ISSN 1669-9106

SPECIAL ARTICLE

MEDICINA (Buenos Aires) 2018; 78: 83-85

ACROMEGALY: A RARE DISEASE?

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Abstract Acromegaly is generally considered a benign and uncommon disease. However, some recent data bring support to the idea that it is more frequent than previously thought. Besides, acromegaly can significantly shorten the length of life due to its cardiovascular and metabolic complications. Since its clinical signs are insidiously progressive for many years, there is a considerable delay in its detection. Usually, many different specialists have been consulted before reaching diagnosis of acromegaly. Those specialists include cardiologists, pulmonologists, dentists, rheumatologists, and diabetes specialists. Possible means to achieve earlier detection are based on increasing awareness of doctors and the public in general. In this paper, the author analyzes the factors related to delayed diagnosis and the potential ways to ameliorate awareness of the disease with particular attention to screening procedures.

Key words: acromegaly, pituitary tumors, rare diseases, screening

Resumen ***¿Es la acromegalia una enfermedad rara?*** Existe la idea generalizada de que la acromegalia es una enfermedad benigna e infrecuente. Sin embargo, el paciente acromegálico ve comprometida su vida a causa de complicaciones cardiovasculares y metabólicas. Por otra parte, trabajos recientes muestran que su frecuencia parece mucho mayor que lo supuesto previamente. Dado que los signos y síntomas de la enfermedad se instalan lenta e insidiosamente, existe una demora considerable en su diagnóstico. Habitualmente, los pacientes han consultado diversos especialistas antes de que el trastorno sea detectado. Los mismos incluyen cardiólogos, neumonólogos, odontólogos, reumatólogos y diabetólogos. Un camino posible para lograr una detección temprana es el incremento del grado de concientización de los médicos y de la comunidad. En este artículo se analizan los factores vinculados al retraso diagnóstico y los medios posibles para mejorar el conocimiento y detección precoz de la enfermedad.

Palabras clave: acromegalia, tumores pituitarios, enfermedades raras, detección

Frequently, when I start a presentation on acromegaly I ask the attending doctors: "*How many of you have ever seen in the street, subway or at an airport someone who seems to be an acromegalic person? If positive, raise your hands*" The usual response is many risen hands. So, is acromegaly such a rare disease? The disease is mostly caused by a pituitary adenoma which overproduces growth hormone (GH) in a pulsatile manner, resulting in increased secretion of insulin growth factor 1 (IGF 1). The burden of acromegaly is due to the development of associated comorbidities which are linked to delayed diagnosis in many cases. An earlier diagnosis would allow for earlier initiation of appropriate treatment, leading to more successful disease management and better outcomes.

Received: 4-XI-2017 Accepted: 26-II-2018

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Epidemiology

A rare disease has been defined in Europe as a disease which affects less than 1 in 2000 persons. There are around 6000 rare diseases, most of them of genetic origin (~ 80%), and ~ 50% presenting in childhood. Acromegaly, mostly diagnosed in adult people, makes part of the list[1].

From a classic epidemiological point of view, it has been a common place to say that acromegaly has an estimated prevalence of 40 to 70 per million in the general population[2, 3] with an annual incidence of 3 to 4 new cases per million inhabitants[4]. Some countries have developed registries of acromegaly and extrapolated from them the prevalence of the disorder. Indeed, that work has been carried out mainly in European countries such as Spain, Germany, Belgium, Italy and Denmark[5-9]. To the best of my knowledge, the only non-European registry published is the Mexican registry which is the largest one up to now, with 2057 registered cases[10]. The estimated prevalence of the disease derived from those databases oscillates between 18 to 39 cases per million inhabitants, clearly below the classical estimation of 40-70 per million. A recent

analysis of Lavrentaki et al. suggests that the prevalence and incidence of this condition is 2.8-13.7 cases per 100000 people and 0.2-1.1 cases/100000 people/year, respectively[11]. This surely reflects a great level of sub diagnosis of acromegaly, since those figures depend on the diagnosed (declared) cases and not on a systematic search for the disease. The panorama could be even more complex in big countries with an uneven distribution of medical resources and skills. On the other hand, some publications have shown that pituitary adenomas may be more frequent than previously thought, including a prevalence of acromegaly of around 100-130 cases per million inhabitants[12]. A systematic screening of acromegaly in Germany, through IGF 1 determinations performed at the primary care level of patients of the general population, found a prevalence of biochemical acromegaly even higher (1043 per million)[13]. Finally, a recent publication coming from Brazil gives a prevalence of 300 cases per million inhabitants, not as high as in the German study but still higher than the classical estimations[14].

