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High likelihood for atrial fibrillation in Cushing's syndrome

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Abstract. – OBJECTIVE: This review analyzes the prevalence of the most important comorbidities associated with atrial fibrillation (AF) in the growing population of patients with Cushing's syndrome (CS).

MATERIALS AND METHODS: The review is arranged in a way to list important risk factors for AF and the references, which suggest the significant prevalence of these particular risk factors in CS. The search is conducted on PubMed, Science Direct, Springer, Wiley, SAGE, Oxford Press, and Google Scholar. PubMed search for "Cushing's syndrome atrial fibrillation" on 8/7/2019 revealed 4 papers only. None of them either analyzed or implicated high risk for AF in CS.

RESULTS: Arterial hypertension (AHT) can be found in approximately 80% of adult individuals with endogenous CS and in 20% of patients with exogenous CS. The reported prevalence of diabetes mellitus (DM) is from 13% to 47% in CS patients and the risk for de novo DM is approximately two-fold higher in individuals treated with glucocorticoids. High risk for myocardial infarction (MI) with hazard ratio (HR) 3.7 (95% confidence intervals, CI 2.4-5) in patients with endogenous CS was found. In CS patients the obesity can be detected in up to 41% and overweight in 21-48%. Left ventricular hypertrophy (LVH), pulmonary thromboembolism (PTE), infections, and hypokalemia are also more prevalent in CS as compared to healthy population. All cited comorbidities have been associated with AF. Therefore, clustering of the important factors associated with AF is confirmed repeatedly in CS.

CONCLUSIONS: The prevalence of AF in CS should be studied more precisely, both in a scientific way and at the individual patient's level.

Key Words:
Atrial fibrillation, Cushing's syndrome, Arterial hypertension, Diabetes mellitus, Heart failure, Obesity, Coronary artery disease.

Introduction

It is well-known that AF is the most prevalent chronic arrhythmia, with high impact on patients' thromboembolic events and survival[1]. CS, particularly in its iatrogenic form, is not rare at all[2]. With the high significance of AF, the aim of this review is to analyze the prevalence of the known diseases – risk factors for AF in CS.

Materials and Methods

The review is arranged in a way to list important risk factors for AF and the references which suggest the significant prevalence of the risk factors in CS. The search is conducted on PubMed, Science Direct, Springer, Wiley, SAGE, Oxford Press, and Google Scholar. PubMed search for "Cushing's syndrome atrial fibrillation" on 8/7/2019 revealed 4 papers only. None of them either analyzed or implicated high risk for AF in CS.

Results and Discussion

Arterial Hypertension (AHT)

Growing evidence closely links AHT with an elevated risk of developing AF, as well as with the risk of recurrent AF and AF-related complications[3,4]. AHT is independently associated with AF[4].

AHT (Table I) is the most prevalent comorbid clinical condition described in 50-85% of CS patients, frequently presenting comorbidity, as well[5]. AHT exists in approximately 80% of grown-up individuals with endogenous CS (predominantly in adrenal CS and in individuals with ectopic

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Table I. Prevalence and the risk for occurrence of AF risk factors in CS.

Risk factor for AF	Prevalence (%)/risk (RR/HR/OR) for occurrence in CS	Reference
Hypertension	70%-90%	Koracevic et al[2]
Diabetes mellitus	20%-50%	Tsurutani et al[10]
Heart failure	HR 6.0 (2.1-17.1)	Isidori et al[7]
MI	RR 3.26 (2.60-4.09) for high-dose GCs users	Koracevic et al[2]
Obesity	32-41%	Schernthaner et al[5]
OSA	HR 2.82 (95% CI: 1.67-4.77)	Wang et al[24]
LVH	24-42%	Kamenický et al[28]
PTE	OR 17.82 (95% CI 15.24-20.85, $p<0.00001$) of unprovoked VTE (e.g., PTE/DVT) in endogenous CS	Wagner et al[32]
Infections	HR 4.9 (95% CI 3.7-6.4) in endogenous CS	Dekkers et al[38]
Hypokalemia	85.7% in ectopic CS	Sathyakumar et al[40]

Legend: AF – atrial fibrillation; CS – Cushing's syndrome; GCs – glucocorticoids; HR – Hazard ratio; OR –Odd ratio; RR –Rate ratio; MI – myocardial infarction; OSA – obstructive sleep apnea; LVH – Left ventricular hypertrophy; VTE – venous thromboembolism; DVT deep venous thrombosis; PTE – pulmonary thromboembolism.

