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Potential involvement of mineralocorticoid receptor activation in the pathogenesis of central serous chorioretinopathy: case report

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Abstract. – BACKGROUND: Recently it has been suggested that excessive glucocorticoid-dependent choroidal mineralocorticoid receptor (MR) activation may be involved in the pathogenesis of central serous chorioretinopathy (CSCR).

AIM: To present a 38 year-old woman with an impressive improvement of CSCR following MR antagonist eplerenone administration.

CASE REPORT: At presentation, visual acuity (VA) was 0.2 in the left eye and 1.0 in the right eye. Optical coherence tomography (OCT) of the left eye showed extended serous retinal detachment including the macular area.

RESULTS: After six weeks of treatment with eplerenone (25 mg/day) total resorption of subretinal fluid with an increase in VA to 0.8 was observed. At that point the therapy with eplerenone was discontinued, with no recurrence in the left eye during five months follow-up. Two months after the discontinuation of eplerenone, subretinal fluid accumulation in the right eye was revealed by OCT. Four weeks after reintroducing the treatment with eplerenone (25 mg/day) almost total resorption of subretinal fluid in the right eye was observed.

CONCLUSIONS: The effectiveness of MR antagonism in unresolved CSCR supports the hypothesis that excessive choroidal MR activation may be a potential pathological pathway leading to CSCR, and MR blockage may be an effective treatment option for CSCR. Controlled clinical trials are necessary to evaluate this therapeutic approach.

Key Words:
Central serous chorioretinopathy, Eplerenone, Mineralocorticoid receptors.

Introduction

Central serous chorioretinopathy (CSCR) is characterized by subretinal serous fluid accumulation and retinal detachment. Pathogenesis of CSCR is complex and not fully understood. The acute form of the disease may resolve spontaneously; however, some patients develop chronic CSCR leading to irreversible visual acuity (VA) loss resulting from chronic macular oedema and photoreceptor atrophy in the fovea[1,2].

The main risk factors for CSCR are systemic and/or locoregional glucocorticoids use and conditions characterized by endogenous hypercortisolism, such as Cushing's syndrome, psychological stress, type A personality and pregnancy[3]. Several other risk factors associated with CSCR have been described, such as male sex, hypertension, collagen vascular diseases and Helicobacter pylori infection[4].

Glucocorticoids have the affinity both to the glucocorticoid and mineralocorticoid receptors (MR). Mineralocorticoid receptors are present in kidney, vascular smooth muscle and endothelial cells. Excessive MR activation may promote vascular oxidative stress and inhibit vascular relaxation. Subsequently, it may contribute to vessel inflammation, fibrosis and remodeling, and lead to cardiovascular disease[5]. Several studies have shown beneficial effects of MR antagonism in the cardiovascular system, even when aldosterone levels are not elevated[6].

Recently, it has been shown that MR are expressed in several types of the neuroretina[6-8]. Excessive MR activation may result in the promotion of retinal neovascularization, inflammation and increased reactive oxygen species production, as observed in the diabetic retinopathy. Moreover, protective effects of MR antagonism on retinal vascular pathology have been demonstrated[7].

It has been also suggested that MR activation by endogenous or exogenous glucocorticoid excess is a potential pathological pathway leading to the vascular chorioidopathy in CSCR[9]. Two patients with chronic unresolved CSCR with a marked improvement after MR antagonist eplerenone treatment have been reported so far[9]. This report presents an impressive improvement of CSCR following eplerenone administration in a 38 year-old woman.

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Case Report

A 38 year-old Caucasian woman had suffered from impaired, blurred vision in the left eye since June 2012. On the basis of ophthalmologic evaluation including VA assessment, fundoscopy, intraocular pressure measurement and optical coherence tomography (OCT; iVueSD-OCT, Optovue, Inc., Fremont, CA, USA) she was diagnosed with central serous chorioretinopathy. At the time of diagnosis VA was 0.2 in the left eye and 1.0 in the right eye. OCT of the left eye showed extended serous detachment of the neurosensory retina including the macular area, without retinal pigment epithelial (RPE) detachment. The extent of retinal detachment is presented on Figure 1a. The right eye was unaffected. Among systemic factors associated with CSCR type A personality and recent stressful events were identified. Other systemic factors associated with CSCR, such as glucocorticoid use, hypertension, pregnancy and Helicobacter pylori infection were excluded. Morning serum cortisol was 16.9 μg/dl (normal range: 4.45-22.7). Endogenous hypercortisolism (Cushing's syndrome) was excluded on the basis of the test with 1 mg of dexamethasone (serum cortisol after oral administration of 1 mg of dexamethasone – 0.91 mg/dl). Serum testosterone was 2.07 nmol/l (normal range: 0.198-2.68). As there were no clinical signs and symptoms of the excess of aldosterone, such as hypertension and swelling, the concentration of aldosterone was not tested.

