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EDITORIAL

Twelve years of the Spanish acromegaly registry: a historical view of acromegaly management in Spain

El registro Español de acromegalia doce años después: visión histórica del manejo de la acromegalia en España

Gemma Sesmilo[a,*], Susan M. Webb[b], on behalf of the Neuroendocrinology Group of the Spanish Society of Endocrinology and Nutrition[◆]

[a]*Endocrinology Service, Institut Universitari Dexeus, 08028 Barcelona*
[b]*IIB-Sant Pau and Endocrinology Service, Department of Medicine and Center for Biomedical Research in Rare Diseases (CIBER-ER Unit 747), Sant Pau Hospital, Autonomous University of Barcelona, 08025 Barcelona*
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Introduction

Acromegaly is a rare disease with an estimated incidence of 2.5 cases per million (cpm) per year according to Spanish national data.[1,2]

In 1997 the Spanish Acromegaly Registry (*Registro Español de Acromegalia* [REA]) was set up. The main objective of the project was to collect epidemiological, clinical and biochemical data, as well as data on treatments and outcomes of acromegaly in Spain. Data entry was prospective and retrospective. Peak data entry was recorded between 1998 and 1999, and declined thereafter. In 2004 data were analyzed and the results were published in the European Journal of Endocrinology.[2]

Twelve years after the database was set up, the neuroendocrine group of the Spanish Society of Endocrinology and Nutrition (*Sociedad Española de Endocrinología y Nutrición* [SEEN]) urged for new data entry, updating of previous patients and new data analysis. The main aim of the project is to define trends in acromegaly treatment and outcomes in Spain. We also aim to provide mortality data using both local information and information drawn from the National Mortality database.

History of the REA

In 1997, the neuroendocrine group of the SEEN set up an electronic database for acromegaly data collection. The aims of the project were to study the epidemiology, clinical characteristics, treatments and outcomes, co-morbidities and mortality rates of the disease in Spain.[2]

Each participating physician had a password to enter the on-line database and only had access to his or her own patients. The variables collected included the following: patient demographics, diagnosis (acromegaly, gigantism or ectopic growth hormone-releasing hormone secretion), estimated date of initial symptoms and diagnosis, pituitary imaging (with tumor size and tumor extension), tumor persistence after surgery, visual fields, baseline growth hormone (GH), GH after an oral glucose tolerance test (OGTT) and insulin-like growth factor-1 (IGF-I) concentrations. GH and IGF-I measurements were performed in each center, and IGF-I (reported as normal or abnormally high or low, according to local reference values) was also recorded. Date of diagnosis and co-morbidities were included, and the following were specifically enquired about: gallstones, osteoarthritis, obstructive sleep apnea, visual field defects, goiter, headache, hypopituitarism, diabetes mellitus or

*Corresponding author.
E-mail address: 30064gsl@comb.cat (G. Sesmilo).
◆The list of the members of the Neuroendocrinology Group of the SEEN participating in the REA is available at Appendix 1

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glucose intolerance, carpal tunnel syndrome, high blood pressure, neoplasms with specification of their nature, and other entities. Data on medical, surgical and radiation treatments were also collected. Discontinuation of the study because of death or loss to follow-up was also recorded.

Most tertiary referral centers throughout the country participated in the project, which was made possible by both the involvement of the neuroendocrine group of the SEEN and an unrestricted grant from Novartis.

Since 1997,the accuracy of data entry has been supervised by two simultaneous database managers: an endocrinologist and a webmaster and study coordinator. These two managers and a statistician are the only people with access to the complete database. Data are analyzed periodically by the statistician using SAS 8.2 software on an SQL database. Possible inconsistencies and missing data are identified and queries are sent to the reporting investigators for completion.

