A SUGGESTION FOR PROACTIVE CARDIOLOGIC APPROACH TO CUSHING’S SYNDROME OR DISEASE

Goran Koračević¹,², Miloš Zdravković², Maja Koračević², Dimitrije A. Pavlović³, Miodrag Damjanović¹, Milorad Pavlović¹, Sonja Dakić¹, Predrag Cvetković¹, Katarina Mladenović², Milan Stojković⁶

¹Department for Cardiovascular Disease, University Clinical Center Niš, Serbia
²Faculty of Medicine, University of Niš, Serbia
³Department of Plastic and Reconstructive Surgery, University Clinical Center Niš, Serbia
⁴Department of Thoracic Surgery, University Clinical Center Niš, Serbia
⁵Faculty of Science, Department of Biology and Ecology, University of Kragujevac, Serbia
⁶Department of Internal Medicine and Geriatrics, Bethel Clinic (EvKB), Bielefeld, Germany

Abstract. Numerous studies and reviews agree about the increased cardiovascular risk in Cushing’s syndrome. Therefore, the aim of the paper is to suggest a few common diagnostic and therapeutic cardiologic preferences for the majority of Cushing’s syndrome/Cushing’s disease (CS/CD) patients which are not yet routine but have the rationale to become standard procedures. This may serve as an initial working document, to be improved by the experts in the field. A narrative review is used to present synthesis and deduction of several approaches in cardiology regarding the actual topic. Results are systematized as the risk factors or co-morbidities list (prevalent in CS/CD) coupled with current and adapted cardiologic suggestions for practice.

Key words: Cushing’s syndrome, Cushing’s disease, ACE inhibitor, spironolactone, statin, holter monitoring

Introduction

Cushing’s syndrome (CS) is important due to the high prevalence [1] of its exogenous (mostly iatrogenic) form [2,3]. Numerous comorbidities are often present in CS / Cushing’s disease (CS/CD) [4,5]. The mortality rates are increased in CS/CD [4,6] in the range between 1.8 and 7.4-fold higher [5]. Numerous studies and reviews agree about the increased cardiovascular risk in CS/CD [2,4-6]. Cardiovascular risks ought to be repeatedly estimated in clinical practice and care should be taken to control them optimally, because they are pronounced and persistent - it is not easy to eliminate hypercortisolism and even if it is achieved cardiovascular risk factors may still be present [7].

Unfortunately, abundant evidence of high cardiovascular risk in CS/CD is sub-optimally translated into practical recommendations [5]. There is a step between recognizing increased risk in the medical literature and incorporating this knowledge into the physicians’ usual care for the patient. The cardiologic part of such interdisciplinary recommendations (endocrinologic and cardiologic) is largely missing [5].

Therefore, the aim of the paper is to suggest a few common diagnostic and therapeutic cardiologic preferences for the majority of CS/CD patients which are not yet

Materials and Methods

A narrative review is used to present the synthesis and deduction of several approaches in cardiology regarding the actual topic. We performed a search in the following databases: Medline, Springer, Elsevier, SAGE, Oxford Press, Wiley, and the search engine Google Scholar. Results are systematized as the risk factors or co-morbidities list (prevalent in CS/CD) coupled with current and adapted cardiologic suggestions for practice.

Results

Arterial hypertension (HTN) (Table 1) is very prevalent in CS/CD in the range of 70% to 90% [6,5]. Blood pressure (BP) may increase early in CS/CD. For example, HTN starts during the first day of oral intake of 80 mg – 200 mg cortisol daily and peak BP increase occurs after 4 or 5 days [8]. Ambulatory BP monitoring (ABPM) is now very important for HTN detection and evaluation [9-11]. ABPM can be recommended for many CS/CD patients, particularly if long-standing and/or severe [12]. Importantly, ABPM can be used to detect masked arterial hypertension (MAHT) [9-11] in CS/CD patients because
they have numerous characteristics associated with MAHT [12]. Additionally, there is a place of ABPM in CS/CD patients with sustained HTN – to evaluate antihypertensive therapy [9].

Obesity and DM increase the likelihood of uncontrolled or masked uncontrolled HTN (MUCH) [9] and they are persistent factors of CS/CD [5]. Moreover, in CS/CD there is often persistent hypercortisolism, which promotes HTN [7]. In the pathophysiology of HTN in CS/CD numerous factors play a role: obesity, elevated cardiac output, activation of the renin-angiotensin-aldosterone system (RAAS), increased cardiovascular sensitivity to vasopressin, angiotensin II and catecholamines, reduced efficacy of vasodilatory mechanisms, higher total peripheral vascular resistance, mineralocorticoid action of cortisol and mineralocorticoid hormones co-secretion (e.g., deoxycorticosterone), sleep apnoea, etc.[5,7,8,13-15].

