Editorial

Let's focus more on regional diversity of acromegaly

Sylvère Störmann^

Department of Medicine IV, University Hospital, LMU Munich, München, Germany

Correspondence to: Sylvère Störmann. Medizinische Klinik und Poliklinik IV, LMU Klinikum, Ziemssenstr. 5, 80336 München, Germany.
Email: sylvere.stoermann@med.uni-muenchen.de.

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Acromegaly is a rare and incapacitating disease that results from over-secretion of growth hormone (GH), mostly due to pituitary tumors. Owing to the GH excess it leads to a vast array of different symptoms affecting virtually every tissue and organ of the human body, potentially causing serious harm (1). Over the past few decades numerous studies have elaborated on epidemiology, natural history, and effects of the different treatment strategies. Many insights have been derived from these studies that now guide clinicians in the diagnostic workup and treatment strategy of their patients with acromegaly (2-4). One drawback, however, is that many of these insights stem from North American and European countries (especially Nordic countries with their excellent registries). No matter how elaborate a study may be, its findings are never fully generalizable. Differences in epidemiology, disease presentation and sometimes even therapy between sexes have been described for various diseases, including acromegaly (5-8). The same holds true for regional or ethnic differences. One such example that has been well-established is the geographic difference in gastric cancer incidence and mortality (9), where incidence rates are highest in Eastern and Central Asia and Latin America. The published estimates on both the incidence and prevalence of acromegaly (including data from several national registries) also offer a wide range: the incidence can be as low as 2/1,000,000/year up to 12 cases per million person-years and the prevalence estimates range from 28 to 137 acromegaly patients per million population. These differences may be attributed to the geographical areas and health systems the data come from (8). We therefore need to acknowledge that beyond regional variation of epidemiology, there may also be a location-dependent disparity of clinical signs and symptoms as well as treatment outcomes of acromegaly.

Yet, as most publications stem from European and North American countries data from other countries remain under-represented, especially from some Asian, many South American, and most African countries. The few published studies allow only small glimpses into the epidemiology and management of acromegaly in these countries (10-15). But even if we were to assume world-wide homogeneity of the disease, every health system has its own peculiarities that directly or indirectly influence the diagnostic and therapeutic approach to diseases and thereby outcomes. Therefore, medical treatments also need to be investigated in the context of their health system and there is an urgent need to learn more about these differences. That means we need so much more data from so many countries.

One such work has now recently been published in the *Annals of Translational Medicine*. In their retrospective analysis of 163 patients with acromegaly, Zhao and colleagues present intriguing real-world data from China (16). The study analyzed octreotide effectiveness in a cohort from the Peking Union Medical College Hospital (PUMCH). A total population of 320 acromegaly patients matched the inclusion criteria of treatment with long-acting octreotide and at least three visits at the hospital during the observation period between 2010 and 2020. However, almost half of these were ruled out due to exclusion criteria, namely irregular treatment, prior treatment with other

^ ORCID: 0000-0002-5465-3491.

somatostatin analogs, lack of baseline information, and need for surgery or radiotherapy during the observation period. In this highly selected study population only 17.8% achieved complete response, defined as insulin-like growth factor I (IGF-I) levels within the age- and sex-matched reference range and basal GH levels inferior to 2.5 ng/mL. Partial response, that is a decrease in GH and/or IGF-I of more than 50% compared to baseline, was observed in 25.2%. Thus, 43% of patients experienced a beneficial effect of octreotide, leaving more than half of the study population to be non-responders.

Many studies have investigated the efficacy of somatostatin analogs in acromegaly and the most common published figure for patients achieving biochemical control on first-generation somatostatin analogs is approximately 55% (17,18). In unselected patients without prior treatment success rates are lower, ranging in the area between 20% and 40% (19). The even lower response rate of the selected cohort of Zhao and colleagues surprises. Even compared to data from their geographically close neighbors in Japan the success rate seems remarkably low: Oki *et al.* investigated the efficacy and safety of octreotide long-acting release (LAR) in Japanese patients with acromegaly in whom 36.7% achieved complete remission and a further 36.7% at least partial remission (20). This deserves further consideration.

Firstly, the patients in the cohort received a fixed dose of 20 mg octreotide LAR every 4 weeks without dose up-titration. Dose escalation of somatostatin analogs can provide additional biochemical control of acromegaly and is usually well-tolerated (21). But octreotide LAR is expensive and with a price tag around 10,000 Chinese Yuan per single dose (~1,500 USD) many patients couldn't afford this treatment, as the Chinese national medical insurance system didn't cover these expenses until 2018. The inability of most patients to pay for higher doses could have shifted expectations and preferences in terms of an individual cost-benefit ratio. Thereby, alleviation of symptoms may have become a priority defining the benefit of therapy at a cost that could just be handled, while reaching biochemical control (without any perceived immediate benefit to the patient) could have been deemed not worth the extra investment. So instead of aiming for biochemical remission patients found satisfaction in symptom relief accepting continued biochemical activity of acromegaly. Arguably, this is medically inadequate and morally wrong [and probably economically short-sighted given the increased cost of comorbidity in poorly treated acromegaly (22)], but plausible.

There is a high number of patients with prior radiotherapy in the study population: one third of all patients had undergone irradiation. Radiotherapy is typically associated with more severe and therapy-refractory cases of acromegaly, which would explain resistance to somatostatin analogs. According to Zhao and colleagues this is not the case in this cohort. Presumably, the limitations to cover medical cost in China have led to a preponderance of radiotherapy. In developed countries radiotherapy is less frequently used, but it is considered a cost-effective alternative in developing countries with limited resources (23). This raises other important questions: How much of the effect observed in the study is attributable to irradiation? Does the prospect of a therapeutic effect of radiation therapy influence drug prescription or even initiation of medical therapy? In how far has insurance coverage of octreotide therapy changed the use of somatostatin analogs and radiotherapy?

Lastly, some methodological details need to be mentioned as well. The authors chose a GH threshold of 2.5 ng/mL at random basal measurement to discern patients with biochemically controlled versus active acromegaly. This relies on the 2013 Chinese guidelines on acromegaly which were chosen due to the retrospective nature of the study. The recent update of these guidelines from 2021 recommends IGF-I levels within the age- and sex-matched reference range and random GH levels below 1.0 ng/mL to define remission (24). Assay-specific Chinese reference ranges for the interpretation of IGF-I are available and were used in the study (25). But the use of the less stringent 2.5 ng/mL GH threshold classifies more patients as responders compared to using 1.0 ng/mL. Conversely, the response rate would turn out even lower if modern criteria for cure were applied. Furthermore, due to some of the exclusion criteria certain patients were not included in the analysis despite an intention-to-treat (such as those patients that required further surgery during the observation period). Essentially, this means that response rates would be even lower if those patients were to be included.

At the core of diagnostics and treatment of every disease is the structural framework in which it is embedded. Studies such as the one by Zhao and colleagues demonstrate how important and considerable the influence of health systems and local habits are on outcome data. In order to advance the field even further, we'll have to learn more about the regional diversity of acromegaly.

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