Screening of Acromegaly in Latin America

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Abstract

Acromegaly is an “orphan” or “rare” disease. Worldwide, it is an underdiagnosed or late diagnosed disease, characterized by significant morbidity and a high mortality rate. The evolution of symptoms is insidious and prolonged, which hinders and delays the diagnosis in decades. The lack of familiarity of physicians with the disease is a cause of the delay in diagnosis. In addition, comorbidities appear late and are common in the general population, so the usefulness of early diagnosis is unquestionable. Early diagnosis allows the prevention of the appearance of complications and the improvement of existing comorbidities in most patients with acromegaly. Programs or strategies that promote the education of general practitioner, health personnel and the general public and the adoption of simple screening techniques based on phenotypic alterations of the disease can be a profitable and effective method for the early identification of acromegaly. The implementation of screening strategies in Latin American countries must be economic, easy to carry out and addressed to the population at risk.

Keywords: Acromegaly; Epidemiology; Screening; Latin America; Ecuador

Introduction

Acromegaly is a “rare” disease associated with significant morbidity and a high mortality rate. Mortality is two to four times higher than the general population, and is predominant due to cardiovascular, metabolic and pulmonary comorbidities [1].

Acromegaly is included in the classification of “rare” or “orphan” diseases, that is, an infrequent (rare) disease that affects less than 200,000 people in the United States [2], or less than 5 per 10,000 people in the European population [3,4].

Worldwide, acromegaly is an underdiagnosed disease [1,5] or a late diagnosis [5]. Few studies have evaluated the epidemiology of acromegaly in Latin America. The first non-European registry of patients with acromegaly is the one performed in the Mexican program EPIACRO, and almost simultaneously appears the record of Ecuador with a prevalence calculated in both countries of 18 cases per million inhabitants [6,7]. With respect to the annual incidence, in Europe an average of between 3 and 4 cases per million inhabitants have been reported in the different series [7-10]. While in Latin American countries incidence figures are not reported; only in Ecuador has an incidence of 1.3 cases per million persons per year been reported [7,11].

National health care systems in Latin American countries vary widely in their organizational structure and in the provision of health services [12,13]. Access to health resources varies widely not only between countries, but also within countries and even in cities or provinces [14]. Although most Latin American countries have hospitals or referral centers capable of treating patients with acromegaly, the resources and priorities assigned to acromegaly care are different from those in Europe or the United States and vary from country to country due to specific local circumstances, such as the availability of qualified specialists and economic resources to pay expensive pharmacological treatments and/or highly complex therapeutic interventions [15].

The cultural, economic and social reality of the developing countries in Latin America is different in each one, which makes it essential to consider these diversities when planning diagnosis and treatment strategies for acromegaly in our region. The recognition of these diversities led to the publication of specific guidelines for Latin America in 2010 [16].

In the absence of the classic phenotypic features of the disease, the arguments that support the “clinical suspicion” of acromegaly depend on the degree of personal suspicion of each physician, which is influenced by his or her academic background, experience with the disease and interest in diagnosing it [17].

There is a general agreement on the need to investigate acromegaly in patients who have a typical phenotype or imaging results consistent with an adenoma in the pituitary gland [18]. However, there are not objective recommendations on which patients should be screened for acromegaly [14,16,19].

Early diagnosis allows the prevention of the appearance of complications, and the improvement of existing comorbidities in most patients with acromegaly [20]. Consistent with this, some guidelines recommend that the disease be screened with the measurement of serum IGF-1 in those subjects that present with two or more comorbidities associated with acromegaly and in absence of any known pituitary disease [21,22]. However, in a series of 1209 patients with high blood pressure (HBP) and without a known pituitary tumour, no case was found with acromegaly (in the absence of enlargement of the extremities), although these patients presented with two or more comorbidities associated with acromegaly [17].

We should not also overlook that cases of patients with unexplained high levels of IGF-1 and without acromegaly have been described in the literature [17,23,24].

Comorbidities associated with acromegaly.

