

# Clinical challenges in Cushing's syndrome

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs Universitet kommer att offentligen försvaras i Hjärtas Aula, Sahlgrenska Universitetssjukhuset, Vita Stråket 12, Göteborg, onsdagen den 25 Maj 2022, kl 13:00  
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## Avhandlingen baseras på följande delarbeten

- I. Papakokkinou E, Jakobsson H, Sakinis A, Muth A, Wängberg B, Ehn O, Johannsson G, Ragnarsson O. **Adrenal venous sampling in patients with ACTH-independent hypercortisolism.** *Endocrine.* 2019;66(2):338-348
- II. Papakokkinou E, Johansson B, Berglund P, Ragnarsson O. **Mental fatigue and executive dysfunction in patients with Cushing's syndrome in remission.** *Behav Neurol.* 2015;2015:173653.
- III. Papakokkinou E, Olsson DS, Chantzichristos D, Dahlqvist P, Segerstedt E, Olsson T, Petersson M, Berinder K, Bensing S, Höybye C, Edén-Engström B, Burman P, Bonelli L, Follin C, Petranek D, Erfurth EM, Wahlberg J, Ekman B, Åkerman AK, Schwarcz E, Bryngelsson IL, Johannsson G, Ragnarsson O. **Excess morbidity persists in patients with Cushing's disease during long-term remission: A Swedish nationwide study.** *J Clin Endocrinol Metab.* 2020;105(8).
- IV. Papakokkinou E, Piasecka M, Carlsen HK, Chantzichristos D, Olsson DS, Dahlqvist P, Petersson M, Berinder K, Bensing S, Höybye C, Engström BE, Burman P, Follin C, Petranek D, Erfurth EM, Wahlberg J, Ekman B, Åkerman AK, Schwarcz E, Johannsson G, Falhammar H, Ragnarsson O. **Prevalence of Nelson's syndrome after bilateral adrenalectomy in patients with Cushing's disease: a systematic review and meta-analysis.** *Pituitary.* 2021;24(5):797-809.

# Clinical challenges in Cushing's syndrome

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## Abstract

Cushing's syndrome (CS) is caused by prolonged exposure to cortisol excess. CS is associated with cardiovascular diseases, infections, and fractures, as well as with cognitive impairment and affective disorders. This thesis, based on four studies, aimed to investigate various aspects of the management of CS: the diagnostic work-up as well as the morbidity after successful treatment.

A retrospective analysis on the usefulness of adrenal venous sampling (AVS) in patients with cortisol excess and bilateral adrenal lesions or morphologically normal adrenal glands, showed that AVS contributed to the decision-making of the treatment in two out of ten patients (*Paper I*). In a cross-sectional study, patients with CS in remission experienced mental fatigue and had impaired executive function, assessed with the self-administrated Mental Fatigue Scale (MFS) and Trail Making Test (TMT), respectively (*Paper II*). In a nationwide population-based study, excess morbidity was found in patients with pituitary CS (Cushing's disease, CD). A more than 3-fold increased incidence of stroke, thromboembolism, and sepsis was found even in remission compared to the background population (*Paper III*). A systematic review and meta-analysis on patients with CD treated with bilateral adrenalectomy showed that every fourth patient developed progression or new onset of a pituitary tumor (Nelson's syndrome, NS) and every fifth patient received treatment for NS. Also, NS occurred up to four decades after bilateral adrenalectomy (*Paper IV*).

In conclusion, this thesis illustrates that patients with CS have excess morbidity due to stroke, thromboembolism, sepsis as well as cognitive impairment and mental fatigue despite treatment. Also, this thesis highlights the need for life-long follow-up of patients with CS. Despite the major progress achieved in the management of patients with CS, there are still challenges to overcome, both in the diagnostic work-up and treatment.

**Keywords:** Cushing's syndrome, Cushing's disease, cortisol excess, Nelson's syndrome, morbidity, remission, mental fatigue, cognitive function, adrenal venous sampling