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Published in:
Polish Archives of Internal Medicine

DOI (link to publication from Publisher):
10.20452/pamw.16270

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

EDITORIAL

Sex differences in acromegaly

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Acromegaly is a rare systemic disease characterized by hypersecretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1).[1] Several diseases show sex dimorphism, and as far as pituitary disease is concerned, prolactinomas occur more frequently in women than in men. However, the question as to whether acromegaly is influenced by sex is still debated.[2]

During the last decades, the focus on acromegaly has been increasing and several diagnostic improvements have evolved, such as new imaging techniques and more accurate GH and IGF-1 assays as well as modern medical treatment modalities and increasingly advanced surgery techniques.[3] This has contributed to the growing prevalence of acromegaly but also to a change in disease characteristics. Before the 1990s, the prevalence of acromegaly was most often reported to range between 40 and 60 cases per 1 million persons; however, in more recent studies the prevalence has been shown to be as high as 80 to 100 per 1 million persons.[1,4] A time-dependent shift toward a milder phenotype of acromegaly and a change in sex distribution from initial female predominance to a more even sex balance was observed in a Danish cohort study.[5] This is in keeping with recent population-based surveys showing a higher overall disease prevalence and a more even sex distribution.[1] Female predominance has been reported, although most of the observations originate from registries demonstrating a low disease prevalence, which could indicate underdiagnosis of a subgroup of patients, including older men with mild acromegaly.

Due to an insidious disease onset, a diagnostic delay of 5 to 10 years is common, although this period has been reported to be decreasing.[6] In the study by Bogusławska et al,[7] published in the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), no association between sex and diagnostic delay was reported; however, according to a recent meta-analysis, female patients with acromegaly are older at the time of diagnosis and also experience a longer diagnostic delay.[5] This could be related to sex-specific differences in the clinical presentation, where the most common symptoms leading to the initial diagnosis of acromegaly are growth changes and headaches.[8] Men seem prone to classic physical changes, such as prognathism and growth of hands and feet,[9] whereas women are more likely to show symptoms such as headache and musculoskeletal pain.[10] Moreover, symptoms such as sweating and amenorrhea could be interpreted as menopausal in female patients, which could cause a delay of the diagnosis.[8]

A sex-specific difference in the relationship between GH and IGF-1 in patients with active acromegaly, namely, a lower IGF-1 concentration in female patients is well known,[5] and was also observed in the study by Bogusławska et al.[7] The size of adenoma was found to be similar in both sexes, which is in accordance with a recent meta-analysis.[6] The low IGF-1 levels in female patients have been ascribed to a suppressive effect of circulating estrogen on hepatic IGF-1 production, although additional underlying mechanisms may exist. In a recent study focusing on postmenopausal patients with controlled acromegaly, the same relationship with relatively higher GH levels seemed to persist. This is in line with observations from studies focusing on biochemical discordance, where women with acromegaly were prone to exhibiting elevated GH levels and normalized IGF-1 concentration.[11] The mechanism driving the sex differences in GH secretion in postmenopausal women could involve a paracrine action of estrogen on the central stimulation of GH secretion. This mechanism is supported by the observation that a blockade of estrogen action by tamoxifen reduces GH secretion in postmenopausal women but not in men.[12] It has been proposed that local estrogen in the pituitary is mainly derived from local aromatization of testosterone; however, further studies are needed to explore the underlying mechanisms and the potential clinical implications.[12]

Most acromegaly-related complications show no sex-specific differences[1]; however, some studies showed a greater prevalence of hypertension,

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Received: May 31, 2022.
Accepted: June 1, 2022.
Published online: June 29, 2022.
Pol Arch Intern Med. 2022;
132 (6): 16270
doi:10.20452/pamw.16270

diabetes mellitus, and impaired glucose metabolism in women.[1,2,13] At the time of acromegaly diagnosis, women exhibit a worse metabolic profile than men, despite similar GH and IGF-1 values. This includes insulin resistance and several features of metabolic syndrome ascribed to visceral fat dysfunction.[14] Insulin resistance in acromegaly is linked to the lipolytic effects of GH, which cause insulin resistance in both the muscle and fat.[14] A recent study suggested a subtle sex difference in the metabolic regulation, since women showed higher fasting free fatty acid levels and a higher insulin response to glucose during the oral glucose tolerance test than men, despite comparable IGF-1 levels.[9]

