CARDIOVASCULAR COMPLICATIONS OF CUSHING'S SYNDROME

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ABSTRACT

Cushing's syndrome (CS) is a condition caused by chronic exposure to excess glucocorticoids. Mortality rates are four times higher in CS than in the normal population and myocardial infarction, stroke, congestive heart failure and venous thromboembolic complications appear to be the main causes of mortality. In addition, hypertension, insulin resistance, obesity and dyslipidaemia are other contributing cardiovascular risk factors. Even after the disease cure, patients with CS still possess increased prevalence of cardiovascular disease. This contributes for high mortality and morbidity and they deserve to be screened, diagnosed and treated appropriately according to general acceptable practice. Management directed both against hypercortisolism and cardiovascular risk factor control seems to minimize cardiovascular events in CS.

Keywords: Cushing's syndrome, cardiovascular risk factors, metabolic syndrome, hypertension.

INTRODUCTION

Cushing's syndrome (CS) is a condition caused by chronic exposure to excess glucocorticoids. Cardiovascular disease is the major cause of morbidity and mortality in Cushing's syndrome, and excess risk remains high even in effectively treated patients (1). Cardiovascular disease in glucocorticoid excess arise from the effects on the heart, liver, skeletal muscles and fat tissues (2). Hypertension, truncal obesity, hyperglycemia, insulin resistance and dyslipidemia are important findings in CS and these give rise to an increased risk of cardiovascular disease. This clustering of cardiovascular risk factors can also occur in the general population and is known as the metabolic syndrome. Moreover altered clotting and platelet functions also contribute for high cardiac risk in CS (2,3).

CARDIOVASCULAR RISK FACTORS

1. HYPERTENSION

In patients with subclinical CS, both systolic and diastolic blood pressures are significantly elevated compare to controls (4). Hypertension was a feature reported in majority of original Cushing's cases and was found in around 80% (5,6). Diagnosed patients with Cushing's disease (CD) do not show the nocturnal blood pressure dipping and appear to have abnormal heart rate values which do not resolve after short-term remission. These features are only partially improve in the long run (7). Additionally, approximately 30% of patients tend to have

persistent hypertension after the disease remission (7).

Cortisol-induced hypertension is not simply explained by mineralocorticoid induced salt and water retention or sympathetic nervous system over activity. Cortisol is the likely responsible steroid in the hypertension of Cushing's syndrome (1). The well recognized glucocorticoid stimulated increase in angiotensinogen does not lead to increased plasma angiotensin II concentrations, and it is unlikely to be a key causal mechanism in human glucocorticoid hypertension (1). The mechanism of glucocorticoid induced blood pressure appears to be multifactorial, involving increased responsiveness to vasoconstrictors and decreased vasodilator production (7). Both cardiac output and peripheral resistance have been reported to be high in Cushing's syndrome (8). Pressor responsiveness to catecholamines is increased by cortisol treatment (9). Inhibition of vasodilator nitric oxide is a strong candidate for the genesis of glucocorticoid hypertension (10).

Routine detection of blood pressure is useful for early verification of the persistence of CS. Currently available antihypertensive drugs are indicated in CS, with no special preference due to the disease itself (7).

2. HEART

There is evidence for cardiac structural changes associated with CS. Reduction of mid-wall systolic performance and diastolic dysfunction related to CS

may contribute to the high risk of cardiovascular events observed in this patient population (11). Hypertension related organ remodeling, especially cardiac hypertrophy, is a frequent finding in CS. Long term exposure to excess circulating cortisol also may contribute directly to left ventricular concentric remodeling (12). Some studies showed about 40% of patients with cortisol excess tend to have myocardial hypertrophy and impaired contractility (11). Moreover CS can manifest as cardiomyopathy (13, 14).

In CS there is a sympatho-vagal imbalance with relative increase of parasympathetic activity. Although the pathophysiological significance of this autonomic dysfunction is still unknown, this cardiac autonomic disturbance is linked with increased mortality (15). In addition, coronary flow reserve which is an index of coronary microvascular function has been demonstrated to be pathologically low in a small study done on CS patients without clinical evidence of ischaemic heart disease. This Impaired microvascular functions may contribute for high cardiac mortality (16).

3. ATHEROSCLEROSIS AND ENDOTHELIAL DYSFUNCTION

When compared with a population with similar cardiovascular risk factors, more severe form of atherosclerosis is demonstrated in CS and this may be due to long term exposure to cortisol (17). Endothelial dysfunction is the initiating event for atherosclerosis and this can be multifactorial in CS. Recent assessments of endothelial functions through flow mediated dilatation of brachial artery have showed impairment of endothelial functions in patients with CS compared to controls. This method may be useful to identify high risk individuals earlier than conventional methods (18).

Though cortisol typically behaves as an anti-inflammatory hormone, in excess it can provoke inflammation and accelerated atherosclerosis via insulin resistance, pro inflammatory cytokine regulation and alteration in cortisol binding protein (19). Androgen excess in adreno-cortical stimulation may accelerate the atherosclerosis in both males and females (20). Hyperhomocysteinemia and reduced serum folate concentrations are associated with cortisol excess while homocysteine levels are normalised during remission. Elevated homocysteine levels may cause the prothrombotic state which leads to high cardiovascular risk (21). Elevated blood endothelin-1 levels and osteoprotegerin levels are also found in CS and this may play a role in early and accelerated atherosclerosis (22).