ACTH production i.e., ectopic CS), while 20% of patients with exogenous CS develop AHT[6]. According to available records, 70-85% of grown-up patients, as well as 50-78% of paediatric patients who have endogenous CS exhibit AHT[7]. Approximately 95% of grown-up individuals with ectopic ACTH secretion display AHT[2].

CS can underlie the resistant AHT, with a larger prospective for hypertension-mediated organ damages (HMODs)[2]. Moreover, around 30% of CS patients show a tendency to have persistent AHT after achieving remission of CS[8]. This was especially observed in individuals with endogenous CS where prevalence of AHT remains notably high (>50%) after attaining remission[2]. Schernthaner-Reiter et al[5] reported that AHT represents the most frequent comorbidity at the time of diagnosis of CS showing resolution in 32.8% of patients after CS remission.

Diabetes Mellitus (DM)

DM is associated with an increased risk of AF, raising the risk of developing "new-onset" AF, as well as the risk of recurrent AF and AF-related complications[4,9]. DM is independently associated with AF[4]. DM shows high prevalence in CS[2]. CS is frequently associated with DM or impaired glucose tolerance (IGT) (Table I)[10]. Type 2 DM is a common condition that can occur secondary to CS and around 80% of CS patients have either DM or IGT as a result of insulin resistance[11]. In CS patients, both insulin resistance, as well as disturbed insulin production underlay the presence of DM[2]. IGT is present in 14% to 64% of patients with CS, and the reported prevalence of DM extends from 13% to 47% in CS patients[5]. In adrenal CS, overt DM was reported in 20-50% of patients, while IGT was found in additional 10-60% of these patients[2]. No difference was found in DM prevalence between individuals with pituitary CS and adrenal CS[12]. According to Baroni et al[13], in a group of patients treated with exogenous glucocorticoids (e.g., prednisolone), glucocorticoid-induced DM was diagnosed in 50% of these patients. According to Koracevic et al[2], the risk for *de novo* DM is approximately two-fold higher (odds ratio, OR 1.5-2.5) in individuals treated with glucocorticoids.

Heart Failure (HF)

HF is recognized to be independently associated with AF[4]. HF raises the risk of developing AF, recurrent AF, as well as AF-related complications[4]. Hypercortisolemia is reported among hormonal derangements recognized as etiologic factors of HF[14].

In patients with active CS, reported HR for HF is six-fold higher in comparison to matched subjects (Table I)[7]. Transitory HF in patients with CS, caused by adrenal adenoma, was reported in numerous patients, as well as dramatic enhancement of cardiac function following treatment of CS[15]. As far as exogenous CS is concerned, reported rate ratio for HF was 3.72 (2.71-5.12) for patients treated with high-dose corticosteroids (>7.5 mg of prednisolone per day, for 1-5 years) compared to controls[2].

Coronary Artery Disease (CAD)

Ischemia of atrial myocardium due to CAD can induce AF[9]. MI is independently associated with

AF and increases the risk of developing AF, as well as recurrent AF[4].

Increased prevalence of coronary calcifications, as well as higher non-calcified coronary plaque volumes, have been described in CS patients in comparison with control subjects matched for age, gender, and body mass index (BMI)[16]. The incidence of MI is increased in CS patients[17]. High risk for MI (HR 3.7, 95% CI 2.4-5) in patients with endogenous CS has been reported[2]. Rate ratio for MI was also remarkably increased for patients treated with high-dose corticosteroids (>7.5 mg of prednisolone per day, during 1-5 years) compared to controls (Table I)[2]. The prevalence of CAD was also assessed in CS patients following long-term remission, showing that CS patients in remission of disease for a mean length of 11 years, especially females and younger individuals still have high risk of cardiovascular events[18]. The increased risk for MI appears to be permanent in CS patients[2].