The REA over the last 12 years

The database was opened in 1997 for prospective and retrospective data entry; in 2004 and 2006 improvements in the on-line data collection platform were implemented. In the first 2 years, peak data entry and follow-up were registered, reflecting initial reporting of both prevalent and incident cases; after 2000, new cases have been reported each year but at a much lower rate, and up-dating of data of patients previously included was very slow. In 2004 the results of data analysis performed in January 2004 were published.[2] A total of 1,219 patients with a mean age at diagnosis of 45 years had been included. Prevalence–excluding three regional communities that had not reported any data–was 36 cpm. Incidence varied from 11.8 cpm per year in 1997 to 0.5 cpm per year in 2004, probably due to underreporting in the last years. Prevalence also varied among regions across the country: from 15 cpm in the Canary Islands compared with 75 cpm in the Basque region–figures that almost certainly reflect reporting bias across distinct regions. Indeed, the overall prevalence of 34 cpm is somewhat lower than reported rates of 50–70 cpm in other studies,[7–9] suggesting that not all cases were entered in the database. Database activity was very low between 2004 and 2007. From 2007, after a call from the neuroendocrine group of the SEEN, some participants committed themselves to enter all new cases diagnosed at their centers and to accurately follow-up cases previously entered. Members of the Neuroendocrinology Group of the SEEN have ensured complete participation of some of the most important tertiary level referral centers in the country. The latest data analysis (October 2009) indicates that 1,570 patients are now included in the registry and 605 of these have complete follow-up data and are therefore suitable for accurate data analysis. Since the main emphasis has been placed on data accuracy and since not all acromegalic patients have been included in the registry, disease incidence and prevalence in our country will not be assessed.

Changes in the management of acromegaly over the last 12 years

Over the last 12 years important developments in acromegaly have taken place.

Diagnosis of acromegaly and criteria for cure

When the database was set up in 1997, established criteria for ruling out acromegaly and for cure of the disease were a GH after OGTT ≤ 2 ng/ml (μg/L) and normal age- and sex-matched IGF-I concentrations. With the more sensitive immunoradiometric assays (compared with older polyclonal radioimmunoassay), we have learnt that in non-acromegalics, GH after glucose suppresses more than previously thought.[3] There has been a great deal of discussion about the cut-off used to define controlled acromegaly (preferred term rather than cure). In general, a patient is considered to be controlled if GH is reduced to < 1 μg/L after OGTT and IGF-I levels are normal.[4,5] Moreover GH concentrations in pegvisomant treated patients are not useful in the assessment of disease control and therefore we have to rely on IGF-I levels.[6] In the registry, both the IGF-I value (at diagnosis and every 1–2 years) and normality of IGF-I according to the local laboratory, are collected. To be better able to analyze the results of GH and IGF-I at diagnosis and follow-up, in 2007 we added two further variables to the database: type of assay used for GH and IGF-I.

Medical treatment of acromegaly

Important advances in medical treatment over the last 12 years have impacted on the acromegaly treatment scheme. In 1997 the long-acting somatostatin receptor ligand (SRL) lanreotide was launched[7] and thrice daily subcutaneous octreotide administration was supplanted by a twice monthly regimen. One year later, in 1998, another long-acting SRL with a longer half-life, octreotide-LAR, became available in Spain and the drug could be administered on a monthly basis.[8] Lanreotide autogel was approved in Spain in 2002.[9] More recently, longer administration intervals for depot SRLs (6–8 weeks) and higher doses for partial responders have been proven to be effective.[10,11] Pasireotide, a new long-acting SRL with affinity not only for somatostatin receptor subtypes 2 and 5 but also for subtypes 1 and 3, is currently being used in a multicenter phase III clinical trial.[12] Long-acting SRLs have been a hallmark of acromegaly treatment but their use in presurgical treatment is still debated. Presurgical medical treatment with an SRL, especially for macroadenomas with a low probability of surgical cure, has been proposed. Some studies indicate that pretreatment with an SRL can improve cure rates after surgery,[13] whereas others have found no benefits of pretreatment.[14] The costs of presurgical treatment with SRL have also been analyzed and indicate that presurgical use of SRLs increases treatment costs by 30%.[15]