As a consequence of growth-promoting properties of circulating cortisol and/or increased vascular oxidative stress there is a hypertrophic remodeling in subcutaneous small resistance arteries (23). Persistently elevated cardiovascular risk in CS despite remission of hypercortisolism has been shown in a study using multi-detector CT coronary angiogram. This study demonstrated that patients at remission for mean duration of 11 years, especially women and younger patients are still at high cardiovascular risk (24 – 26). Therefore more longitudinal studies are required to determine the implications of specific coronary abnormalities, and effect of medical treatment and lifestyle modifications.

4. DYSLIPIDEMIA

Dyslipidaemia in CS is likely to be multifactorial, including direct effect of cortisol on very low-density lipoprotein (VLDL) synthesis, free fatty acid production, and hepatic endothelial lipase activity (27). Insulin resistant state is also likely to be responsible for abnormal lipid metabolism in CS (28). These include elevated VLDL, low-density lipoprotein (LDL-cholesterol), triglycerides, and total cholesterol levels with decreased high-density lipoprotein (HDL-cholesterol). Persistence of dyslipidemia and central obesity after long-term remission of CS have been demonstrated in one study recently (25).

5. IMPAIRED GLUCOSE TOLERANCE, INSULIN RESISTANCE, AND DIABETES MELLITUS

Glucose levels are higher in patients with CS irrespective of aetiology (29-31). Elevated fasting blood glucose level is a feature of active CS than in remission and this may even be found in subclinical CS (32,33). However this is more common in exogenous glucocorticoid administration. Insulin resistance is another feature and elevated insulin levels persists five years after cure of CD (26, 34). Age, genetic predisposition and lifestyle, in combination with duration and degree of hypercortisolism, may contribute to the impairment of glucose tolerance in the natural history of CS (7).

6. METABOLIC SYNDROME

According to National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria to diagnose metabolic syndrome, there should be at least 3 out of the following; central obesity (waist circumference ≥ 102 cm or 40 inches in males; ≥ 88 cm or 36 inches in females); fasting hypertriglyceridemia (TG ≥ 1.7 mmol/L or 150 mg/dL), fasting low HDL-

cholesterol (HDL-C < 40 mg/dL in males, <50 mg/dL in females); blood pressure $\geq$ 130/85 mmHg or current use of antihypertensive medications; fasting plasma glucose $\geq$ 5.6 mmol/L (100 mg/dL), a diagnosis of diabetes or current use of glucose lowering medication (35).

Metabolic syndrome is more frequent in CS and it tends to persist for at least five years after the cure (36). Both hypertension and central obesity are more prevalent in active CS patients than in remission, and they tend to persist for long term, for a mean of eleven years (37). Elevated total trunk fat mass and low lean body mass are characteristics of active CS. Persistence of these abnormalities of body composition with an unfavorable adipokine profile and persistent low grade inflammation are confirmed in cured subjects (38-40). Therefore CS should be considered as a state of low grade inflammation, even after long term remission and this leads to increased cardiovascular risk (41).

7. CEREBROVASCULAR

Even though little is known about the prevalence of cerebrovascular disease in CS, it is known to be increased (38). High prevalence of conventional cardiovascular risk factors, and hypercoagulability probably contribute for this (42). Data from the HypoCCS database supports an irreversible effects of prior hypercortisolism on the cerebrovascular system (38).

8. PROTHROMBOTIC STATE

Venous thromboembolism was described as the cause of death in up to 1.9% of CS. Non provoked venous thromboembolism risk is doubled in CS. Risk of postoperative venous thromboembolism is varied between 0 and 5.6% (43). High levels of fibrinogen, factor VIII, factor IX, von Willebrand factor and the evidence of enhanced thrombin generation are the suggested reasons for glucocorticoid induced hypercoagulopathy. Additionally, surgery, and obesity almost certainly contribute for this thrombotic tendency (44).

Up regulation of the synthesis of plasminogen activator inhibitor type 1, which is the main inhibitor of the fibrinolytic system and enhanced metabolic function of endothelial cells with secondary hyperfibrinolysis are also suggested contributory factors for pro-thrombotic state in CS (44-47). These patients are predisposed to thrombotic events during

inferior petrosal sinus (IPS) sampling as well as during post-surgery. Therefore patients with active CS must be considered as hypercoagulable state and antithrombotic prophylaxis should be offered.

CONCLUSIONS

Majority of CS patients get some manifestations of metabolic syndrome and they tend to persist even after disease remission. This contributes for high mortality and morbidity and they deserve to be screened, diagnosed and treated appropriately according to general acceptable practice. Even after the disease cure, they still possess increased prevalence of clinical and biochemical abnormalities like atherosclerosis, obesity, hypertension, impairment of glucose tolerance, hyperlipidemia, and hypercoagulability. Cardiovascular risk typical of active CD was reported high even 5 years after remission. Their carotid artery walls are stiff with markedly reduced caliber. At the same time the prevalence of carotid atherosclerotic plaques is high compare to sex- and age-matched control populations. Persistent unfavourable adipokine profiles, vascular damage, accumulation of central body fat and low grade inflammation despite biochemical disease control lead to persistently high mortality. Because of the underlying microvessel remodeling and associated essential hypertension, hypertension in CS may persist despite the remission.

Oral glucose tolerance test, 24-hour ambulatory blood pressure monitoring, echocardiography, electrocardiogram, and carotid ultrasound have been proposed in patients with CS as well as during follow-up of patients with biochemical cure to establish the cardiovascular risk. Management directed both against hypercortisolism and cardiovascular risk factor control seems to minimize cardiovascular events in CS. The assumption of resolution of cardiovascular risk after normalization of hypercortisolism is currently questioned and the awareness of this persistently increased cardiovascular risk in patients after cure must steer to strict control of improvable cardiac risk factors.

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