Obesity

Obesity increases the risk of AF, showing a progressive risk-increase in correlation with BMI[4]. Obesity amplifies the risk of developing AF, as well as the risk of recurrent AF following successful ablation[19,20]. Obesity is independently associated with AF[4].

Obesity shows high prevalence in CS, while centripetal obesity represents one of the characteristic features of CS[2,21]. Weight gain remains the most prevalent clinical feature of CS and the reported prevalence extends up to 82%[5]. Obesity is found in up to 41% of CS patients, as well as overweight, which is displayed in 21-48% of these patients (Table I)[5]. In endogenous CS, obesity can be present in about 95% of adult patients with CS and in all pediatric CS patients[2]. Weight gain was described as the most prevalent clinical finding at the time of diagnosis of CS, and there was no difference in BMI when patients with pituitary CS and adrenal CS were compared[12]. Even ten years from resolution of CS, these patients still exhibit accretion of centripetal fat, as well as unsatisfactory adipokine profile[5].

Obstructive Sleep Apnea (OSA)

There is evidence of a positive association between OSA and AF, and OSA is independently associated with AF[4,22]. Not only does OSA increases the risk of developing AF, but it also raises the risk of recurrent AF and AF-related complications[4].

Significant prevalence of OSA has been demonstrated in CS[2]. Higher prevalence of OSA (50% *vs.* 23%, $p=0.003$) has been reported in CS patients in comparison to controls matched for age, sex and BMI[23]. According to the findings, CS patients, irrespective of their gender, have an increased risk for the development of OSA later in life in comparison with non-CS individuals[24]. The risk of OSA is approximately 3-fold higher in the presence of CS (Table I)[24]. Authors revealed that CS is an independent risk factor of consequent OSA irrespective of the presence of adiposity, indicating a potential play of cortisol in sleep apnea pathophysiology, and ability of increased cortisol values to promote OSA[24,25].

Left Ventricular Hypertrophy (LVH)

LVH is associated with an elevated risk of AF[9]. It has been demonstrated that every standard deviation rise in left ventricular mass (LVM) increases the risk of developing AF by 1.2 (95% CI 1.07-1.34) in a five-year follow-up[26].

Increased prevalence of LVH has been found in patients with CS, as well as higher occurrence of concentric remodeling and left ventricular (LV) systolic/diastolic dysfunction[27]. Even though AHT is a well-recognized factor that promotes LVH, the latter was also detected in CS patients without elevated blood pressure[27]. According to reports of echo-based surveys, LVH was found in considerable percentage of CS patients (Table I)[28]. Near 70% of individuals with active CS displayed abnormal LV mass parameters; 42% had concentric hypertrophy, and another 23% had concentric remodeling[29].

LVH displays a tendency to be more severe in CS compared to non-CS hypertensive controls both with essential and secondary AHT[2]. A dramatic regression of LVH has been described after CS treatment[2]. After CS treatment, LVH can be at least partly reversible[30].

Pulmonary Thromboembolism (PTE)

PTE is recognized as one of many acute non-cardiac conditions associated with AF, and as one of numerous potentially "reversible" causes of AF[9]. Notably, high prevalence of AF, as well as a high incidence of consequent AF, have been reported in patients who have PTE[31].

Hypercoagulability due to glucocorticoid excess increases four times the occurrence of venous thromboembolism (VTE), e.g., deep venous thrombosis (DVT), as well as PTE in CS[2]. The prevalence of VTE is about 10 times higher in

CS patients[2]. In the first year after diagnosis of CS, HR appears to be up to 20.6 (95% CI 7.8-53.9)[2]. According to recent meta-analysis, risk of both unprovoked and postoperative VTE in CS is markedly increased in comparison to the overall population and estimated OR of unprovoked VTE in endogenous CS happens to be considerably high compared with overall population (Table I)[32].

