Göteborg, 2022

Acromegaly

Mortality, Morbidity and Treatment Patterns

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs Universitet kommer att offentligen försvaras i Sahlgrens aula,
Sahlgrenska Universitetssjukhuset, Blå stråket 5, Göteborg,
den 3 juni 2022, kl 9:00

av **Daniela Esposito**

Fakultetsopponent:
Professor Diego Ferone
University of Genoa, Genoa, Italy

Avhandlingen baseras på följande delarbeten

I. **Decreasing mortality and changes in treatment patterns in patients with acromegaly from a nationwide study**
Esposito D, Ragnarsson O, Granfeldt D, Marlow T, Johannsson G, Olsson DS.
European Journal of Endocrinology, 2019 180 (2):X1-X3.
European Journal of Endocrinology, 2018 178 (5):459-469

II. **Prolonged diagnostic delay in acromegaly is associated with increased morbidity and mortality**
Esposito D, Ragnarsson O, Johannsson G, Olsson DS.
European Journal of Endocrinology, 2020 182 (6):523-531

III. **Incidence of benign and malignant tumors in patients with acromegaly is increased: a nationwide population-based study**
Esposito D, Ragnarsson O, Johannsson G, Olsson DS.
The Journal of Clinical Endocrinology & Metabolism, 2021 106 (12):3487-3496

IV. **Impact of diabetes on morbidity and mortality in patients with acromegaly**
Esposito D, Olsson DS, Franzén S, Gudbjörnsdottir S, Miftaraj M, Nåtman J, Svensson A-M, Johannsson G.
Manuscript

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ABSTRACT

Background: Acromegaly is a systemic disease associated with multiple comorbidities. The clinical characteristics of acromegaly develop insidiously over several years and the diagnosis is usually delayed. Progress has been made in diagnostic and treatment strategies for acromegaly but whether this has led to an improvement in survival remains to be shown. The aim of this thesis was to determine mortality, morbidity, and the impact of diagnostic delay and other comorbidities on long-term outcome in patients with acromegaly.

Methods: Patients with acromegaly were identified in the Swedish National Patient Registry, which was linked to five other national registries via personal identification numbers. To study mortality and morbidity in acromegaly, standardised mortality ratios (SMRs) or standardised incidence ratios (SIRs) were calculated with 95% confidence intervals (CIs) using the Swedish population as reference. To study the impact of diabetes on outcomes, patients with acromegaly and associated diabetes were compared with those without diabetes using Cox regression analysis.

Results: Mortality in patients with acromegaly was increased (SMR 1.3, 95% CI 1.2–1.5) and was mainly ascribed to circulatory diseases. The diagnosis of acromegaly was delayed by a mean (SD) of 5.5 (6.2) years [median 3.3 (0.0–25.9)] and diagnostic delay had an important impact on outcome. The number of comorbidities was higher with longer diagnostic delay and mortality was significantly increased only in patients with diagnostic delay ≥10 years. Patients with acromegaly also had increased incidence of both benign (SIR 2.4, 95% 2.1–2.7) and malignant tumours (SIR 1.3, 95% 1.1–1.5). Specifically, the incidence of colorectal and anal cancer (SIR 1.5, 95% CI 1.0–2.2) as well as renal and ureteral cancer (SIR 4.0, 95% CI 2.3–6.5) was increased, while the incidence of thyroid, lung, brain, breast and prostate cancer was not. However, mortality due to malignancy was not increased. The presence of diabetes was associated with a worse outcome. In patients with acromegaly and associated diabetes, overall mortality was increased by 60% (hazard ratio [HR] 1.6, 95% CI 1.1–2.2), cardiovascular mortality 2-fold (HR 2.1, 95% CI 1.1–4.1) and the risk of cardiovascular diseases by 50% (HR 1.5, 95% CI 1.2–1.8) compared with patients without diabetes.

Conclusions: Despite improvements in the management of acromegaly, prognosis is still poor, especially in patients diagnosed with a longer delay and in those with associated diabetes. These findings highlight the importance of early diagnosis and the need of optimising care of acromegaly and its associated complications to improve long-term outcome.

Keywords: acromegaly, morbidity, mortality, cardiovascular disease, diagnostic delay, cancer, diabetes

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