RAAS blocker (ACE inhibitor or angiotensin receptor blocker (ARB)) is one of the first choices for HTN treatment in CS/CD [15,16], RAAS blocker is generally a part of the preferred combination to start antihypertensive therapy with [9] RAAS blocker is also indicated in obese HTN patients [9] and most of the patients with CS/CD are obese [5].

In addition to the RAAS blocker, a direct suggestion for antihypertensive therapy in CS/CD patients is a mineralocorticoid receptor antagonist (MRA) [16]. One of the reasons for this recommendation is the known characteristic of hypercortisolism (particularly if severe) that the kidney enzyme 11b-hydroxysteroid dehydrogenase type 2 cannot convert all cortisol to cortisone. As a result, an excessive amount of cortisol binds to the mineralocorticoid receptor and produces the effects of mineralocorticoid surplus, including salt and water accumulation with BP increase and K⁺ decrease [13]. Therefore spironolactone or e.g. eplerenone can be recommended for patients with CS/CD. MRA spironolactone is expected to be advantageous [14] due to excessive action of both glucocorticoids and mineralocorticoids "non-selective" CCBs are also candidates for CS/CD patients [16] because they are an essential part of the most triple antihypertensive therapies [9].

The additional reason to consider CCBs in CS/CD patients is that short-term variability of BP is higher in CS patients [17] and it is known that CCBs and ACE inhibitors diminish visit-to-visit BP variations [18] particularly if they are obese and their HTN is severe. The escalation of antihypertensive treatment is to be expected, because HTN was controlled in only 15% of CS patients [19].

In addition to its own significance dyslipidemia is an important problem in CS/CD patients because it is prevalent and clustered with other risk factors of atherosclerosis [5]. Moreover, this association between risk factors is quantitative, e.g., LDL-cholesterol is significantly and independently associated with systolic BP in CS/CD [38]. A common pattern of dyslipidemia in CS/CD is represented by the increase in LDL-cholesterol and triglycerides and decrease of HDL-cholesterol [39].

Chronic hypercortisolism leads to insulin resistance; therefore CS/CD is the metabolic syndrome’s archetype. Overweight or obesity is found in > 50% of CS/CD patients and DM is also very prevalent (up to 50%) [40]. The obesity and DM, prevalent characteristics of CS/CD patients, make hyperlipidemia more difficult to control [41]. It is particularly so if hypercortisolism is not controlled. Even following the effective therapy of CD (despite a decrease of BP and body mass index) the majority

<table>
<thead>
<tr>
<th>Comorbidity /Characteristic of CS/CD</th>
<th>Reference confirming that this comorbidity /characteristic is prevalent in CS/CD</th>
<th>Drug (or diagnostic procedure) suggested for PRIMARY prevention /EARLY treatment (or early diagnosis)</th>
<th>Reference confirming the rationale for the cited drug (or diagnostic procedure) for particular co-morbidity /characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN (early treatment)</td>
<td>[5,6]</td>
<td>RAAS blocker, spironolactone, consider timely (using ABPM) CCB, diuretic and BB depending upon FHS or SCORE, consider statin</td>
<td>[15,16]</td>
</tr>
<tr>
<td>Hyperlipidemia (early treatment)</td>
<td>[5]</td>
<td>RAAS blocker, spironolactone</td>
<td>[20-22]</td>
</tr>
<tr>
<td>HF (primary prevention)</td>
<td>[5,23]</td>
<td>Pretest probability of CAD, ECG, exercise test, CT calcium score</td>
<td>[24,25]</td>
</tr>
<tr>
<td>CAD (early diagnosis)</td>
<td>[5,26,27]</td>
<td>Consider aspirin and statin</td>
<td>[28,29]</td>
</tr>
<tr>
<td>CAD (primary prevention)</td>
<td>[5,26,30]</td>
<td></td>
<td>[29,31]</td>
</tr>
<tr>
<td>Hypokalemia (early treatment)</td>
<td>[32]</td>
<td></td>
<td>[33,34]</td>
</tr>
<tr>
<td>VTE (early diagnosis)</td>
<td>[35]</td>
<td></td>
<td>[36,37]</td>
</tr>
</tbody>
</table>

of patients (56%-76%) one year later still had obesity, HTN, DM, high cholesterol, and triglyceride levels [40].

In line with this, obesity (especially visceral) often continues even after surgical remission in CS/CD patients [41]; it may contribute to the persistence of hypercholesterolemia and hypertriglyceridemia [39]. This persistence of dyslipidemia can result from the continuation of increased BMI [41].