Biochemical response to SRLs is not universal, since only about 60% of patients respond biochemically and only 30% show some tumor regression. After pegvisomant was launched on the Spanish market in 2004, a broader spectrum of patients could be controlled.[6] Pegvisomant alone or in combination with SRLs has allowed disease control in previously uncontrolled patients and has contributed to a change in treatment algorithms, especially regarding the place of radiation therapy.[5,16] One of the main aims of the current project of the Spanish registry is to provide data on the therapeutic sequence in acromegaly treatment in Spain

in clinical practice and how it has changed according to distinct clinical characteristics of the disease.

Surgical treatment of acromegaly

New surgical procedures such as computerized navigation, endoscopy, and intraoperative magnetic resonance imaging (MRI) may also impact on cure rates or will do so in the near future.[17,18] Surgical cure of acromegaly in general and in the last analysis of the Spanish registry in particular is poor (40% in REA published data),[2] similar to that reported in another European registry in Belgium, 34% in 418 patients.[19] A further important aim is to analyze trends in surgical cure rates over time.

Radiation therapy

Radiation therapy for acromegaly has nowadays passed from a second-line treatment option, to a third-line option in most treatment algorithms.[5] However, this treatment remains controversial and its use will depend on patient and disease characteristics, as well as the treatment facilities available. Response to conventional radiation treatment may take 10 to 15 years for a 60% response rate.[20–22] Newer, single-dose, focused radiotherapy, such as that achieved with the gamma knife or linear accelerator, may provide 29 to 60% remission rates at 5–10 years according to some authors.[23,24] However, studies are biased by patient selection and there are still no clear recommendations in favor of one or other technique. Long-term data are lacking for the newer focused administrations. The main concern about radiation therapy is safety, especially when other, safer treatment modalities exist. Long-term complications, particularly neurocognitive defects, hypopituitarism, second tumors and cerebrovascular events due to radiation vasculopathy are a concern. However, there are no clear epidemiological data on these long-term complications. In Spain, a few centers provide single-dose focused radiation therapy but in the last few years, stereotactic administration and dose fractioning have improved. One of the aims of the REA is both to analyze the use of radiotherapy in acromegaly in Spain and to evaluate long-term morbidity in patients who have received this kind of treatment.

REA's response to advances in acromegaly

The on-line data collection has been modified over the years to include the newer medical options that have been marketed (which appear as a multiple choice bar) as well as the different radiation therapy techniques. Pasireotide was included in 2009. To better analyze our data regarding GH and IGF-I concentrations compared with GH after OGTT in the definition of disease control, a variable including the type of assay used for each variable in each center was added in 2006. The on-line case report forms were implemented in 2004 and 2006. In May 2009, during the Spanish Endocrine meeting, specific aims for the next data analysis and a time line for data entry were defined.

The main aim of the next analysis is to define current treatment of acromegaly and changes over the last few years in the types and sequence of treatments as well as clinical factors that may influence treatment sequence. As discussed above, newly available medications have displaced radiation therapy as a third-line treatment of acromegaly in some treatment algorithms. However, it is important to individualize the treatment sequence in each patient as well as to consider lifetime costs.

Another important goal of the present analysis is to evaluate treatment outcomes and cure rates. We aim to compare cure rates in the last 12 years. In 2004 we found that less than 50% of acromegalic patients fulfilled the criteria to be considered cured in Spain and these results are similar to those reported in the Belgian acromegaly registry in 2004 and 2005.[19] We hope that with the advent of the newer medical treatments the proportion of cured patients will increase. Another primary endpoint is to obtain mortality and morbidity data. At present, among the 605 patients whose data have been accurately updated, there has been a 30% loss to follow-up rate. These patients may have died and therefore it is important to check the National Registries when necessary, to determine the exact mortality rate of the disease, as well as cause and age at death. Access to the National Mortality database has been specifically requested for this study.