The clinical course of the disease had been monitored with OCT without any specific treatment in the expectation of spontaneous resolution. Three months after the onset of symptoms no significant improvement was observed (Figure 1b). Laser photocoagulation was planned if retinal detachment persisted in subsequent three weeks. Fluorescein angiography was scheduled prior to laser photocoagulation in order to localize the foci of RPE leakage.

Based on the last report of Zhao et al[9], suggesting that blockage of mineralocorticoid receptors could be effective in the treatment of CSCR, treatment with MR antagonist eplerenone at 25 mg/day was started resulting in impressive decrease of subretinal fluid accumulation after three weeks, as evidenced by OCT (Figure 1c). VA in the left eye increased to 0.6. The patient had subsequently been on eplerenone (25 mg/day) for the next three weeks. The treatment resulted in total resorption of subretinal fluid (Figure 1d) with an increase in VA to 0.8. At that point the therapy with eplerenone was discontinued, and no recurrence has been observed in the left eye during five months follow-up (Figure 1e). The tolerance of the therapy was very good. Blood pressure was not significantly affected by the treatment with eplerenone (110/70 mmHg before the treatment and 105/65 mmHg after six weeks of treatment). No significant changes in kaliemia and plasma creatinine were observed during the therapy. As the subretinal fluid resolved after eplerenone treatment, fluorescein angiography and laser photocoagulation were not performed.

Two months after the discontinuation of eplerenone, subretinal fluid accumulation in the right eye was revealed by OCT (Figure 2a). VA in the right eye was 0.8. The therapy with eplerenone (25 mg/day) was reintroduced. After four weeks of treatment with eplerenone almost total resorption of subretinal fluid in the right eye (Figure 2b) with an increase in VA to 0.9 was observed.

Discussion

Over the past years several treatment options have been attempted in CSCR with variable outcomes, such as β-adrenergic antagonists, carbonic anhydrase inhibitors, glucocorticoid receptor antagonists, low-dose aspirin, laser photocoagulation, photodynamic therapy with verteporfin, intravitreal injections of bevacizumab – monoclonal antibody against VEGF, and others[1,2]. Laser photocoagulation is often effective in achieving retinal reattachment in acute form of CSCR; however, there is some risk of development of subretinal neovascularization[2]. Nevertheless, no validated treatment for CSCR is currently available.

Men account for 72-88% of patients with CSCR[2]. Therefore, the possible contribution of testosterone to the pathogenesis of CSCR has been suggested. However, such association has not been confirmed so far[10,11]. In the presented 38-year-old woman with CSCR serum testosterone level was within normal range.

Although the exact pathogenesis of CSCR remains unclear, increased levels of endogenous or exogenous glucocorticoids have been identified as a significant risk factor for the development of CSCR[3,4,12]. Conditions characterized by endogenous hypercortisolism, such as Cushing's syndrome, type A behavior, psychological stress and pregnancy, have been associated with CSCR. Moreover, unlike in other types of choroiditis, the treatment with glucocorticoids was found to exacerbate the clinical course of CSCR[3].

