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EDITORIAL

Special issue: Cushing's disease update

Maria Fleseriu[1]

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This special issue of *Pituitary* is devoted to highlighting recent advances in diagnosis and management of Cushing's Disease.

Diagnosis of Cushing's syndrome (CS) is challenging, with most patients experiencing delayed diagnosis; morbidity is increased and mortality is still high, especially if not appropriately treated. Cushing's disease (CD), caused by a corticotroph pituitary adenoma affects predominantly women; despite novel genetics discovery breakthroughs, the cause of the sex divergence remains unknown.

Increased awareness of CS and screening protocols, accurate diagnosis and differential diagnosis, personalized treatment selection, as well as better long-term management are needed to optimize patient outcomes [1].

Screening for CS includes measuring salivary cortisol [2], urinary free cortisol and performing an overnight Dexamethasone suppression test [3], each with specific caveats. Excluding non-tumoral hypercortisolemia is also paramount in many patients [4]. Localization of ACTH excess is intricate and new protocols, including corroboration of dynamic testing [5] and pituitary imaging, as well as whole body CT, MRI and PET scans [6] will likely enhance sensitivity.

While pituitary surgery [7] remains first line treatment for CD, recurrence [8] post initial surgery is much higher than initially thought, approaching 35%. Elevated salivary cortisol levels are the earliest reflection of disease recurrence. Medical treatment is increasingly being used [9–12], including preoperatively or as primary therapy. From no FDA-approved medication for CS in 2012, there are now four, with different mechanisms of action: mifepristone for hyperglycemia associated with CS, pasireotide and osilodrostat for CD and levoketoconazole for CS treatment;ketoconazole and metyrapone have been also recently approved in Europe. Choosing the precise treatment for each patient is essential; drug selection, either single or combination therapy should be guided by availability, efficacy rates and clinical scenario, cost, and patient preference [1]. Radiation [13] and bilateral adrenalectomy [14] are mostly used as 3rd line options, but sometimes earlier in the disease course in patients with large pituitary adenomas and very severe CS not responsive to medical therapy or in women desiting pregnancy, respectively.

Several complications of CS have recently been more readily recognized, requiring new personalized treatment and prohylaxis protocols. These include hypercoagulability [15] and increased risk of venous thromboembolism (up to 18 times higher than normal population), cardiovascular disease [16] as the main cause of mortality and associated multifactorial bone disease [17]. In some patients, although growth hormone deficiency [18] may improve after surgical resection, low IGF-1 has been linked to persistent myopathy.

Prevalence of CD in children is rare, but frequently occurs with more severe disease or associated with genetic mutations [19]; an unstable genome has been shown to potentially predict pituitary adenomas aggressive behavior.

While there are encouraging signs on improvement over the last decade in diagnosis, imaging, surgery techniques, medical treatment, stereotactic radiation, genetics' understanding [20], more needs to be done. Incorporating quality of life assessment [21] in daily clinical practice is fundamental to understand the effects of long-term hypercortisolism and the impact on patients' life. Care in Pituitary Centers of Excellence [22] is also highly desirable to improve patients' outcomes.

Much appreciation to the thousands of patients who have contributed time and energy for the many research studies allowing us improved insights in etiology, complications and discovery of new treatments for this fascinating disease.

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✉ Maria Fleseriu
fleseriu@ohsu.edu

[1] Departments of Medicine and Neurological Surgery, Pituitary Center, Oregon Health & Science University, 3303 South Bond Avenue, Mail Code CH8N, Portland, OR 97239, USA

Guest editor,
Maria Fleseriu

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Declarations

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