In CS patients undergoing surgical procedure, VTE prevalence rate extends up to 20%, with higher rate in patients with pituitary CS undergoing trans-sphenoidal surgical procedure than in those with adrenal CS undergoing adrenalectomy[33]. Almost 60% of VTEs occurred in long-term glucocorticoid users and treatment with oral glucocorticoids happened to be associated with a four-fold increased risk of PTE in a time- and dose-dependent manner[34]. According to reports, the current use of oral glucocorticoids is associated with an increased risk of recurrent PTE (OR 3.74; 95% CI 2.04-6.87)[35]. VTE was reported to be a cause of death in about 1.9% of CS patients[8].

Infections

Infections are associated with developing AF, meaning that infections are associated with both occurrence and maintenance of new-onset AF[36]. Viral infections are recognized as one of many acute non-cardiac conditions associated with AF[9].

Glucocorticoids are well-known immunosuppressive agents which make individuals with CS predisposed to infections[2]. CS patients display increased frequency of infections, and severe protracted CS may cause immunosuppression, predisposing the development of opportunistic infections[17,37]. Near five-fold increased risk of infections in patients with endogenous CS has been reported (Table I)[38]. Infections were described in 17.8% of pediatric patients with endogenous CS, and their presence was in positive correlation with elevated cortisol values (e.g., serum cortisol, as well as urinary free cortisol)[39]. In Sathyakumar et al[40], almost half of patients with ectopic CS exhibited the life-threatening infections (e.g., bacterial, mycobacterial, as well as mycotic etiology). The infections are one of the main comorbidities, as well as mortality factors in CS patients[39], and the most significant cause of death during the initial period from CS diagnosis[2].

Hypokalemia

It was previously demonstrated in an extensive follow-up survey that hypokalemia (<3.5 mmol/l) is associated with an increased risk of AF[41]. Faxén et al[42] conducted a study on patients hospitalized with suspected acute coronary syndrome (ACS) and revealed that hypokalemia (serum potassium <3.0 mmol/L) at admission was allied with new-onset AF during hospitalization, and that this relationship sustained after adjusting for all covariates.

Hypokalemia may occur in CS as a consequence of excessive kaliuresis induced by excess of adrenal corticosteroids[43] since the excess of cortisol is able to activate the mineralocorticoid receptor once the 11ß hydroxysteroid dehydrogenase type 2 was overwhelmed[44]. Hypokalemia has been confirmed in 22-23% of patients with CS[2]. Hypokalemia was found in a majority of CS individuals with ectopic ACTH secretion (Table I)[40]. Greater prevalence of hypokalemia has been reported in CS patients with ectopic ACTH secretion (i.e., ectopic CS) (90% *vs.* 0%) and larger part of these patients required hospitalization, as well as parenteral potassium correction[40]. A higher occurrence of hypokalemia in patients with ectopic CS (57%) in one series in comparison with pituitary CS (10%) in another series has also been described[44].

In a larger series of 64 individuals with ACTH-dependent CS, unprompted hypokalemia was found in 8.3% of patients with pituitary CS and among all ectopic CS patients[45], and this inconsistency can be explained by the severity of hypercortisolism in patients with ectopic CS[44].

From the above data, we can highlight that CS is an important cause of AF since it promotes symptoms, increases morbidity and mortality rates[1]. Numerous diseases and conditions have been observed in the guidelines as associated to AF[3,4,9,14]. Many of them (no less than 10 that we cited, such as obesity, AHT, DM, etc.) are significantly more prevalent in CS in comparison to overall population (Table I).

In spite of this, guidelines about AF do not list CS as a disease at risk for AF[4,9,46-49].

Conclusions

This review and analysis of the available evidence suggest high probability of AF in CS. At least 10 well-known risk factors associated with AF have been more prevalent in CS in comparison with the referent population. Therefore, the prevalence of AF in CS should be studied more precisely, both in a scientific way and at the individual patient's level.

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Conflict of Interests

This paper is neither submitted nor prepared for submission to another medical journal in part or as a whole. Authors declare that they have no conflict of interests.

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