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Cardiovascular mortality in patients with subclinical Cushing

Mortalité cardiovasculaire dans les syndromes de Cushing infracliniques

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Abstract

Patients with adrenal incidentaloma (AI) and subclinical hypercortisolism (SH) show a high prevalence of cardiovascular risk factors and an increased prevalence and incidence of cardiovascular events. Furthermore, some recent data suggest that in these patients, the cardiovascular mortality is also increased. Unfortunately, to date, the diagnosis of SH is still a matter of debate, and, therefore, it is still not possible to address the treatment of choice (i.e. surgical or conservative approach) in many AI patients. Overall, the available data show that in AI patients with established SH the surgical removal of the adrenal mass causing SH can lead to the improvement of hypertension and diabetes, but in many patients with possible SH the effect of surgery is still largely unknown. Finally, no data are available on the effect of the recovery from SH on the cardiovascular events. Therefore, randomized studies are needed to investigate the possibility of predicting the usefulness of surgery by using the available indexes of cortisol secretion in the individual AI patient. Finally, the development of safe and well-tolerated drugs aimed to control cortisol secretion will be among the goals of the future research.

Keywords: Adrenal incidentaloma; Subclinical hypercortisolism; Cardiovascular mortality

Résumé

Chez les patients atteints d'incidentalomes surrénaliens (IS) et d'hypercorticisme infraclinique (HI), la prévalence des facteurs de risque cardiovasculaire et la prévalence et l'incidence des événements cardiovasculaires sont élevées ; certains résultats récents suggèrent que la mortalité cardiovasculaire serait elle-même élevée. Malheureusement, à ce jour, le diagnostic du HI reste controversé, et il n'est pas, à l'heure actuelle, possible de mettre en œuvre un traitement adapté (chirurgical ou conservateur) dans beaucoup de cas d'IS. D'une façon générale, quand l'IS est associé à un HI confirmé, les données disponibles montrent que la résection de la masse surrénale responsable du tableau d'HI peut améliorer l'hypertension et le diabète, mais que l'effet de la chirurgie reste là démontrer dans beaucoup de cas où le HI n'est qu'hypothétique. Actuellement, les données manquent quant à l'effet bénéfique de la rémission du HI sur le risque accru d'événements cardiovasculaires. Des études randomisées seront donc nécessaires pour évaluer ces possibilités et pour prédire les résultats de la chirurgie en utilisant les indices actuels de la sécrétion individuelle du cortisol par les patients atteints d'IS. Finalement, un des buts de la recherche à venir sera de développer des médicaments sûrs et bien tolérés pour contrôler la sécrétion du cortisol.

Mots clés : Incidentalome surrénalien ; Hypercorticisme infraclinique ; Mortalité cardiovasculaire

1. Introduction

The term "subclinical" or "preclinical" Cushing syndrome defines a pathological condition of increased cortisol secretion in the absence of the classical and specific signs and symptoms of hypercortisolism [1]. Most authors consider the term "subclinical hypercortisolism" (SH) preferable because the progression

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to an overt Cushing syndrome is infrequent [2]. However, clinicians should not be worried about the possible evolution of the disease towards an overt hypercortisolism, since this latter condition may be easily suspected and diagnosed on clinical basis, at variance with SH, which, being asymptomatic, can remain undiagnosed for several years. Indeed, nowadays it is well accepted that, although SH has to be considered a different entity from Cushing syndrome, its consequences are not irrelevant. Moreover, at variance with Cushing syndrome, SH is not infrequent. Depending on the diagnostic criteria used, SH is present in about the 5–26% of patients with incidentally adrenal incidentaloma, (AI) with an estimated overall prevalence of 0.2–2% [3]. Unfortunately, in the absence of the typical clinical features and symptoms of cortisol excess, the diagnosis is difficult and based on a set of hormonal evaluations. The principal and recommended test for the detection of SH is the 1 mg-dexamethasone suppression test (1 mg-DST) with different cortisol cutoffs (from 1.8 to 5 μg/dL). In order to increase the SH diagnostic accuracy, this parameter has variously been associated with other parameters as low ACTH levels (to confirm the adrenal origin), high urinary cortisol levels (UFC) and low DHEAS levels [2–4].

A consensus on SH diagnostic criteria has not been achieved. The difficulty in the detection of SH leads to underestimate its possible consequences. In a study of our group, the SH criterion characterized by the presence of two alterations out of 1 mg-DST > 3 μg/dL, elevated UFC, ACTH < 10 pg/mL, seemed to be the best in predicting the presence of chronic manifestations of SH [5].

