Journal of Clinical & Experimental Pathology

Gavilanez et al., J Clin Exp Pathol 2018, 8:1
DOI: 10.4172/2161-0681.1000337

Mini Review Open Access

Acromegaly: Current Challenges and Future Directions in Latin America

Enrique Lopez Gavilanez[1*], Noemi Bautista Litardo[2], Mario Hernández Bonilla[1], Manuel Navarro Chavez[3], Hamilton Abad Gualpa[3], Angel Segale Bajana[4], Kempis Guerrero Franco[4], Narcisa Solorzano Romero[3], Luis Vaca Burbano[5] and Angelo Caputi Zúñiga[4]

[1]*Endocrinology Service, Teaching Hospital National Police 2, Guayaquil, Ecuador*

[2]*Endocrinology Service, Kennedy Alborada Clinical Hospital, Guayaquil, Ecuador*

[3]*Endocrinology Service, Omni Hospital, Guayaquil, Ecuador*

[4]*Internal Medicine Service, Teaching Hospital National Police 2, Guayaquil, Ecuador*

[5]*Neurosurgery Service, Teaching Hospital National Police 2, Guayaquil, Ecuador*

***Corresponding author:** Dr. Enrique Lopez Gavilanez, Endocrinology Service, Teaching Hospital of the National Police, Guayaquil 2, Avenue of the Americas S/N and E. Noboa, Guayaquil, CP: EC090150, Ecuador, Email: enrique_lopezg57@hotmail.com

Received date: January 25, 2018; **Accepted date:** February 7, 2018; **Published date:** February 12, 2018

Abstract

Acromegaly is a rare disease, associated with significant morbidity and high mortality. The international literature provides different figures on the epidemiology of acromegaly in different populations, mainly in Europe and US. However, there are few studies that address its epidemiology in Latin America. The creation, starting in the 1990s, of national acromegaly registries in developed countries has stimulated the need to create them in our region, being Mexico the only country that has developed a national Registry. The clinical and biochemical characterization of patients with acromegaly in our region does not seem to be different from that described in the international literature; however, population studies are necessary to establish the epidemiological trends in Latin America.

Keywords: Acromegaly; Epidemiology; Incidence; Prevalence; Latin America; Ecuador

Introduction

Acromegaly is an infrequent disease, is associated with high morbidity, and has a mortality rate 2 to 3 times higher than expected [1-3]. The epidemiology of the disease has changed in recent decades, due to advances in diagnostic techniques and recent treatments. In 2010, recommendations on the management of acromegaly specifically for Latin America were published [4]. In Mexico and Brazil [5,6], guides have also been developed at the national level. In the present mini-review, we address the particularities of the epidemiology of acromegaly in Latin America, as well as trends in clinical presentation, diagnosis and treatment modalities. Finally, we analyze the present and future challenges that arise in the region for the early detection and optimization of the treatment of acromegaly.

Epidemiology of Acromegaly in the World

Information on the epidemiology of acromegaly has been obtained from the national registries that were created in Europe from the 90s and from the data obtained in a limited number of cases attended in highly specialized centers. This information is the best reflection of the specific trends in each country of the epidemiology, diagnosis and treatment of the disease [7-10].

Although the prevalence figures tend to differ depending on the region and/or country examined, these range between 40 and 95 cases per million inhabitants [11], with an estimated average of approximately 69 cases per million inhabitants [12,13] .

In Latin America it has been described above all in the studies carried out since the year 2000, lower prevalences of around 18 cases per million inhabitants [14,15]

The estimated incidence in Europe averages approximately 3-4 cases per million inhabitants [13,16]. While, in the Latin American countries, incidence figures are not reported; only in Ecuador has an incidence of 1.3 cases per million persons/year been described [15].

National Registries of Acromegaly

In Europe, at the end of the 1990s, national acromegaly registries were started to establish the epidemiological characteristics and design adequate diagnosis and treatment strategies. The best organized records are those of Spain, Belgium and Germany [7,8,16,17].