Another aim of the project is to compare our data with those from other ongoing European registries to determine whether we share some of the reported characteristics of the disease seen in other countries.

Summary and conclusions

The REA is a powerful tool to provide data on the clinical characteristics and outcomes of acromegaly in Spain. Given the substantial changes that have occurred in the treatment of this disease over the last 12 years, we aim to analyze time changes in the treatment of acromegaly as well as cure rates. We are particularly interested in obtaining mortality data by using National Registries and in comparing our results with those reported by other European registries.

Appendix 1. Members of the Neuroendocrinology Group of the SEEN participating in the REA

Victoria Alcázar Lázaro, Hospital Severo Ochoa, Cristina Álvarez Escolá, Hospital Universitario la Paz, Madrid, Paula Álvarez Vázquez, Complejo Hospitalario de Ourense, Orense, Ignacio Bernabeu Morón, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Concepción Blanco Carrera, Hospital Príncipe de Asturias, Alejandro Cámara Balda, Hospital San Pedro, Rosa Cámara Gómez, Hospital La Fe, Valencia, Emilia Cáncer Minchot, Hospital de Fuenlabrada, Ignasi Castells Fust, Hospital de Granollers, Barcelona, Carlos Del Pozo Picó, Hospital Mutua de Terrassa, Barcelona, Juan José Díez Gómez, Hospital Universitario la Paz, Madrid, Alberto Díez Hernández, Hospital del Bierzo, Carmen Fajardo Montañana, Hospital de la Ribera, Valencia, Lluis Forga Llenas, Hospital de Navarra, Navarra, Rogelio García Centeno, Hospital Gregorio Marañón, Madrid, Honorato García Fernández, Hospital Son Dureta, Mallorca, Manuel Gargallo Fernández, Hospital Virgen de la Torre, Sonia Gaztambide Sáenz, Hospital de Cruces, Bilbao, Irene Halperin Rabinovich, Hospital Clínic, Barcelona, Juan Ángel Hernández Bayo, Hospital de la Palma,

Miguel Angel Jaunsolo Barranechea, Hospital Severo Ochoa, Camelia Martí Ippoliti, Hospital de Sant Pau, Barcelona, Miguel Ángel Martínez Olmos, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Francisca Mas, Hospital de Manacor, Mallorca, Alberto Moreno Carazo, Complejo Hospitalario de Jaén, Jaén, Basilio Moreno Esteban, Hospital Gregorio Marañón, Madrid, Jesús Moreno Fernandez, La Mancha Centro Endocrinología y Nutrición, Gabriel Obiols Alfonso, Hospital Vall d'Hebron, Barcelona, Herminia Pascual Saura, Hospital Morales Meseguer, Antonio Picó Alfonso, Hospital General de Alicante, Alicante, María Pilar Ruiz-Valdepeñas Herrero, Hospital 12 de Octubre, Madrid, Isabel Salinas i Vert, Hospital Germans Trias i Pujol, Barcelona, María Concepción Sanabria Pérez, Complejo Hospitalario Ciudad Real, Ciudad Real, Piedad Santiago Fernández, Alicia Serra-clara Pla, Hospital 12 de Octubre, Madrid, Gemma Sesmilo León, Institut Universitari Dexeus, Barcelona, Alfonso Ll. Soto Llorens, Hospital Universitario Virgen del Rocío, Sevilla, Elena Torres Vela, Hospital Universitario San Cecilio, Granada, César Varela Dacosta, Hospital Infanta Sofía, Madrid, Eva Venegas Moreno, Hospital Universitario Virgen del Rocío, Sevilla, Carles Villabona Artero, Hospital de Bellvitge, Barcelona, Susan Webb Youdale, Hospital de Sant Pau, Barcelona.

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