Moreover, these criteria were the best in predicting duration of post-surgical hypoadrenalism of at least 12 months [6].

2. Cardiovascular risk and mortality

In the last two decades, SH has been variously associated with the presence of several negative conditions such as type 2 diabetes mellitus, arterial hypertension, fragility fractures and lastly, a bad quality of life [7–11]. In particular, several studies have demonstrated in SH patients the presence of specific cardiovascular risk factors such as impaired anticoagulation system parameters, visceral fat accumulation, high epicardial fat thickness and left ventricular mass [12–14]. Moreover, the presence of a "non-functional" adrenal incidentaloma itself has been associated to the presence of cardiovascular risk factors such as diabetes and several markers of systemic atherosclerosis [15–18]. The group of Evram et al., recently confirmed these data and reported that heart rate, end-diastolic diameter, end-systolic diameter and carotid intima-media thickness values of the patients with adrenal mass were significantly higher than those of the healthy control group [18]. The presence of cardiovascular damage in patients with "non-functional" adrenal incidentaloma supports the hypothesis that the parameters actually used to diagnose SH are not enough sensitive, and that some patients with AI with a negative endocrine work-up for SH are, in fact, affected with a subtle cortisol hypersecretion. Despite the evidence of the presence in IA patients of an increased cardiovascular risk, the occurrence of major cardiovascular events (CVE) in these patients have been explored only in few recent studies. Some authors have demonstrated that in patients with SH (or with cortisol after 1 mg-DST > 1.8 μg/dL) the prevalence of CVE, in particular coronary heart disease and stroke, is higher than in patients with a non-secreting AI (Table 1) [19–23]. Unfortunately, the only study including a control group of patients without AI, failed to demonstrate a difference in CVE prevalence between patients with non-functioning AI and the control group (i.e 13 vs. 14%, respectively) [18]. It should be considered that in this latter study, the overall prevalence of CVE was higher than that reported in other studies, and that in the control group the cortisol levels after 1 mg-DST had not been measured. In a subsequent study of our group, carried on in a sample of 518 AI patients, the CVE were associated with cortisol levels after 1 mg-DST > 1.8 μg/dL (OR: 2.46, 95% CI: 1.5–4.1, $P = 0.01$), regardless of many confounding factors (e.g. smoke habits or age). Interestingly, this results was confirmed also bye an analysis with the artificial neural networks, an adaptive system able to modify its internal structure in relation to a function objective and for this reason particularly suited for solving nonlinear problems and therefore extremely useful in dissecting complex diseases [23]. Moreover, in a first study, we found that in AI patients with SH the extrapolated annual rate of CVE was 3.1% (similar to that of populations at risk such as diabetic or hypertensive patients) and that SH was an independent risk factor for the occurrence of new CVE overtime [19]. The same unadjusted hazard ratio for new cardiovascular events was found by Di Dalmazi et al. [22]. Importantly, in this latter study the authors found that after a long-term follow-up (mean 7.5 years) the survival rate for all-cause mortality was lower in AI patients with stable cortisol levels after 1 mg-DST > 1.8 μg/dL or with SH (defined in the presence of cortisol levels after 1 mg-DST > 5 μg/dL) compared with those with stable non-secreting masses (57% vs. 91%). Interestingly, mortality was associated only with age and mean cortisol concentrations after 1 mg-DST. Similarly, unadjusted survival for cardiovascular-specific mortality was lower in patients with either stable cortisol levels after 1 mg-DST > 1.8-5 μg/dL or SH and in those with worsened secreting patterns as compared with patients with stable non-secreting AI. At variance, the cancer related mortality was similar among these groups. These results were subsequently confirmed by the study of Debono et al., who found in patients with AI that mortality from both cardiovascular diseases and infections was increased in the presence of a low-grade cortisol excess [21]. In consideration of all the above-mentioned evidences and notwithstanding the recently released ESE-ENSAT guidelines that do not highlight this aspect, in all AI patient an adequate clinical and biochemical follow-up, carefully evaluating the cardiovascular risk factors, should be performed [24,25].

3. Management of SH

The treatment of choice in patients with AI is still debated. As demonstrated in a recent meta-analysis, several studies have described an improvement of some complications (in particular diabetes, hypertension and obesity) in patients with AI and SH after adrenalectomy [26,27].

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