of acromegaly and last follow-up) performed to identify parameters related to death in patients given radiotherapy, failed to identify any significant features: however, the backward method revealed that the most relevant
factor related to probability of dying after radiotherapy was longer time between diagnosis and last follow-up (associated with older age). Normalization of IGF-I concentration did not attain statistical significance in relation to survival after radiotherapy; however, of all the other features analysed it was the only one that showed a trend.

Mortality was also clearly greater in patients who had never achieved a basal GH (51 compared with five deaths; 95% CI 0.039 to 0.193; \( P = 0.001 \)) or a post-OGTT GH, 2 ng/ml (48 compared with eight deaths; 95% CI 0.074 to 0.257; \( P = 0.001 \)), most frequently from a cardiovascular cause. Similarly, if IGF-I had never been normal, mortality was also greater (41 compared with 15 deaths; 95% CI 0.170 to 0.396; \( P = 0.001 \)). No correlation of mortality with hypopituitarism, greater reported IGF-I values or date of treatment (before or since 1991) was observed. More patients never treated with somatostatin analogues died than among those exposed at some stage to this medical treatment (37 compared with 19; 95% CI 0.229 to 0.470; \( P = 0.016 \)) (Table 5).

**Discussion**

**Demography**

The mean age of the acromegalic patients at diagnosis (45 years) did not differ from those reported in previous series from other countries (41–48 years (2, 9–12)). However, there was a female predominance that has otherwise been reported only in an epidemiological study of a small Spanish population in the Basque Country (\( n = 74 \) with 65% females) (3), and in the recently presented West Midlands Acromegaly database (\( n = 419; 57.5\% \) females) (12). Two further Spanish studies of acromegaly also showed a female predominance, although these were not epidemiological studies (13, 14). In contrast, Beauregard et al. (11) reported more males (58%) than females.

**Prevalence and reported incidence** The global prevalence of 36 c.p.m. varied between regions, reflecting differences in the level of reporting in the various Spanish Autonomous Communities and the existence of referral hospitals that receive patients from neighbouring areas for operation, treatment or for follow-up. In areas with a high reporting index and a large population (Basque Country, Navarre, Madrid, Catalunya and Cantabria), the prevalence varied between 46 and 75 c.p.m. Previous reports on smaller populations recorded a prevalence of between 38 and 69 c.p.m. (1–5, 15). A recent study from Finland, where all patients are cared for in five teaching hospitals, revealed a globally greater prevalence of 120 c.p.m. (10). Reporting was maximal in 1997 when the database was set up, most probably reflecting initial reporting enthusiasm by all participants.

**Treatment outcome** The low surgical cure rate (40.3%) compared with that reported in prestigious reference neurosurgical centres (11, 16–23) is probably a closer to that encountered in clinical practice, as less experienced neurosurgical centres rarely publish their results (23–25); the cure rate increased to 60% in

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**Table 4** Neoplasms in acromegaly. Prevalence is calculated from the total registry of 1219 cases.

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Prevalence (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1.8 (3.1*)</td>
<td>23</td>
</tr>
<tr>
<td>Colon</td>
<td>1.2</td>
<td>15</td>
</tr>
<tr>
<td>Lung</td>
<td>0.4</td>
<td>5</td>
</tr>
<tr>
<td>Gastric</td>
<td>0.3</td>
<td>4</td>
</tr>
<tr>
<td>Other malignant neoplasms†</td>
<td>3.5</td>
<td>43</td>
</tr>
<tr>
<td>Patients with malignant neoplasms</td>
<td>7.5</td>
<td>91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign neoplasms</th>
<th>n</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon polyps</td>
<td>9.5</td>
<td>39.4</td>
</tr>
<tr>
<td>Other benign neoplasias§</td>
<td>2.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Other neoplasias</td>
<td>0.3</td>
<td>7.9</td>
</tr>
</tbody>
</table>

*Women alone.
† Included the following cancers: bladder (6), skin (3), ovarian (3), cervix adenocarcinoma (2), lymphoma (2), kidney (2), parotid (2), endometrial (2), cerebral (7), eye (1), pancreas (1), pleural (1), testicular (1), thyroid (2), neurinomatosis (1), reticulosarcoma (1), adenocarcinoma not otherwise specified (1), liver (1), dermofibrosarcoma (1), melanoma (1), carcinoid (1) and scrotal (1).
§ Only patients in whom colonoscopy was performed are included.
‡ Included: meningioma (5), uterine leiomioma (3), prostatic adenoma (3), benign ovarian neoplasia (3), other fibromatosis (3), benign neoplasia not otherwise specified (2), benign bone tumour (1), vocal cord polyps (1), breast cyst (1), thyroid follicular adenoma (1).

**Table 5** Mortality among patients with acromegaly who were treated or not treated with somatostatin analogues (SSa).

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>n</th>
<th>%</th>
<th>% (excluding unknown)</th>
<th>Treated with SSa</th>
<th>Not treated with SSa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data missing</td>
<td>15</td>
<td>26.8</td>
<td>–</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>5.4</td>
<td>–</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>15</td>
<td>26.8</td>
<td>39.4</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5</td>
<td>8.9</td>
<td>13.2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>3</td>
<td>5.4</td>
<td>7.9</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>9</td>
<td>16.1</td>
<td>23.7</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>10.6</td>
<td>15.8</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>100.0</td>
<td>100.0</td>
<td>19</td>
<td>37</td>
</tr>
</tbody>
</table>
large experienced hospitals. Even in published series, cure rates vary tremendously and an inverse correlation has been found between the number of neurosurgeons operating in one centre and the cure rate (23, 26), varying between 37% and 91% for microadendromas (20, 27). More patients underwent radiotherapy before 1991 once somatostatin analogues became available.

