The landscape of bilateral adrenal incidentalomas associated with subclinical hypercortisolism

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Since the first report of a “subclinical” Cushing’s syndrome dated back to the early 1970s [1], a great deal of effort has been put to understand the molecular pathogenesis and the clinical correlates of this condition. Despite the exponential number of publications over the last years, it is still difficult to draw definitive conclusions on the clinical impact of incidentally diagnosed hypercortisolism, not associated with a clear Cushing’s phenotype. As every physician involved in the management of adrenal diseases knows, the main source of uncertainty resides in the definition of this pathological condition, which generates difficulties in achieving comparable results among different studies, and the lack of well-designed prospective studies covering a long time span, leading to difficulties in estimating the prevalence of cortisol-associated comorbidities and long-term consequences. However, keeping in mind those limitations, evidence from long-term retrospective studies has indirectly shown that a mild, but sustained, cortisol hypersecretion can be related to an increased risk of cardiovascular and metabolic correlates, which seems to be related to the cortisol secretion, as well as to the progressive secreting pattern over time [2–4].

Most of the studies on long-term consequences are focused on unilateral adrenocortical tumors, which represent the most frequent entity in radiological series. Lately, an increasing number of studies have been focused on the analysis of hormonal and clinical characteristics of bilateral incidentalomas, raising attention to the difficulties of the

clinical management of those tumors. The recent advances in the biology of cortisol-secreting tumors have also shed light on the molecular events underlying bilateral adrenocortical tumors, which can be very different from their unilateral counterpart and involve novel pathogenic pathways and previously unknown regulatory mechanisms. The discovery of mutations in the *ARMC5* gene in a substantial number of patients with bilateral adrenal hyperplasia and hypercortisolism [5] has broadened the view on the molecular mechanisms underlying adrenocortical hyperplasia, adding an important piece of knowledge to our understanding of tumorigenesis and hormonal hypersecretion in adrenal tumors. Research on aberrant receptors and paracrine regulation of cortisol secretion has provided evidence that the pathophysiology of bilateral masses can be extremely complex. According to the results of in vivo and in vitro studies, the presence of illegitimate receptors is indeed a frequent event among patients with bilateral adrenocortical hyperplasia, with a prevalence that rises up to 87 % [6]. Moreover, after the first pioneering studies [7], the discovery of intra-adrenal adrenocorticotrophic hormone (ACTH) production in a substantial number of patients with hypercortisolism [8] has completely changed the knowledge on the feedback mechanisms involved in adrenal steroidogenesis.

The review published by Paschou and colleagues [9] was aimed to investigate the relationship between morphological characteristics of the adrenal glands and the secretory pattern, with focus on incidentally discovered adrenocortical tumors and subclinical hypercortisolism. Based on the data provided by six studies published between 2011 and 2015, the main finding of the review is that the overall prevalence of subclinical hypercortisolism is increased in bilateral adrenal incidentalomas vs. unilateral adenomas. Surprisingly, the

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prevalence of comorbidities potentially related to mild cortisol excess was not different between unilateral and bilateral adrenocortical masses, when analyzed independently of the secreting pattern. However, it must be pointed out that the data on comorbidities are not representative of the whole cohort, since they are presented only in half of the total group of patients considered in the meta-analysis. Despite this limitation, the data provided on the prevalence of comorbidities are interesting and may find their explanation in the regulation of cortisol chronobiology, which seems to be different in bilateral vs. unilateral adrenocortical incidentalomas [10], due to the different molecular background, and is likely to have some impact on the cortisol-related comorbidities and their progression.

The detection of bilateral adrenocortical tumors and the increasing prevalence of subclinical hypercortisolism in this pathological condition represent a major challenge for physicians, due to difficulties in diagnosis and follow-up. Indeed, no radiological guidelines have been provided yet for bilateral incidentalomas. The cutoff of 10 mm, frequently adopted for the definition of adrenal incidentalomas, is arbitrary and better directions for lesions below this cutoff would help to characterize patients with micronodules or adrenal gland enlargement. Moreover, the current options for the management of subclinical hypercortisolism should be reviewed in the light of a tailored approach. In fact, considering that the reported rate of malignant transformation of incidentally discovered adrenocortical masses is extremely low [11], it is questionable whether a radiological follow-up is really necessary in those patients, provided that an initial evaluation has been performed properly. Given the linear relationship between cortisol secretion and adrenocortical mass volume in subclinical hypercortisolism [12], it is conceivable that a radiological evaluation may be repeated in case of a significant modification of the hormonal profile, in light of a surgical approach. The possibility to identify the lateralization of cortisol secretion, if any, is a feasible strategy that can be applied to guide the choice of the surgical procedure for bilateral adrenocortical incidentalomas, with significant advantages for the patient. To this scope, adrenal vein sampling has been successfully performed to identify the source of cortisol secretion in patients with bilateral adrenal incidentalomas [13], even if this method has not gained popularity so far. More research is definitely needed to assess the risk/benefit ratio and investigate the usefulness of this invasive procedure. Recent evidence highlighted that adrenal scintigraphy with ^{131}I -6 β -iodomethylnorcholesterol may be another useful option in identifying the lateralization of cortisol excess [14]. Finally, pharmacological treatment targeting specific pathways according to the underlying alteration is already an encouraging perspective, as an alternative to the surgical approach, for treatment of bilateral

diseases in case of illegitimate receptors [15], even if more research is definitely required in this field.

In conclusion, the review by Paschou and colleagues [9] draws attention to the topic of bilateral adrenocortical tumors, which has been the subject of exciting discoveries during the very last years. More research is now needed to understand the clinical significance of subclinical hypercortisolism in bilateral adrenal diseases, in order to plan reliable follow-up strategies for this non-negligible number of patients.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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