Diagnosis of acromegaly is delayed

As with other infrequent diseases, misinterpretation of common symptoms can hide the diagnosis of acromegaly, since patients consult for diverse reasons to cardiologists, pulmonologists, dentists, rheumatologists, diabetes specialists, etc. who frequently are not aware of this possibility, leading to misdiagnosis and delayed treatment. The lack of scientific knowledge and quality information on the disease results in a delay in diagnosis which has been estimated in around 8 years. Acromegaly is a disabling condition and the patient's quality of life is affected by the chronic, progressive, degenerative, and frequently life-threatening aspects of the disease. In addition, this also results in heavy social and financial burdens on patients. One common misconception in many cases is that acromegaly is a chronic disfiguring disease which does not compromise the life of patients. Nothing farther from the truth. It has been clearly demonstrated that the curve of survival of non-treated acromegalic persons who bear elevated levels of GH and/or IGF-1 is significantly worse than in the general population of New Zealand[15]. Moreover, some associated morbidities as diabetes and hypertension imply an even worse prognosis[16]. The curve of mortality of acromegalics can be reverted to normal by good control of the disease[15]. Although with some limitations, this is now possible in most cases because of the extraordinary development of different modalities of therapy including advances in microscopic and endoscopic transsphenoidal pituitary surgery, highly collimated radiosurgical procedures with gamma knife or linear accelerator and advances in pharmacotherapy with D_2 receptor agonists (cabergoline), somatostatin analogs (octreotide, lanreotide, pasireotide) and a growth hormone receptor antagonist (pegvisomant)[17]. Besides, new drugs are in the investigating bench which foretells a promising future for pharmacological management of this disease[18]. Nevertheless, even if the patients are "cured" (that is, if they show normalization of biochemical parameters), joint aches and deformities, diabetes, and self-consciousness about their appearance may lead to psychological distress, negative impact on the quality of life[19-21].

In summary, we can say about acromegaly that: a) albeit being rare, it is a more frequent disease than previously thought, b) it is a disorder associated to different morbidities, d) it can significantly shorten the probability of survival, c) there are effective therapies that can control the disease, and e) many cases are frequently overlooked by physicians who are consulted for different reasons. The last item deserves a special attention. Indeed, many factors contribute to the lack of awareness of doctors about acromegaly: a) in many Schools of Medicine all over the world, not only in underdeveloped but also in developed countries, infrequent diseases are excluded from the study programs, b) doctors do not diagnose what they do not know, c) health authorities and professional associations do not push for diffusion of knowledge on acromegaly (same for many other infrequent diseases). As a result, acromegaly remains largely under-recognized. This was also the conclusion of a study on 324 patients showing that clinical, biochemical and tumor size characteristics at diagnosis remained unchanged from the period 1981-1994 compared to the period 1995-2006 revealing that doctors were still not more aware of the early signs of the disease[22].

How to make diagnosis earlier?

The advantages of an earlier diagnosis are suggested in a recent publication by a group of Japanese investigators[23]. In a recently published paper, we thoroughly analyzed and discussed how to proceed to make earlier diagnosis, avoid complications, reduce mortality and estimate more accurately the real prevalence of acromegaly[24]. We arrived at the conclusion that the best way is through systematic screening techniques, taking into consideration some related items. They have to be preceded by awareness campaigns oriented to inform and sensitize the population and doctors about the problem. Concerning the population, this can be done by different means: interviews in the radio and on TV broadcasts, TV and cinema spots, articles in newspapers and magazines, a web page. As for doctors, the usual means comprises classical courses, teleconferences, written and digital material. Once this phase is completed, the second step could be the implementation of a screening program. Usually, programs are focused on screening for frequent diseases such as breast, prostate or colorectal cancer in subjects who do not present signs or symptoms. Among others items, the condition to be

screened: 1) should be an important health problem, 2) there should be a treatment available for it, 3) facilities that allow diagnosis and treatment should be available, 4) there should be a ''latent'' stage of the disease, 5) there should be a test or examination currently available for the condition, 6) the test should be acceptable to the population, 7) the natural history of the disease should be adequately understood, 8) there should be an agreed policy on whom to treat[25]. Generally, that kind of screening is called "mass" screening[26]. On the other hand, a "targeted" screening is the one applied only to certain previously well-defined populations. In the case of acromegaly, the "targeted" type could be more acceptable and cost/effective. The best approach would be probably to screen on the basis of phenotypic alterations in patients at risk, i.e. facial or acral changes in subjects having type 2 diabetes, sleep apnea, insulin resistance, carpal tunnel syndrome, artrhosis, or hypertension with cardiac hypertrophy. In those targeted subjects the best test for screening would be a measurement of serum IGF 1 standardized by age[27]. However, there are some limitations to be considered, which include the possibility of false positive or negative results leading to over diagnosis or sub diagnosis. In the face of an altered result, the patient should be referred to a specialized endocrinologist. When discussing the feasibility of conducting a screening program, we agreed that it would be prudent to implement a pilot study during a limited period, in a given region of a given country and to evaluate the results before extending the program to other Latin American countries. The last question, as yet not answered was: Who will pay for the costs…?

Conflict of interest: The author has been speaker, received grants for investigation and travel and participated in different studies on the subject of this paper from Novartis, Sanofi Aventis-Ipsen, Pfizer and Química Montpellier.

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