Many comorbidities are common in the general population and therefore would not, in isolation, trigger a search for acromegaly [5]. Although they may occur frequently in the general population, certain comorbidities in particular have been associated with acromegaly, and according to some guidelines [21,22] they could be taken into account in the search for acromegaly. Among those that deserve to be highlighted are menstrual irregularities in young women (oligomenorrhea, amenorrhea, polycystic ovary syndrome (PCOS) with or without hirsutism, diabetes or glucose intolerance, hypertension, diffuse arthralgia, carpal tunnel syndrome and dental alterations or malocclusion.

Menstrual disorders, polycystic ovary syndrome, hyperandrogenism

A very common complaint in medical visit is the menstrual irregularity in young women. The combination of signs of hyperandrogenism and amenorrhea may be signs of an underlying undiagnosed pathology [25]. The PCOS phenotype can occur in up to 50% of women with acromegaly, and there is evidence that the increment of IGF-1 may play an important role in the development of PCOS [26]. The evidence of an association between acromegaly, hyperandrogenism and menstrual irregularities comes mostly from report cases whose presence was ultimately explained by the excess of GH secretion by a microadenoma in the pituitary gland. In our search for literature we have identified eleven published cases. Most of these cases presented mild or severe hirsutism, menstrual irregularities, and polycystic ovaries on ultrasound [25,27-36]. Usually the signs of hyperandrogenism are initially subtle and slowly progressive over time. It is very rare that acromegaly initially presents hirsutism; in one series it was the earliest presentation of the disease in only 1.1% of patients [5]. From puberty they present, facial hair growth, deepening of the voice, acne, frontal baldness, excessive libido increase, with echographic findings in the ovaries compatible with PCOS [25].

Although the pathophysiology of hirsutism associated with acromegaly has not been established [25], it is well known that GH promotes insulin resistance [37,38] and GH-induced hyperinsulinemia can act directly on the ovaries, potentially increasing the ovarian production of androgens that can result in hirsutism [39]. High levels of GH and IGF-1 can also directly alter the morphology of the ovaries [40], which is usually normalized by decreasing serum levels of IGF-1 [25]. GH decreases serum levels of sex hormone-binding globulin [26,40], which consequently leads to elevated free levels of testosterone, which could also cause hirsutism [25].

In PCOS and acromegaly there may be a significant overlap between menstrual irregularities and hirsutism [25]. Consequently, before making the diagnosis of PCOS, we must consider as a part of the differential diagnosis of menstrual irregularities and hirsutism the possibility of acromegaly, which could promote the early diagnosis of this disease [25].

**Arterial hypertension**

Hypertension is a major complication of acromegaly, contributing to increased morbidity and the mortality of this condition. Hypertension is detected in up to 40% of patients with acromegaly, presumably due to an increase in plasma volume along with an increase in sodium retention [20,41]. The exact mechanisms behind the development of hypertension in patients with acromegaly remain obscure but may include several factors depending on chronic exposure to excess GH and/or IGF-I [42]. It has been considered among several supposed mechanisms to explain hypertension in acromegaly, that there is evidence that the cardiac volume and the cardiac index increase, while the systemic vascular resistance is reduced [43]. Previous studies demonstrated that the level of aldosterone is increased in patients with active acromegaly [42].

**Diabetes and glucose intolerance**

Hyperglycemia, due to glucose intolerance or diabetes mellitus, is a common complication of acromegaly and is directly attributable to the excess of circulating growth hormone and IGF-1 concentrations [22,44]. Although a series of metabolic changes in acromegaly predispose to diabetes mellitus, the most important mechanism is insulin resistance. GH promotes insulin resistance mainly through lipolysis, which leads to the competition of the fatty acid-glucose-substrate, and to the reduction of the glucose utilization in the muscle, which is aggravated by the gluconeogenesis stimulated by the GH [44]. The prevalence of diabetes mellitus is up to 56% in patients with acromegaly and glucose intolerance is detected up to 46% [45]. In those patients with poorly controlled diabetes attributable to acromegaly, serum IGF-I levels should be measured at a later time when glycemic control has improved [22].

**Diffuse joint pain and carpal tunnel syndrome**

Arthropathy develops early in the course of acromegaly and, as it progresses, it resembles to the active osteoarthritis and often results in substantial disability [22]. Diffuse arthralgias may be present in up to 46% of patients with acromegaly [22]. Joint discomfort may, in part, be due to the enlargement of soft tissues and fluid retention [46]. The most affected joints are the knees, followed by the shoulders, hips, ankles and joints of the hands [47].

