·Scientific Hypothesis·

Role of psychological stress and the hypothalamic-pituitary-adrenal axis in the pathophysiology of central serous chorioretinopathy

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Abstract

• Central serous chorioretinopathy (CSC) is characterized by serous detachment of the sensory retina as a consequence of the focal leakage of fluid from the choriocapillaries to subretinal space through a defect of the retinal pigment epithelium (RPE). The exact cause of CSC has not well unknown. Psychological stress is thought to contribute to CSC, but the physiologic mechanisms are unclear. It is hypothesized that psychological stress can induce CSC through the mechanism of the hypothalamic-pituitary-adrenal (HPA) system. Psychological stress can adversely affect HPA axis and causes glucocorticoid levels to elevate. Increased glucocorticoids constrict choroid vessels, which leads to ischemia of choroids and damage vascular endothelial cells, thus causing vasopermeability to increase. RPE dysfunction will occur as a result of abnormalities in the choroidal circulation. The large molecules including protein may enter the subretinal space through the damaged vessels and RPE.

• KEYWORDS: psychological stress; central serous chorioretinopathy; hypothalamic-pituitary-adrenal system; glucocorticoids

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INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by serous detachment of the sensory retina as a consequence of the focal leakage of fluid from the choriocapillaries to subretinal space through a defect in the retinal pigment epithelium (RPE)[1]. With increasing case reports, ophthalmologists realize that CSC may present in various forms. In fact it has also been described as a peculiar type of secondary retinal detachment, idiopathic serous pigment epithelium detachment, bullous retinal detachment, and multifocal posterior pigment epitheliopathy [2]. Although the morphology changes can be seen clearly by fluorescein and indocyanine green angiography, the exact cause of CSC remains unknown.

Psychological stress is thought to contribute to CSC, although the physiological mechanisms are unclear. Twenty years ago, doctors noticed the association of CSC with psychosocial stress. Geller *et al* [3] found that a very disturbing psychological event had preceded the loss of vision in 91% of a sample of 33 patients with CSC. The patients with CSC showed a significantly higher amount of general physical complaints, measured with a complaints questionnaire (B-L). In a personality inventory (FPI-R), they also scored significantly higher on measures of emotional instability and strain, and significantly lower on a measure of extraversion[4]. A comparison of behavior in patients with CSC and patients with other ocular disorders demonstrated that Type A behavior was significantly more frequent in CSC patients [5]. Recently, Conrad has assessed emotional distress (ED), nine psychopathological symptoms, critical life events, and alexithymia in CSC patients. Conrad found that CSC patients showed elevated ED and high scores on seven psychopathological symptoms, including hostility. Controlling for ED, CSC patients showed elevated alexithymia sum scores. Alexithymia was correlated with hostility [6]. These CSC patients were also more likely to use psychopharmacological medications. These studies indicate that stress and adaptation to stress appear to play a significant role in this disorder[7].

HYPOTHESIS

It is hypothesized that psychological stress can induce CSC through the mechanisms of the hypothalamic-pituitary-adrenal (HPA) system. Psychological stress can increase

HPA activation and this causes glucocorticoid levels to elevate correspondingly. Increased glucocorticoids constrict choroid vessels, which leads to ischemia of choroids and damage to vascular endothelial cells, thus increasing vasopermeability. RPE dysfunction will occur as a result of abnormalities of choroidal circulation. The large proteins of blood circulation may enter the subretinal space, causing leakage of fluid into the subretinal space.

DISCUSSION

Psychological Stress and Corticosteroid Levels Corticotrophin-releasing hormone and arginine vasopressin that are synthesized and released from the hypothalamic paraventricular nucleus are the prime mediators of the HPA axis response to stress. These neurohormones act synergistically to stimulate adrenocorticotophin (ACTH) secretion from the anterior pituitary, culminating in an increase in glucocorticoid circulation in blood. It was found that single acute exposure to restraint, forced swimming, and a change in environment stressors elevated both plasma ACTH and corticosterone concentrations in mice[8]. Michaud *et al* [9] has reported that the impact of stressors leads to a marked increase in HPA activation, resulting in elevated circulating cortisol levels in animals and humans. There are ample data suggesting that stressful events, through their effects on cortisol levels and reactivity, may influence psychological and physical pathology.

Trier Social Stress Test, a widely-used standardized psychosocial stress protocol, has been administered to 73 healthy adults (50 men, 23 women; mean age 47.3 ±7.7 years). Cortisol responses were measured by six saliva samples taken before and after the stress exposure. The results indicated a significant cortisol increase following stress[10].

