Acromegaly: 'You must know it to think of it'

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Abstract

Acromegaly is a debilitating and disfiguring chronic disease, which occurs in both sexes at any age, associated with multiple comorbidities and increased mortality. It is typically caused by a GH-secreting pituitary adenoma that promotes exposure of body tissues to increased concentrations of GH and IGF-I. The diagnosis of acromegaly is still made very late in a substantial number of patients when the disease is already in advanced stages. An epidemiological study from Sweden has elegantly demonstrated that the longer the diagnostic delay in acromegaly, the higher the number of comorbidities. Moreover, about 25% of the Swedish patients had 10 years or more of diagnostic delay and in this group mortality rate was significantly increased. These results reinforce the importance of shortening the latency period between disease onset, diagnosis and treatment to improve patient outcomes. This commentary article discusses strategies to be embraced by the endocrine community to allow early identification of acromegaly among public and health professionals, as internists, primary care clinicians, different specialists and dentists are the first point of contact for most of the patients. We emphasize that acromegaly should be presented as a sporadic, rather than rare, insidious disease, meaning that there is a considerable chance for health professionals to see a patient with acromegaly throughout their careers. The motto 'you must know it to think of it' is advocated in awareness efforts to reduce time to diagnosis, which results in lower rates of morbidity and mortality and might positively impact healthcare costs.

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Acromegaly is a debilitating and disfiguring chronic disease, which occurs in both sexes at any age, and is associated with metabolic, cardiovascular, osteoarticular, respiratory, neoplastic and gastrointestinal complications and increased mortality. The disease is typically caused by a GH-secreting pituitary adenoma resulting in a continuous and prolonged exposure of body tissues to increased GH and IGF-I concentrations. In this century, the natural history of acromegaly has been modified and mortality rates have decreased due to great advances in our knowledge of its pathophysiology, better control of comorbidities and multimodal treatment approaches involving surgery, radiotherapy and medication. Nevertheless, the diagnosis is still made very late in a

substantial number of patients when the disease is already in advanced stages (1, 2).

In a recent issue of the *European Journal of Endocrinology*, Esposito *et al.* (3) present an important message about the impact of diagnostic delay in acromegaly on morbidity and mortality rates. Using data collected between 2001 and 2013 from the Swedish National Patient Registry, they identified a group of 603 patients with acromegaly and defined diagnostic delay as the time between the first registered comorbidity and the diagnosis of acromegaly. The comorbidities were clustered into eight disease categories. In their study, no delay (<1 year) was recorded in 36% of the cohort, between 1–5 years in 23%, between 5–10 years in 17% and ≥10 years in 24%. Only 4% of the

patients were free of comorbidities during the entire period of the study. They observed that number of comorbidities was higher in patients with longer diagnostic delay and that increased mortality was only observed in patients with the longest diagnostic delay.

A potential confounding factor in the results of the Swedish study is that several comorbidities included in the analyses are age-related chronic diseases. The authors considered that age at diagnosis had no major influence in the results, as the findings were similar when the analysis were performed for three subgroups of patients: younger than 45 years, between 45–60 years and older than 60 years. Nevertheless, for each category of diagnostic delay there was a clear and expected increase in the number of comorbidities at diagnosis and at any time with advancing age. They also noted a higher number of complications and a tendency to a longer diagnostic delay in women than in men. Again, this could be influenced by age-related comorbidities, as women can be 7 years older than men at diagnosis of acromegaly (4). However, age at diagnosis and at first comorbidity did not show sex difference in the Swedish cohort, which suggests that consequences of diagnostic delay are really worse in acromegaly women, regardless of age. Interestingly, the most frequent comorbidities were neoplasms, cardiovascular and musculoskeletal diseases, which differ from the data compiled from 19 national acromegaly registers, in which diabetes and hypertension predominated (4). Noteworthy, the ‘neoplasms’ category involved both malignancies and benign tumors, such as thyroid nodules, nasal, larynx and gastrointestinal polyps, impeding any interpretation of the relationship between cancer and diagnostic delay in acromegaly (5). In addition, the longest diagnostic delay was noticed for neuropsychiatric diseases and the shortest diagnostic delay for local effects of the pituitary adenoma. This seems plausible since headache, visual field defects and hypopituitarism are problems more indicative and specific of a pituitary disease than nonspecific manifestations, such as mental disorders, depression and epilepsy, which were grouped in the study as neuropsychiatric comorbidities. In fact, the latter disorders are not commonly listed as complications associated with acromegaly.