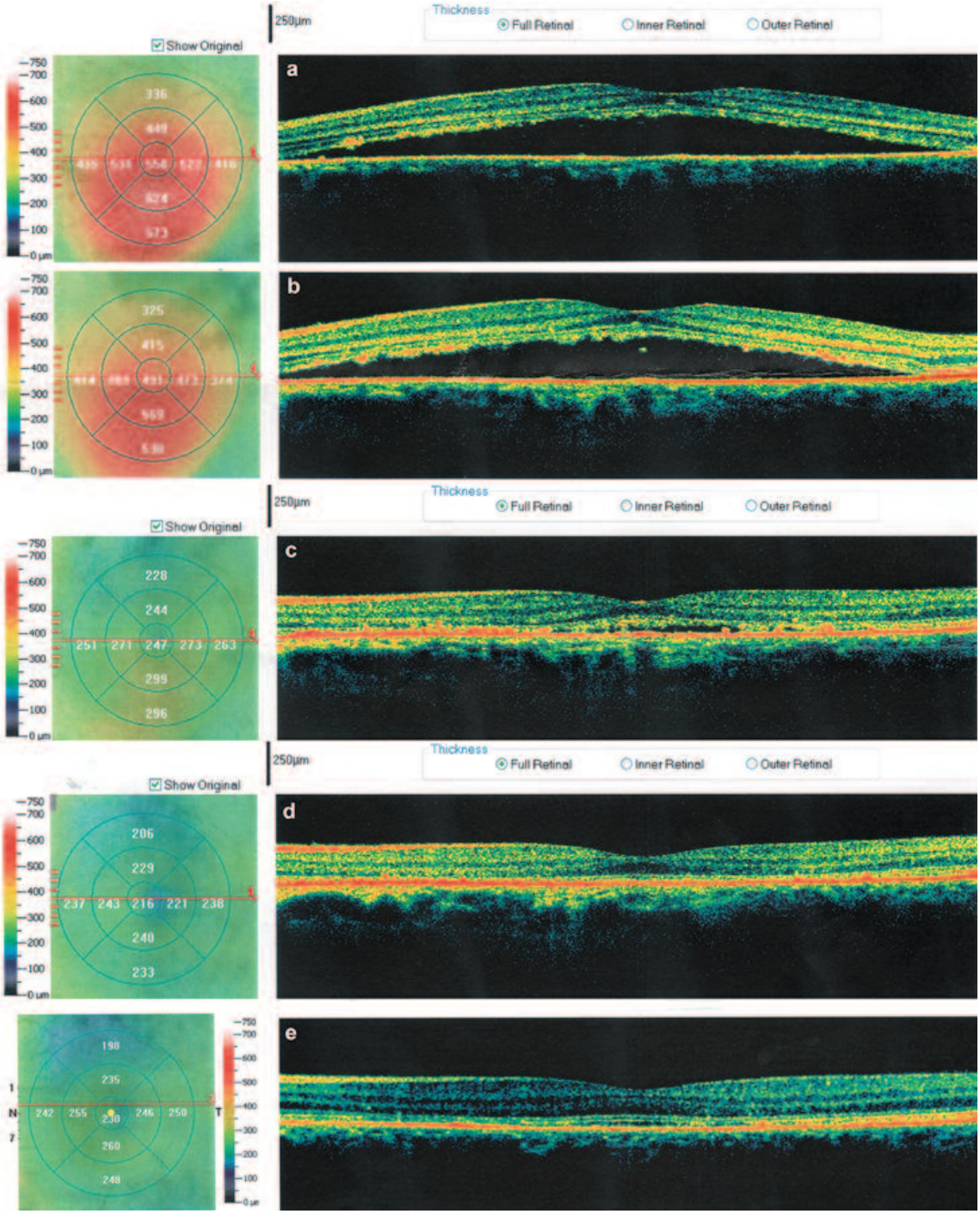

Figure 1. OCT of the left eye in a patient with CSCR before and after eplerenone treatment. At presentation, OCT showed extended serous retinal detachment including the macular area ***(a)***. Three months after the onset of symptoms no significant improvement was observed ***(b)***. Treatment with eplerenone at 25 mg/day for three weeks resulted in impressive decrease of subretinal fluid accumulation and improvement of the visual acuity in the left eye ***(c)***. After subsequent three weeks of treatment with eplerenone, total resorption of subretinal fluid was observed ***(d)***. Therapy with eplerenone was discontinued after six weeks, and no recurrence has been observed during five months follow-up ***(e)***. Left panels show retinal thickness maps divided into 9 regions, and the average thickness of each region (in micrometers) is displayed. The retinal thickness maps are color coded in accordance with thickness, with blue representing the thinnest areas. Circular lines represent 1 mm, 3 mm, and 6-mm scan diameter. The innermost 1 mm-diameter circle represents the fovea, with the foveal thickness displayed inside the circle. The inner macular area is delineated between the 3 mm-diameter circle and the fovea. The outer macular area is delineated between the 3 mm-diameter and 6 mm-diameter circles.