The Spanish [7] and Belgian [8] databases register subjects diagnosed before 1980 and report considerably higher prevalences of 38 and 35 cases per million, respectively. In contrast, the German [9] and Italian [3] registries included patients diagnosed after 1990 and have lower prevalences of 19 and 25 cases per million, respectively.

In Latin America, until now the only national registry of acromegaly cases is the National Epidemiological Program of Acromegaly of Mexico, Epiacro, which issued its first report in 2010 [18], and the Mexican registry of Acromegalia (MAR) recently released [14].

Epidemiology of Acromegaly in Latin America

The countries in which the epidemiology of Acromegaly in Latin America has been most studied are, Mexico [14,18], Brazil [19,20], Argentina [21] and more recently Ecuador [15].

The Mexican registry of acromegaly "EpiAcro" gives an estimated general prevalence of 13 cases per million, which is lower than in other parts of the world and suggests an important sub-diagnosis [18]. More recently in the MAR registry, the first and largest non-European record of the disease, a prevalence of 18 cases per million inhabitants is reported [14].

In Buenos Aires, Argentina, a cohort of pituitary tumors reports a prevalence of 14.07 cases per 100,000 people and a standardized incidence rate of 0.92 cases per 100,000 persons/year [21]. In Brazil, in a screening study, the prevalence reported in 2011 was 294 cases per 1'000.00 inhabitants, and in 2012, 480 cases per 1'000,000 inhabitants [19,20,22].

Recently in Ecuador the epidemiology of acromegaly was described in Guayaquil, the most populated city of Ecuador [23], reporting a prevalence of 18.7 cases/million inhabitants and the incidence of 1.3 cases/million persons/years [15].

Clinical and Biochemical Characterization

The diagnosis of acromegaly is based mainly on clinical manifestations and is generally confirmed by measuring the serum levels of GH and IGF-1 [12]. The clinical manifestations depend on the levels of GH (and IGF-1), age, size of the tumor mass, and the time of delay in diagnosis. Since the clinical effects of excess GH occur insidiously over time, many of the symptoms of acromegaly are nonspecific and similar to other more common diseases, so the diagnosis is often omitted or delayed by 5 to 10 years. Starting from the onset of symptoms [15,18,24].

The first clinical manifestations and reasons for medical consultation in most cases, are alterations of the physiognomy and growth of the acral parts [1,7,12]. These manifestations have not changed in the last 2 decades, and show that acromegaly is still underdiagnosed and remains under-recognized [24].

In all the series a greater incidence of the disease in women is demonstrated [25]. In the Epiacro registry of Mexico, the proportion of women was 60% [18]. In Ecuador, the predominance of females is confirmed (64.5%), with a female-male ratio of 1.8: 1.

In European series, patients are usually diagnosed between the fourth and sixth decades of life, and the estimated time of delay from the onset of symptoms to clinical or biochemical diagnosis varies from 9 to 35 years [11,13].

In Mexico, the main clinical characteristic of the patients was acral enlargement of the hands and feet, headache and fatigue. The prevalence of comorbidities was similar to that described in European registries. [3,7-9,14,17,26], and it is emphasized that diabetes and high blood pressure were more common in women than in men [14,27]. The time between onset of clinical manifestations and diagnosis varied from 5 to 17 years, and approximately one third of patients had an invasive tumor at the time of diagnosis [18].

In Ecuador, the clinical and biochemical characterization in the cases described in the city of Guayaquil was not different from that described in the international literature. There is a predominance of the disease in women; it is diagnosed in the fourth decade with a delay in the diagnosis of about 8 years, which is usually even greater in men [15].

Comorbidities and Mortality in Acromegaly

Active or untreated disease is associated with significant morbidity and mortality, mainly due to cardiovascular and neoplastic causes [28-30]. In studies published before 1995, acromegaly was associated with a two to three fold increase in mortality rates compared to the general population [2]. More recently, due mainly to the availability of modern treatments, an improvement in survival and the standardized mortality rate have been described [3]. The most common causes of death have been cardiovascular diseases and, in some studies, dysfunction of the respiratory system [3,28]. More recently, the cause of death changes from predominantly cardiovascular to deaths predominantly related to cancer [2].