This Swedish epidemiological study raises important issues worth discussing. I well remember that, in medical school, a teacher once told me that ‘the most important factor in making a diagnosis in a rare disease is to think about it’. But to think about it, we must know that the disease exists! Conceptually, acromegaly is a rare disease, which by definition includes any condition affecting not

more than 50 persons in 100 000 inhabitants as established in 1999 by the European Union Regulation on orphan medicinal products (6). This definition involves over 6000 medical entities, with the number of affected individuals varying from disease to disease. Most people represented by the statistics in this field suffer from conditions affecting hundreds or only a few dozen patients (6). The prevalence of acromegaly has varied widely between different European studies, but most recent series from the United Kingdom, Malta and Iceland have reported prevalence of 9.0, 12.4 and 13.3 per 100 000 individuals, respectively, which represents between 46 000 and 68 000 acromegaly patients in Europe (1, 2). Likewise, the global incidence has tripled in the last decades, achieving 1.1 cases per 100 000 individuals in most recent reports (1). Similar numbers are likely seen worldwide and they are certainly not negligible. Therefore, I prefer to teach my students that acromegaly is a sporadic (instead of rare), insidious disease that represents a diagnostic challenge since years go by without it being recognized. I also explain to them that we, endocrinologists, are responsible for the care of these patients, but we are rarely the first point of contact with most of them. In 40% of cases, the diagnosis is suspected by an internist and in the remaining by different specialists (gynecologists, rheumatologists, neurologists, ophthalmologists, dental surgeons etc.) depending on the patient’s complaints (2). In few circumstances it is the patient, a friend or a family member that suspects that something is wrong. In a study conducted in New Zealand, two-thirds of 81 patients with acromegaly felt that an earlier diagnosis was possible according to the evolution of their acral changes, alterations in facial features and oral symptoms (7). It seems clear from these numbers that there is a considerable chance for a physician or a dentist to face a patient with acromegaly at some point in their careers, meaning that they should know that acromegaly exists. This realization is essential to reduce diagnostic delay.

Most patients with acromegaly develop florid physiognomic features over the years, including exaggerated growth of the hands and feet, gigantism, prominence of the brow, enlargement of the nose and lips, soft-tissue hypertrophy, prognatism and macroglossia. In general, these manifestations evolve gradually, meaning that neither the patient nor their families appreciate these physical changes as a real illness until a more disturbing complication arises (1, 2). In doubtful cases, it might help to look at older photos of the patient to establish the diagnosis. Sometimes the diagnosis can be suspected by careful observation of the patient’s facial appearance or

when we shake hands with them. Despite these noticeable characteristics, anecdotal stories about patients presenting with typical physical changes who have spent years in consultations, exams and even underwent surgeries, without the diagnosis being suspected, are fairly common. The unfamiliarity with acromegaly can be exemplified by one-fourth of the Swedish patients being diagnosed after 10 or more years of active disease (3), increasing the patient's risk of having larger pituitary adenomas, several comorbidities, depression, body image distortion, social withdrawal and shorter survival (1, 2, 3). Recent data compiled from four European cohorts demonstrated a median duration of symptoms until diagnosis of acromegaly of 5 years (8). However, these studies were not specifically designed to evaluate diagnostic delay and the data was mainly based on interviews and questionnaires. In this aspect, the best news from the study by Esposito *et al.* (3) in this issue of the *European Journal of Endocrinology* were that 36% of patients had no diagnostic delay at all (less than 1 year interval) and that the median diagnostic delay was only 3.3 years (range 0–25.9 years; mean 5.5 years). This represents a substantial decrease in time compared to that reported in several publications in the last century and almost 2 years lower than the median delay of diagnosis found in the most recent reports (1, 2, 6). However, it is possible that diagnostic delay was underestimated in the Swedish cohort as it was calculated from the first comorbidity of acromegaly and not from the first apparent physical sign or symptom of the disease. Regardless of any possible bias, it is important to note that comorbidities were documented even in the subgroups of patients with no diagnostic delay or in those with more precocious detection of the disease. On average, two comorbidities were already present at diagnosis and four developed over time, with the number of comorbidities increasing with the extension of diagnostic delay (3). Hence, the message is clear: time is critical to improve outcomes of acromegaly patients!