Unfortunately, some drugs used to suppress adrenal glands in CS/CD have unwanted effects in worsening dyslipidemia [41,42], which questions their clinical benefit. The significance of dyslipidemia and its association with other risk factors of atherosclerosis leads to the suggestion for its aggressive therapy [42]. Therefore a scene is set for treating hyperlipidemia in CS/CD. On an individual basis, eligibility for treatment can be estimated using the patient’s Framingham Risk Score (FHS) or Systematic COronary Risk Evaluation (SCORE) [20-22] to evaluate the risk of CAD and mortality (and the need for antihyperlipidemic therapy). As in most other patients, these with CS/CD in the first place, a statin ought to be considered.

The caution is advised because of steroid myopathy which is often present in CS/CD [43]. Proximal myopathy is regarded as additionally suggestive of CS (similarly to purple striae) [43,44]. It is a toxic non-inflammatory myopathy that dominantly affects pelvic muscles with consequent difficulties to stand up and climb up [45]. Steroid myopathy is the most prevalent among drug-induced myopathies; its incidence is around half of corticosteroid-using patients for prolonged periods [45]. The diagnostic approach is not standardized, and it is not easy to quantify the changes and to follow-up such patients adequately [43]. In addition to muscle symptoms (i.e. myalgia), weakness of proximal muscles can complicate statin use [45,46]. Unfortunately, muscle strength testing is not frequently performed; reports demonstrated muscle weakness in >10% of statin users [46]. Therefore, the likelihood of an indication for statin is substantial in CS/CD patients, but the follow-up ought to be adequate, particularly as far as steroid myopathy and hepatic lesions are concerned.

The risk of HF is increased in CS/CD patients, up to 6-fold [32]. The most important risk factors of HF are clustered in CS/CD, such as HTN, CAD, obesity, and DM [5]. Moreover, a direct effect of glucocorticoid excess upon cardiomyocytes is probable [23,47-49]. An echocardiogram is needed in CS/CD patients to evaluate the presence of structural and functional abnormalities of the heart, which are common in CS/CD patients, starting from left ventricular hypertrophy (LVH) as a result of several aforementioned risk factors. The echocardiogram is obviously indicated, and it is hopefully done in most CS/CD patients.

RAAS blocker and potassium sparing diuretic (spironolactone in the first place) can be recommended for HF primary prevention in CS/CD patients with HTN. In CS/CD patients with HTN and “borderline” HF (incipient symptoms with minimal NT pro-BNP elevation): in the first line diuretic (MRA), RAAS blocker, and certain BBs (bisoprolol, carvedilol, metoprolol succinate [50] and nebivolol [25]) can be recommended. An adequate choice of certain BBs is needed because they are a very different class of drugs [51]. Also SGLT2 inhibitors can be suggested for evaluation in CS/CD patients.

Cardiovascular diseases are the main cause of death in CS/CD patients [52]. Therefore, it is reasonable to look for CAD in many CS/CD patients. Their age, symptoms, and risk factors can help us estimate the risk [28]. It is documented that CAD risk in many CS/CD patients is high or very high [26]. Moreover, CAD is more prevalent in CS/CD vs. controls (general population) up to 17 times [27].

In addition to the estimation of CAD probability for early diagnosis, several methods are widely available including ECG, exercise test, coronary artery calcium score, etc. Moreover, Holter is needed for arrhythmia and ischemia detection, as the risk of atrial fibrillation is also increased in CS/CD [32]. Indeed, for the estimation of AF risk, various risk scores can be useful [53]. In CS/CD at high risk of CAD we ought to consider ASA [29] and statin [20-22] in the primary prevention. In CS/CD patients with HTN at high risk of CAD, there is a rationale to consider RAAS blocker, and CCB or BB [9].

For early detection of VTE, one should recognize elevated risk in CS/CD patients. It is reasonable to use clinical prediction rules, D dimer, and venous ultrasound more liberally and more frequently in patients with CS/CD vs. without it.

To sum up, it is important that the clustering of cardiovascular risk factors in CD and CS due to ongoing long-term administration of high-dose glucocorticoid treatment is estimated by FRS and SCORE as high or very high [5]. Therefore, the cardiologic approach is typical for patients at high risk of CAD, with additional attention on more regular use of holter and ABPM.

**Conclusion**

The risk of cardiovascular events is high enough or will be high enough in the majority of CS/CD patients to warrant a cardiologic work-up. Due to scarce data on the individual benefit of examinations and tests more studies are needed to explore the cost-effectiveness of several cardiologic diagnostic and therapeutic procedures.

To our opinion, the vast majority of CS/CD patients ought to be evaluated as candidates for Holter and 24h ABPM in addition to echocardiography, due to the increased risk of numerous cardiovascular diseases. Aspirin, RAAS blocker, MRA, and statin may be subjects of the individual evaluation for the primary cardiologic prevention of CAD and HF in CS/CD patients.
A Suggestion for Proactive Cardiologic Approach to Cushing’s Syndrome or Disease