Trends in the Treatment of Acromegaly in Latin America

The objectives of treatment are to eliminate morbidity and recover life expectancy. The treatment must control the growth of the tumor mass and restore the normal secretion of GH. The biochemical control criteria are to reduce the plasma IGF-1 values to the normal ones according to age and sex and to achieve suppress the serum levels of GH to less than 1 ng/ml during the TTGO [4,14,31]. In guidelines and consensus statements specific to Latin America, it is generally recommended as primary therapy in acromegaly, surgery or, if there is a low probability of surgical cure somatostatin analogues (SSAs) [4].

The percentage of surgical cure described in the literature varies from 80% to 100% for microadenomas and 50 to 65% for macroadenomas, depending on the chosen cure criteria [32]. In the MAR registry, in 500 patients almost 40% were considered as cured. The surgical cure rate was higher in microadenomas than in macroadenomas. These figures are similar to the cure rates reported by the different European registers [14].

In Chile, a study in 53 surgically treated patients reported disease control in 66.7% of the microadenomas and 21.4% of the macroadenomas [33].

In Ecuador, the main treatment is transsphenoidal surgery (in 81% of patients), followed (and sometimes proceeded) by somatostatin analogues (sustained-release octreotide). In general, the surgical cure rate was much lower (3%) than that of the surgical series reported by other reference hospitals, ranging between 21% and 95% [11,15,16,25,26].

Pharmacological Therapy

Despite recent advances in the treatment of acromegaly with surgery, drugs and radiation therapy, some patients do not achieve hormonal control.

Somatostatin analogues

The evidence to support the use of SSAs as primary pharmacological treatment is now extensive and includes several studies in Latin American populations [34-38]. Specific guidelines for Latin America [4] generally recommend therapy with SSAs as the next line of treatment in patients with insufficient control of GH secretion after surgery [39,40].

In most Latin American countries the cost of pharmacological treatment, particularly, SSAs are absorbed by the state. The formulations of octreotide and lanreotide Depot are actively marketed and are prescribed in Argentina, Brazil, Chile, Colombia, Mexico, Peru, Ecuador (only octreotide) [15] and Venezuela [36].

Treatment with SSAs may improve surgical outcomes [41], similarly surgical reduction of the tumor mass may improve the outcome of SSAs treatment in patients resistant to primary therapy with SSAs [40,42]. In Mexico, 187 patients who were treated mainly or in addition with SSAs were analyzed [14] and the results in relation to

primary therapy with SSAs were similar to those reported by European registries [8,13,16].

Dopamine agonists

Cabergoline is usually reserved for patients with relatively low concentrations of GH and IGF-1, or those in whom an oral drug is preferred over injectable therapy [40]. It is widely available in Latin America, it is less expensive and can improve the response in patients not controlled only with SSAs [6,39,43,44]. It is considered as an alternative treatment (although less effective) in situations in which SSAs are not available [40].

GH receptor antagonist

Pegvisomant is usually reserved for third line therapy [40], is used less frequently due to its higher cost [45], requires daily injections and is not available throughout Latin America. It may be effective as an additional therapy in cases with partial response to SSAs [40,46,47].

Other Pharmacological Therapeutic Options Used in Latin America

Some therapeutic options less explored in the international literature have been used in Latin America. Although they may be less effective and discontinued in some countries, in selected cases, these drugs alone or in combination may be useful, less expensive and are available in some countries of Latin America.

Estrogens

Estrogens were used in the past to treat acromegaly, achieving almost a 50% decrease in IGF-1 values, but these drugs were discontinued due to the side effects caused by the high doses administered and the undesirable effects [48-50]. In women of reproductive age, without contraindications, oral contraceptives would be an option. In postmenopausal women, oral estrogens, tamoxifen and raloxifene may be useful [48].