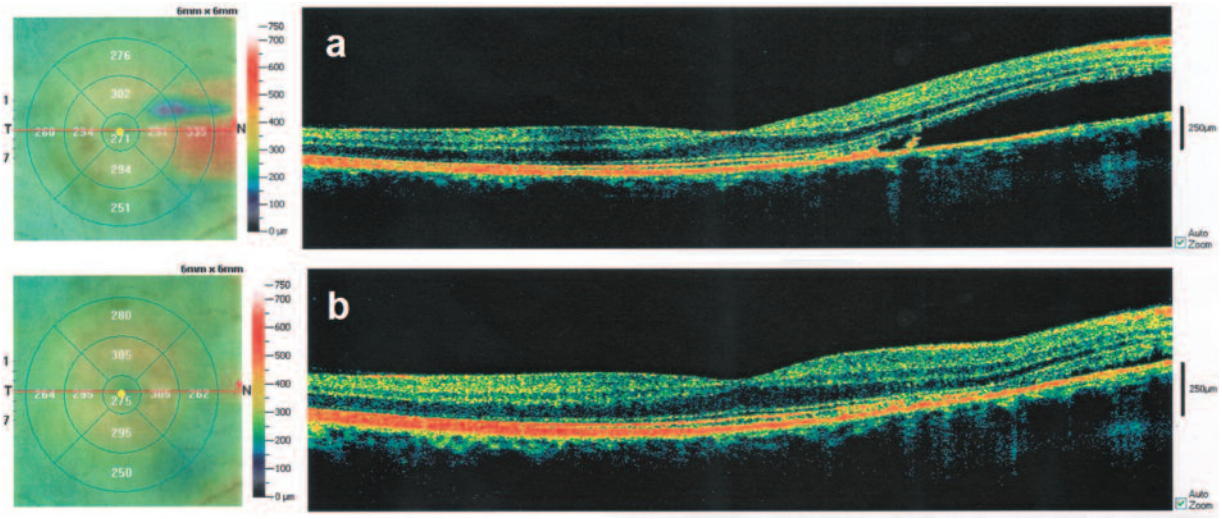

Figure 2. OCT of the right eye in a patient with CSCR before ***(a)*** and after four weeks of eplerenone treatment ***(b)***.

Based on the suggested role of glucocorticoids in the pathogenesis of CSCR, drugs suppressing adrenal steroidogenesis (ketoconazole) and type 2 glucocorticoid receptor antagonist (mifepristone) have been proposed as a medical therapy for CSCR. In a study concerning chronic CSCR, median lesion height assessed with OCT remained unchanged during four weeks of treatment with ketoconazole, and decreased after eight weeks[13]. In another small study in patients with acute CSCR, the treatment with ketoconazole did not result in a significantly better outcome[14]. Glucocorticoid receptor antagonist mifepristone had beneficial effect in 14/16 patients with chronic CSCR[15].

Although *in vivo* aldosterone is a much stronger mineralocorticoid than cortisol, *in vitro* cortisol and aldosterone have the same affinity for the MR[16]. Recently Zhao et al[9] have shown in rat studies that intravitreous injection of glucocorticoid corticosterone or a specific MR activator aldosterone, induced dilation of choroidal vessels and leakage. The Authors suggested that excessive activation of MR by glucocorticoids may be present in the choroid of patients with CSCR. They treated two patients with chronic nonresolved CSCR with MR antagonist eplerenone and reported resolution of choroidal vasodilation and retinal detachment accompanied by improved VA[9]. Similar impressive improvement of CSCR following eplerenone treatment was observed in the presented patient.

In aldosterone-sensitive tissues the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) preserves MR specificity for aldosterone by converting cortisol to its inactive metabolite cortisone (in rodents – corticosterone to 11-dehydrocorticosterone). As cortisone and 11-dehydrocorticosterone are not ligands for MR, 11βHSD2 protects MR from inappropriate activation by glucocorticoids[17]. 11βHSD2 has been detected in the retina[7], however in some cases its activity may be not sufficient due to the presence of 11βHSD2 inhibitors (such as licorice ingredient glycyrrhetinic acid) or mutations in the gene encoding 11βHSD2, as it happens in the syndrome of apparent mineralocorticoid excess (AME)[16]. The effectiveness of MR antagonism in unresolved CSCR supports the hypothesis that glucocorticoid-dependent choroidal MR activation may be involved in the pathogenesis of CSCR.

Clearly, it is not possible to estimate to what extent the improvement of CSCR in the presented patient and in two patients reported previously[9], is the result of treatment with MR antagonist eplerenone. In many patients with acute form of CSCR spontaneous resolution of retinal detachment is observed within 1.5-3 months without any treatment[2,4]. Therefore, in several cases, including the presented one, the course of the disease is monitored in expectation of spontaneous resolution. If retinal detachment persists for more than 3-4 months, laser photocoagulation directed at foci of RPE leakage should be considered[1,2]. In the presented case spontaneous remission cannot be excluded. However, the improvement in the left eye was seen relatively late after the onset of CSCR.

Conclusions

Our findings together with the recent results of animal studies[6-9] suggest that excessive glucocorticoid-dependent choroidal MR activation may be involved in the pathogenesis of CSCR, and blockade of MR could result in resorption of subretinal fluid and retinal reattachment in patients with nonresolved CSCR. Randomized placebo-controlled clinical trials are necessary to evaluate the effectiveness of MR antagonism in the treatment of CSCR.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editors of this journal.

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Statement of Interest

The Author declares that there is no conflict of interest. This study has not been supported by any grant.

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