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Editorial for Special Issue "Improving Outcome of Cushing's Syndrome-4" (IMPROCUSH-4)

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One-hundred-twelve years after the first report of a patient with Cushing's syndrome (CS), the 22-year-old Minnie G., who happened to be the first patient described by Harvey Cushing in 1912 [1], this disease has proven to be one of the few remaining challenges in clinical endocrinology. Progress in diagnosing and treating Cushing's syndrome has been slow following the first few decades after Cushing's seminal description. Being a true orphan disease with an incidence of 1.5–8.3 patients per year per million technical advances and innovations came mostly as a transfer from more common diseases [2]. Computed tomography, magnet resonance imaging, molecular imaging, advanced genetic techniques also benefitted diagnosis and treatment in CS. A new area started in 2012, when the first drug specifically addressing Cushing's disease was approved by the FDA and EMEA [3]. Since then, five more compounds have marketed, and several more are expected to enter the treatment arena of CS soon.

It was in 2014, that we felt it would be necessary to initiate a focused scientific meeting dedicated to CS. This meeting should summon world experts from all continents and develop collaborative strategies to address the many unmet needs of the disease. The first symposium *Improving Outcome in Cushing's syndrome* (IMPROCUSH) was held in 2014, and it has since become a tradition to have this meeting every two years at the famous Carl Friedrich von Siemens-Stiftung in the vicinity of Nymphenburg Palace in Munich. Over 100 scientists from around the world attended the fourth edition of the IMPROCUSH meeting in June 2023 and discussed a broad spectrum of topics ranging from pathophysiology to treatment.

This special issue includes 7 invited articles summarizing some of the evidence presented in Nymphenburg.

Recent recognition of the impact of cortisol excess on cardiometabolic health has led to more diagnoses of mild forms of CS, particularly in adrenal incidentalomas. The review by Tizianel et al. [4] updates about the diagnostic challenges posed by patients with CS, including typical tricks and traps. It also covers the characterization of functional non-neoplastic hypercortisolism (formerly called pseudo-Cushing), and subtyping of hypercortisolism conditions. It also covers the differential diagnosis of ACTH-dependent forms and new genetic classifications, including adrenal CS, mild autonomous cortisol secretion, and bilateral adrenal adenomas.

Hyperandrogenism in Cushing's syndrome can be a diagnostic challenge due to its overlap with conditions like PCOS. While classical androgens contribute to symptoms, 11-oxygenated C19 androgens (e. g., 11OHA4, 11KT) play a crucial role in CS. These adrenal-specific and potent androgens are physiologically secreted throughout a woman's life and can serve as valuable diagnostic biomarkers in situations of steroid excess and deficiency. Recognizing their importance can improve diagnostic accuracy and clinical management of CS, as pointed out by the article of Nowotny, Braun and Reisch [5].

Pituitary tumorigenesis and particularly the genetic landscape of corticotroph pituitary tumors has evolved in the last 10 years. Somatic mutations in the USP8 gene are most common, particu-

larly in females, while TP53 and ATRX variants are linked to aggressive tumors. Germline defects (e. g., MEN1, CDKN1B, DICER1) are also found in patients with Cushing's disease, though generally rare. The review by Hernández-Ramírez et al. [6] summarizes the genetic drivers, molecular consequences, and clinical consequences of corticotroph tumorigenesis.

In their timely review "*From the First Case Reports to KDM1A Identification: 35 Years of ood (GIP)-Dependent Cushing's Syndrome*" Bouys & Bertherat rap-up newest evidence regarding food-dependent Cushing's syndrome [7]. This is a rare form of hypercortisolism, typically linked to primary bilateral macronodular adrenal hyperplasia (PBMAH) or, less commonly, unilateral adrenal adenomas. It is caused by the aberrant expression of the GIP receptor in adrenocortical cells, leading to cortisol secretion after meals. Recent studies have identified KDM1A gene inactivation as the genetic cause in PBMAH, suggesting genetic screening for food-dependent Cushing's syndrome. Given KDM1A's role as a tumor suppressor, further genetic testing for malignancies is recommended in these patients and their relatives.

Managing CS in older patients is more challenging due to the absence of typical cortisol excess symptoms and the presence of comorbidities. Also, age-related changes in cortisol secretion can affect diagnostic tests, and mortality and quality of life are worse in elderly CS patients. However, there is no consensus on the best treatment for older individuals, and safety data on medical treatments are limited. Zdrojowy-Wełna & Valassi's review [8] summarize the age-related differences in etiology, signs and symptoms, treatment, and outcomes.

Mild autonomous cortisol secretion (MACS) is linked to several comorbidities, with osteoporosis and fractures being particularly prevalent. Recent guidelines define MACS based on serum cortisol levels after a 1-mg dexamethasone test (above 1.8 µg/dL or 50 nmol/L). Previous studies on bone health in adrenal incidentalomas used varying definitions of MACS, leading to inconsistent results on fracture prevalence. The review by Zavatta & Di Dalmazi [9] updates the clinical impact of MACS on fractures and bone health, particularly osteoporosis.

Surgery is the first-line treatment for CS, but may not always be possible or appropriate. In severe cases, steroidogenesis inhibitors offer an alternative to rapidly control hypercortisolism. Recent advances have expanded the understanding and availability of these inhibitors, but large comparative studies are still lacking. Detomas, Deutschbein, and Altieri's review the key characteristics of different steroidogenesis inhibitors and their role in treatment [10].

We hope that the articles in this issue of *Experimental and Clinical Endocrinology & Diabetes* will be informative reading, valuable for the clinician and the scientists involved in patient care.

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Conflict of Interest

The author declares that he has received lecture fees from HRA Pharma and Recordati and has served on advisory boards for Crinetics, Recordati and Lundbeck.

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