The underlying reasons for higher incidence and prevalence and lower diagnostic delay observed in contemporary studies of patients with acromegaly might be related to the better performance of novel GH and IGF-I assays and greater availability and widespread use of imaging, with some patients presenting with apparently normal GH levels or having been initially diagnosed with a pituitary incidentaloma (9, 10). It may also represent a true increase in the incidence or be related to increased awareness of acromegaly among patients and healthcare professionals derived from education programs, patient

support groups, social media and web-driven information (1, 2). It is worth highlighting, however, that this panorama varies from place to place and that diagnostic delay of acromegaly is still a major concern in many settings, representing a considerable medical, social and economic burden. Shortening the latency period between disease onset, diagnosis and treatment is critical to improve patient's health, productivity and quality of life and to reduce the costs associated with treatment of acromegaly and its comorbidities (11). New strategies, as the use of software capable of detecting subtle physical changes over time, clinical scoring systems and deep learning algorithms, offer a future opportunity to aid in the early identification of acromegaly (1, 2). Meanwhile, continuous efforts need to be made by the endocrine community to increase disease awareness in the general population and to teach medical students and health workers 'how to recognize a patient with acromegaly', highlighting that acromegaly should be considered a sporadic, rather than a rare, insidious disease. They should be warned that reducing diagnostic delay in acromegaly improves lives and reduces healthcare costs.

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References

- Colao A, Grasso LFS, Giustina A, Melmed S, Chanson P, Pereira AM & Pivonello R. Acromegaly. *Nature Reviews: Disease Primers* 2019 **5** 20. (<https://doi.org/10.1038/s41572-019-0071-6>)
- Abreu A, Tovar AP, Castellanos R, Valenzuela A, Giraldo CM, Pinedo AC, Guerrero DP, Barrera CA, Franco HI, Ribeiro-Oliveira Jr A, *et al.* Challenges in the diagnosis and management of acromegaly: a focus on comorbidities. *Pituitary* 2016 **19** 448–457. (<https://doi.org/10.1007/s11102-016-0725-2>)
- Esposito D, Ragnarsson O, Johannsson G & Olsson D. Prolonged diagnostic delay in acromegaly is associated with increased morbidity and mortality. *European Journal of Endocrinology* 2020 **182** 523–531. (<https://doi.org/10.1530/EJE-20-0019>)
- Maione L & Chanson P. National acromegaly registries. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2019 **33** 101264. (<https://doi.org/10.1016/j.beem.2019.02.001>)
- Boguszewski CL & Ayuk J. MANAGEMENT OF ENDOCRINE DISEASE: Acromegaly and cancer: an old debate revisited. *European Journal of Endocrinology* 2016 **175** R147–R156. (<https://doi.org/10.1530/EJE-16-0178>)

- 6 Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, Murphy D, Le Cam Y & Rath A. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *European Journal of Human Genetics* 2020 **28** 165–173. (<https://doi.org/10.1038/s41431-019-0508-0>)
- 7 Zarool-Hassan R, Conaglen HM, Conaglen JV & Elston MS. Symptoms and signs of acromegaly: an ongoing need to raise awareness among healthcare practitioners. *Journal of Primary Health Care* 2016 **8** 157–163. (<https://doi.org/10.1071/HC15033>)
- 8 Lavrentaki A, Paluzzi A, Wass JA & Karavitaki N. Epidemiology of acromegaly: review of population studies. *Pituitary* 2017 **20** 4–9. (<https://doi.org/10.1007/s11102-016-0754-x>)
- 9 Boguszewski CL, de Castro Musolino NR & Kasuki L. Management of pituitary incidentaloma. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2019 **33** 101268. (<https://doi.org/10.1016/j.beem.2019.04.002>)
- 10 Butz LB, Sullivan SE, Chandler WF & Barkan AL. ‘Micromegaly’: an update on the prevalence of acromegaly with apparently normal GH secretion in the modern era. *Pituitary* 2016 **19** 547–551. (<https://doi.org/10.1007/s11102-016-0735-0>)
- 11 Ben-Shlomo A, Sheppard MC, Stephens JM, Pulgar S & Melmed S. Clinical, quality of life, and economic value of acromegaly disease control. *Pituitary* 2011 **14** 284–294. (<https://doi.org/10.1007/s11102-011-0310-7>)

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