Increasing Corticosteroids and Central Serous Chorioretinopathy Bouzas observed 60 patients affected by Cushing's syndrome, three (5%) of whom developed one or more episodes of CSC during the period of active disease while plasma cortisol levels were high [11]. Gass *et al* [12] has reported that three patients with CSC developed bilateral bullous serofibrinous exudative retinal detachment following treatment with systemic corticosteroids. Mndrinos *et al* [13] illustrated an unusual case of CSC, presenting as bilateral and multifocal isolated serous retinal pigment epithelium detachments (RPEDs) following corticosteroid treatment. In a sample of 46 CSC patients, 27 patients had been taking exogenous corticosteroids (oral, intravenous, inhalative, cutaneous, and intraarticular) up to 4 weeks prior to the onset of symptoms [14]. Symptoms occurred in some patients when their daily corticosteroid dosage was elevated, and the visual complaints ameliorated or even disappeared in some cases upon discontinuation of the corticosteroid therapy [15]. Zhang *et al* [16] found adrenaline can result in choroidal capillary, venous congestion and serous neurosensory retina detachment.

Corticosteroids, Choroid Vessels, and Retinal Pigment Epithelium Steroid hormones play various roles in vascular functions through specific receptors localized in the endothelium and underlying vascular smooth muscle cells (VSMCs)[17]. In anesthetized rabbits, the topical application of dexamethasone to the ear produced an initial vasodilation followed by a vasoconstriction with long delay (120 minutes)[18]. Glucocorticoids act on vasoconstriction through reduced prostacyclin production, increased alpha-adrenoceptor numbers, and inhibition of NO synthase. Mineralocorticoids induce hypertrophy and hyperplasia of the VSMCs and perivascular fibrosis, and cause peripheral vascular resistance, in addition to changes in vascular electrocyte permeability. Recent studies have also demonstrated that steroid-producing or steroid-metabolizing enzymes are expressed in the vascular wall, suggesting local regulation of steroids in the vascular system[17]. Experimental studies have suggested that aldosterone and glucocorticoids may play a role in the pathogenesis of endothelial dysfunction. Acute short-term systemic administration of aldosterone results in endothelial vasodilator dysfunction in normal men, providing evidence for an aldosterone-induced vasculopathy[19]. This may be particularly relevant to damage of choroid vessels. The leakage that occurs in CSC may emanate from a localized injury of the choriocapillaris with the associated abnormally elevated leakage from these vessels[20].

In a study of 32 patients with acute or chronic CSC, all patients demonstrated a localized delay in arterial filling followed by choroidal hyperperfusion in the area of the damaged RPE. This is frequently associated with dilated capillaries and dilated draining venules in one or more choroidal lobules. These changes corresponded to the areas with pigment epithelial detachment or focal leakage from the RPE found in fluorescein angiography (FA). Furthermore, in some patients, localized choroidal ischemia could be observed in additional areas throughout the central fundus in both the diseased eye and the normal eye [21]. In idiopathic serous pigment epithelium detachment, 83.3% of a sample of patients showed choroidal hyperpermeability. An irregular

dilatation of the choroidal veins at the site or within an area of one disk diameter from the detachments could be visualized using indocyanine green videoangiography in 33.3% of affected eyes[22]. In active CSC, indocyanine green angiography showed a choroidal filling delay (71%), venous dilation (61%), and focal choroidal hyperfluorescence (96%) surrounding the leakage from the RPE. Focal choroidal hyperfluorescence was present in unaffected areas of the affected eyes (55%). The choroidal venous dilation (36%) and choroidal hyperfluorescence (62%) were noted even in unaffected fellow eyes[23].

Early in the 1980s, it was suggested that corticosteroids could damage the RPE barrier and predispose a patient to serous retinal detachments[24]. In most cases, there is leakage of fluorescein-stained fluid from one or more small lesions in the RPE. FA demonstrates that choroidal vascular leakage is associated with histologically irregular, narrow choroidal arterioles and choriocapillaris, hypertrophy of Bruch's membrane, and loss or degeneration of the overlying RPE [25,26]. It can be inferred that increased plasma cortisol concentrations might alter the permeability of the choriocapillaris in one or more focal area in the posterior fundus so that large proteins gain entrance to the RPE and subretinal space, causing leakage of fluid into the subretinal space. Moreover, abnormal choroid vessels may cause RPE damage and incapacitation.

CONCLUSION

It has been known for a long time that psychological stress is associated with CSC, but the exact cause was not clear. The hypotheses of this paper provide a possible pathophysiology mechanism for CSC induced by psychological stress. We hope that this will provide useful information for further research and the development of treatment for CSC.

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