SERMs

In men, due to obvious side effects, estrogen would not be an option. For them and for postmenopausal women who are not candidates for estrogen therapy, selective estrogen receptor modulators (SERMs) may be an option [51]. There are studies in men and women with clomiphene [52], tamoxifen [53] and raloxifene [54,55]. In men, especially in hypogonadics, clomiphene could achieve good results [51,52].

Rosiglitazone

Rosiglitazone, a selective agonist of PPAR gamma receptors, has been used in patients with acromegaly with different results [56-58]. In some selected patients, rosiglitazone can decrease the levels of GH and IGF-1 [56,58]. Additional research with rosiglitazone, alone or in combination with other treatment modalities, is required to define its usefulness in the long-term treatment of acromegaly.

Radiotherapy

Radiation therapy in most of its modalities is used more frequently in the region, due to its relatively low cost and proven efficacy [45]. Radiosurgery is considered an option in selected cases when no control of the disease is achieved with surgery and drug therapy, especially if the pegvisomant is not available. [40] Radiosurgery and modern external-beam radiation therapy can be an effective, low-cost, and reasonably safe means of controlling the activity of acromegaly, although it has a long latency period for its efficacy [59,60]. The results of transsphenoidal surgery, radiotherapy and treatment with somatostatin analogues described in publications in Latin America, are comparable to those achieved in Europe and the United States [35,60-65].

Challenges and Future Directions in the Management of Acromegaly in Latin America

The main challenges that Latin American countries face are the early and efficient detection of cases and the registration of cases in national and/or regional databases, for which we must carry out screening programs and implement national acromegaly registries. Other challenges involve achieving better access to modern diagnostic tools (biochemical, genetic, radiological), pharmacological resources (current) and multidisciplinary teams of experts.

Screening of Acromegalia

Since acromegaly is rare disease, it can be difficult to establish strategies that help in diagnosis and detection in an effective and cost-effective manner [66]. Early recognition of typical clinical manifestations of the disease can help to identify patients at risk, instead of focusing on comorbidities, which generally appear at later stages and are not always present in all cases. The implementation of screening programs for these at-risk patients could anticipate diagnosis in decades. For a screening program for a rare disease (such as acromegaly) to be viable and effective, the total cost/benefit ratio of the search for a case must be in balance with the medical expense as a whole [66]. The treatment of comorbidities associated with delayed diagnosis increases the overall costs of care. Therefore, the type of screening of choice should be directed to the population at risk [66].

Implementation of National Acromegaly Registries

The importance of registering patients with acromegaly through computerized databases is to obtain data on clinical characteristics, prevalence, morbidity and mortality, and response to treatments. This information represents a useful tool for designing local or regional health strategies in the medium and long term. Scientific societies in coordination with public health institutions in each country play a fundamental role in the creation of these national registries. In our Central and South America region, the Latin American Society of Neuroendocrinology (SLANE) groups a large number of specialists dedicated to the study and dissemination of programs related to acromegaly. Its main guidelines are to encourage the formation of national groups that implement the creation of the registry of cases of the disease. In Ecuador, since 2000, the Association of Clinical Endocrinologists of Ecuador (AECE) has carried out the systematic search of cases in the main hospitals of the public health network in the city of Guayaquil and is committed to developing an online registry of cases at the national level. We hope that these efforts bear fruit in the short term.

Conclusion

In summary, in Latin American countries specialists in pituitary surgery are not always available or centralize their professional practice in the 2 or 3 main cities of the country; the economic and material resources, especially the last generation drugs, are scarce or difficult to access for the majority of the population. This determines that doctors use treatments that are not indicated in international guidelines but are more accessible in our countries. The education of general practitioners and the performance of simple screening studies based on phenotypic characteristics can be a cost-effective method for the early identification of acromegaly. Finally, we believe that a national registry system for patients diagnosed with acromegaly should be implemented in all the countries of our region, with the objective of coordinating the design of adequate health care strategies in the region.

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