**Morbidity**

Associated morbidity was that reported by the physician and, given the observational nature of the registry, is probably underestimated, as not all patients underwent all the tests necessary for a systematic elimination of these diseases; thus, the reported prevalence should be considered a minimum. The previously reported prevalence of hypertension in acromegalic patients is around 35%, but varies widely – between 18% and 60% (28) – as a result of the different criteria used to define and to measure hypertension, and the lack of adjustment for sex, age, ethnicity, etc. Hypertension was found to be more prevalent in those acromegalic patients with high IGF-I concentrations than in the total acromegalic or normal populations (9). The prevalence of hypertension in this registry was not affected by the treatment or lack of treatment with somatostatin analogues. Diabetes mellitus is more prevalent in acromegaly than in the general population, greater in the Spanish acromegalic population (especially those exposed to somatostatin analogues) than in New Zealand (20%) (4), but lower in Canada (40% plus 22% glucose intolerance) (11).

The sleep apnoea syndrome reportedly affects 67% and 75% of acromegalic patients when investigated prospectively (29, 30). This is much greater than the prevalence of 13% observed in our registry and presumably reflects a low awareness of the problem by many physicians, who do not specifically ask about snoring and sleep apnoea in all their acromegalic patients. It was more frequent in those treated with somatostatin analogues, probably reflecting both a more active disease and lower postoperative cure rate than in those who had not required medical treatment, and further awareness of the problem in the past decade when these analogues became available.

Increased cancer risk in patients with acromegaly has long been debated (31–33). Data indicate that, even though the incidence of malignancy is not necessarily greater, the overall mortality rate and that from colon cancer, cardiovascular disease and all malignant disease are increased in active acromegaly, but not if post-treatment GH concentrations are less than 2.5 μg/l (33, 34). For bronchial and breast cancer, the correlation is not so clear (34–36). Colon polyps (which may precede the development of colon cancer) do seem to be increased in acromegaly (32), and were more frequent in our patients who had more active disease and required somatostatin analogues at some stage. With the improvement in the management of acromegaly, more patients will reach ages at which cancer incidence increases, and it will be important in the future to compare results from acromegalic patients with those of age-matched populations. Colorectal cancer has been reported in about 1% of acromegalic patients, and prevalence in our population was similar (1.2%), as also were the prevalences of breast cancer (3.1%) and bronchial cancer (0.4%) (35–38). Colonoscopic examinations were not carried out systematically in all patients in this observational registry, which explains the low prevalence of colon polyps identified (9.5%), in comparison with studies in which all patients underwent pancolonoscopy prospectively (9–40%) (32).

**Mortality**

Evaluation of mortality in acromegaly series is problematic, because the numbers of patients are small with large confidence intervals, the patterns of death are changing in the general population, types of GH sampling and standards of GH/IGF-I assays have changed over the years, and IGF-I values are not always calibrated for age or sex. Nevertheless, a last high GH concentration has been reported to be associated with increased mortality in acromegaly in different series (9, 10, 12, 34, 35), in addition to a high IGF-I (4, 11, 18). Orme et al. (35) did not observe an increased Standard Mortality Ratio (SMR) in acromegalic patients when GH post-treatment was less than 2.5 ng/ml whereas, above 10 ng/ml, SMR increased to 4.6. In the study by Swearingen (18) no differences in mortality of operated patients were observed in those patients considered cured (GH < 2.5 ng/ml or normal IGF-I, or both) when compared with the general population. If the disease was active, SMR was greater, at 1.8. A recent Canadian study on mortality in 99 acromegalic patients followed long-term showed no difference in mortality if they were in remission (random GH < 2.5 μg/l, or GH after OGTT < 1 μg/l and IGF-I within the normal range; five of 57 patients, 9%), but was significantly increased in those with persistent disease (38%, P = 0.008), when compared with the normal population (11). A recent study from the West Midlands of England, however, revealed a correlation of increased mortality with a high post-treatment GH concentration (> 4 mU/l, SMR 1.31; 95% CI 1.03 to 1.66; P = 0.05), and also after radiotherapy (SMR 1.7, 95% CI 1.13 to 2.68; P < 0.05), mainly from cerebrovascular disease (SMR 4.42, 95% CI 2.71 to 7.22; P = 0.005), which therefore appears to be deleterious. However, there was no correlation with increased post-treatment IGF-I concentrations (available in 86% of the patients) (12). In that study conducted over 13 years in 419 acromegalic patients, of whom 61% underwent surgical treatment and 50%
radiotherapy. 95 died, giving an SMR of 1.26 (95% CI 1.03 to 1.54). Our registry confirms that radiotherapy and lack of reported normal GH or IGF-I values were associated with a greater risk of mortality, but hypopituitarism requiring any substitution therapy was not.

Mean age at death in the Spanish registry was 60 years, the same as in New Zealand (61 years) (39, 40), but older than in Canada (42 years) (11). The known causes of death in this series are similar to those previously reported in the large retrospective British study on 1362 patients (35), in which the main cause was cardiovascular, accounting for 36.6% of the deaths, similar to our 39.4%; this was followed by cancer (22.7%), also comparable to our 23.7% of deaths. Given the nature of the registry and the Spanish data protection laws, it was not possible to confirm centrally whether the patients included in the registry were dead or alive after the last report sent in to the database by the physician; thus SMR could not be calculated because it will always be underestimated.

In conclusion, although this acromegaly registry lacks the precision of other large series homogeneously followed in one centre, it offers a realistic overview of the epidemiological characteristics, treatment outcome, morbidity and mortality of acromegaly in Spain, and confirms that active disease and treatment with radiotherapy are associated with an increased mortality; thus efforts to control the disease early (i.e. in experienced neurosurgical centres) are desirable.

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