Women with acromegaly were shown to have a lower socioeconomic status than men with acromegaly when compared with a sex-matched control cohort. This included an increased use of social security benefits, a higher risk of early retirement, a lower frequency of being registered in a partnership, as well as a lower frequency of parenthood.[15] The worse outcome in women had begun already during a 5-year period before the acromegaly diagnosis was made.[15] Several factors may contribute to this difference, with a lower number of births possibly due to reduced fertility related to hypogonadism. Self-reported psychological issues, such as negative body image and problems with personal relations have been reported in some quality-of-life questionnaires and may negatively impact parenthood rates.[2] In contrast, male patients did not show a significant reduction in cohabitation and parenthood rates, as compared with the reference population.[15]

In conclusion, sex differences in acromegaly are real and warrant the attention of treating physicians.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST JD received unrestricted research grants and lecture fees from Pfizer and IPSEN. Other authors declare no conflict of interest.

HOW TO CITE Dal J, Rosendal C, Nielsen EH. Sex differences in acromegaly. Pol Arch Intern Med. 2022; 132: 16270. doi:10.20452/pamw.16270

REFERENCES

1 Dal J, Feldt-Rasmussen U, Andersen M, et al. Acromegaly incidence, prevalence, complications and long-term prognosis: a nationwide cohort study. Eur J Endocrinol. 2016; 175: 181-190.

2 Lenders NF, McCormack AI, Ho KKY. Management of endocrine disease: does gender matter in the management of acromegaly? Eur J Endocrinol. 2020; 182: R67-R82.

3 Melmed S, Bronstein MD, Chanson P, et al. A consensus statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018; 14: 552-561.

4 Dal J, Skou N, Nielsen EH, et al. Acromegaly according to the Danish National Registry of Patients: how valid are ICD diagnoses and how do patterns of registration affect the accuracy of registry data? Clin Epidemiol. 2014; 6: 295-299.

5 Dal J, Skov BG, Andersen M, et al. Sex differences in acromegaly at diagnosis: a nationwide cohort study and meta-analysis of the literature. Clin Endocrinol (Oxf). 2021; 94: 625-635.

6 Petrossians P, Daly AF, Natchev E, et al. Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) database. Endocr Relat Cancer. 2017; 24: 505-518.

7 Bogusławska A, Gilis-Januszewska A, Godlewska M, et al. Sex and age differences among patients with acromegaly. Pol Arch Intern Med. 2022; 132: 16232.

8 Kreitschmann-Andermahr I, Siegel S, Kleist B, et al. Diagnosis and management of acromegaly: the patient's perspective. Pituitary. 2016; 19: 268-276.

9 Dal J, Rosendal C, Andersen MS, et al. Sex difference in patients with controlled acromegaly – a multicentre survey. Clin Endocrinol (Oxf). 2022 Apr 26. [Epub ahead of print].

10 Caron P, Brue T, Raverot G, et al. Signs and symptoms of acromegaly at diagnosis: the physician's and the patient's perspectives in the ACRO-POLIS study. Endocrine. 2019; 63: 120-129.

11 Dal J, Klose M, Heck A, et al. Targeting either GH or IGF-I during somatostatin analogue treatment in patients with acromegaly: a randomized multicentre study. Eur J Endocrinol. 2018; 178: 65-74.

12 Birzniece V, Ho KKY. Sex steroids and the GH axis: implications for the management of hypopituitarism. Best Pract Res Clin Endocrinol Metab. 2017; 31: 59-69.

13 Ciresi A, Amato MC, Pivonello R, et al. The metabolic profile in active acromegaly is gender-specific. J Clin Endocrinol Metab. 2013; 98: 51-59.

14 Arlien-Søborg MC, Dal J, Madsen MA, et al. Reversible insulin resistance in muscle and fat unrelated to the metabolic syndrome in patients with acromegaly. EBioMedicine. 2022; 75: 103763.

15 Dal J, Nielsen EH, Rasmussen UF, et al. Disease control and gender predict the socioeconomic effects of acromegaly: a nationwide cohort study. J Clin Endocrinol Metab. 2020; 105: dgaa405.