Symptomatic carpal tunnel syndrome, due to an increase in median nerve edema within the carpal tunnel, can occur in up to 64% of patients and is a frequent source of disability and discomfort [46].

**Dental alterations**

Maxillofacial changes, together with acral enlargement, are the most frequent presenting signs in patients with acromegaly [22]. These changes include maxillary and jaw widening with separation of teeth (diastema), excessive jaw growth, malocclusion of the jaw, and overbite [47], they are present in up to 74% of cases and can be very disabling for patients [22,33,48], Kashyap., et al. suggest that acromegaly should be considered in patients who develop dental malocclusion after adolescence [47].

**The importance of screening acromegaly**

Since the time between the beginning of symptoms and the diagnosis is prolonged (range between 1 and 30 years) [6,7], the detected cases already show the typical physiognomic changes at the time of diagnosis because the disease had not been previously suspected [17]. One of the possible causes for this situation is the lack of familiarity of general practitioner with the manifestations of acromegaly [49]. Most patients report that they have sought medical attention due to the manifestations of the disease long before the diagnosis was finally suspected [1,5].

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Because acromegaly is a rare disease, it can be difficult to establish strategies that help in diagnosis and detection in an effective and cost-effective manner [50]. For a screening program for a "rare" disease (such as acromegaly) to be feasible and effective, the total cost/benefit ratio of the search for a case must be in balance with the medical expense as a whole [50].

Rosario, et al. performed the screening of acromegaly with the application of a simple questionnaire with 2 questions: (1) Has your shoe size increased in the last 5 years?, (2) have you had to change your ring during the last 5 years because it became tight? Those who responded positively to at least one of the questions were asked to measure serum IGF-1 [49]. Early recognition of the typical clinical manifestations of the disease (enlargement of the extremities) is cost-effective, since these changes occur early and are almost universal in acromegaly and are uncommon in the general population [49].

The implementation of this type of screening program can help identify patients at risk and could anticipate diagnosis in decades [8,49].

In general, comorbidities usually appear in late stages and are not always present in all cases, and the treatment of comorbidities associated with delayed diagnosis increases the overall costs of care. Therefore, to obtain the greatest benefit from screening, it should be directed to the population at risk [50].

Recommendations for screening for acromegaly

Among the measures to be taken to improve the early detection of the disease objective recommendations should be established about which subjects should be screened for acromegaly [17].

If the lack of familiarity of the physician is a main cause of the delay of the diagnosis of acromegaly, it would be important to keep in mind the following conditions that could be related to a subtle acromegaly in its beginnings:

- Acral enlargement (hands and feet), that is a universal sign of the disease [5,17,49].
- Presence of a suspicious phenotype (whose definition is left to the doctor's judgment) [14,19].
- Radiological findings in asymptomatic patients (pituitary incidentalomas) [18].
- Hirsutism (hyperandrogenism) [29].
- Menstrual irregularities (PCOS) [25].
- Presence of 2 or more comorbidities associated with acromegaly [17,22] (HBP recently diagnosed or difficult to control [20,22], newly diagnosed diabetes [43,52], diffuse joint pain or carpal tunnel syndrome [51], dental alterations, malocclusion, diastema [33,53].

Conclusion

In conclusion, this set of evidence emphasizes that the importance of early diagnosis of acromegaly is unquestionable, because there is a significant delay in diagnosis, that associated comorbidities usually appear in late stages and that their treatment increases the overall costs of care.

Conflict of Interest

Authors declare no conflicts of interest.

Bibliography


3. European Commission Communication on Rare Diseases. EC Regulation on Orphan Medicinal Products.


17. Rosario PW and Calsolari MR. "Screening for acromegaly in adult patients not reporting enlargement of the extremities, but with arterial hypertension associated with another comorbidity of the disease". *Arquivos Brasileiros de Endocrinologia and Metabolologia* 58.8 (2014): 807-811.


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49. Rosario PW and Calsolari MR. "Screening for acromegaly by application of a simple questionnaire evaluating the enlargement of extremities in adult patients seen at primary health care units". Pituitary 15.2 (2012): 179-183.


