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Original Article

# Serum renalase and cerebellin levels in acute central serous chorioretinopathy

**Mete Guler[1] · Burak Bilgin[2] · Filiz Alkan Baylan[3] · Selma Urfalioglu[1] · Gamze Gizem Duman[1]**

[1]*Department of Ophthalmology, Kahramanmaraş Sütçü Imam University, School of Medicine, Kahramanmaraş, Turkey*
[2]*Department of Ophthalmology, Bahçeşehir University, School of Medicine, Istanbul, Turkey*
[3]*Department of Biochemistry, Kahramanmaraş Sütçü Imam University, School of Medicine, Kahramanmaraş, Turkey*

## ABSTRACT

**Aim:** To compare the blood renalase and cerebellin-1 levels of acute central serous chorioretinopathy (CSC) patients with healthy subjects.

**Method:** A total of 33 eyes with acute naïve CSC (less than 2 months duration) and 31 healthy subjects were enrolled in this study. Idiopathic CSC was diagnosed based on the presence of a serous detachment of the neurosensory retina involving the macula that was confirmed using optical coherence tomography and leakage at the retinal pigment epithelium level using fluorescein angiography. Blood samples were collected and centrifuged at 4000 g for 10 minutes. The serum samples were collected and stored at -80 °C until required for analysis. Serum renalase and cerebellin-1 levels were measured using an ELISA kit.

**Results:** In CSC group 11 patients were female and 22 patients were male. In control group 10 participants were female and 20 were male. The sex was similar between groups. Mean age in CSC group was 41, 04±5, 94, in control group was 40, 67±6, 53. Mean ages were similar between groups. Mean renalase levels in CSC group was 27, 19±14, 01 ng/ml and in control group was 19, 12±15, 57 ng/mL. Mean renalase level was higher in CSC group. Mean cerebellin levels were 57, 76±29, 72 pg/mL and 52, 50±29, 25 pg/mL in CSC and in control groups, respectively. Mean cerebellin levels were similar in groups.

**Conclusion:** Comparing with healthy subjects serum renalase levels were higher and cerebellin-1 levels were similar in CSC patients.

**Keywords:** Cerebellin, central serous chorioretinopathy, optical coherence tomography, renalase.



✉ *Dr. Mete Guler,*
*Department of Ophthalmology, Kahramanmaraş Sütçü Imam University School of Medicine, Kahramanmaraş, Turkey.*
*E-mail: meteglr@yahoo.com*
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## Introduction

Central serous chorioretinopathy (CSC) is a common retinal disease characterized by a localized serous detachment of retina at macular region and has a relative high recurrence rate. Etiology and pathogenesis of CSC still remains ambiguous [1]. Focal retinal

pigment epithelium (RPE) barrier defects are likely related with CSC progression. Mechanical stress caused by intrachoroidal pressure elevation or dilated vessels in choroid, reduced RPE adhesion and RPE atrophy secondary to choriocapillaris hypoperfusion, high cortisol and catecholamine levels are some proposed mechanisms [2,3].

Cerebellin is derived from precerebellin and has neuromodulatory functions such as maintaining of synaptic structures and modulating of their functions. Today four cerebellin subtypes (Cbln1-4) are known [4]. It was previously thought that cerebellin genes were expressed only in the brain. However, it has been determined that cerebellin is secreted from adrenal gland, neuroendocrine system and pancreas [4-6]. Cerebellin mRNA was shown to be expressed in the tumour tissues of phaeochromocytoma, cortisol-producing adrenocortical adenoma, ganglioneuroblastoma and neuroblastoma [7]. Cerebellin has a stimulating effect on the secretion of aldosterone, cortisol and catecholamine from the adrenal glands [8]. Renalase is monoamine oxidase enzyme originating mainly from renal tissues directly degrades circulating catecholamines, (noradrenaline, adrenaline and dopamine) [9].

With the lights of aforementioned information, renalase and cerebellin speculatively may have role in the pathogenesis of CSC. In this study we aimed to compare the blood renalase and cerebellin-1 levels of acute CSC patients with healthy subjects.

## Materials and Methods

The study followed the tenets of the Declaration of Helsinki and was approved by the institutional clinical researches ethics committee (Approval Date: 22th Nov 2017). Informed consent was obtained from all of the participants. A total of 33 eyes of 33 patients with acute naive CSC and 30 eyes of 30 healthy subjects were enrolled in this study. The inclusion criterion for the study group was to have CSC less than 2 months duration. Inclusion criterion for the control group was to be healthy without any systemic disorder. The exclusion criteria included the following; history of systemic disorders such as hypertension, diabetes mellitus etc, systemic or topical use of vaso-active drugs which may affect blood pressure (such as pseudoephedrine, timolol etc). Patients underwent complete ophthalmologic examination including best corrected visual acuity, ocular tonometry, biomicroscopy, detailed fundus examination, fundus fluorescein angiography and optical coherence tomography (OCT). All patients were referred to the internal medicine outpatient clinic for systemic evaluation, especially systemic hypertension. All OCT scans and measurements were acquired through a dilated pupil with using the RTVue XR Avanti with AngioVue (Optovue Inc., Fremont, CA, USA).

Idiopathic CSC was diagnosed based on the presence of a serous detachment of the neurosensory retina involving the macula that was confirmed using optical coherence tomography and leakage at the retinal pigment epithelium level using fluorescein angiography. Blood samples were collected from patients and centrifuged at 4000 g for 10 minutes. The serum samples were collected and stored at -80 $^{\circ}$C until required for analysis.

### *Enzyme-Linked Immunosorbent Assay*

Serum renalase [Human Renalase ELISA kit catalog number: 201-12-3148 Shanghai Sunred Biological Technology Co., Ltd, Shanghai, China] and cerebellin-1 [Human Cerebellin-1 ELISA kit; catalog number: 201-12-3438

Shanghai Sunred Biological Technology Co. Ltd, Shanghai, China] levels were measured using enzyme-linked immunosorbent assay method according to the manufacturer's protocol. Specimen absorbance values were determined on Multiskan FC microplate reader (Scanlt for Multiscan FC 2.5.1, Thermo Fisher Scientific, and Finland) at a wavelenght of 450 nm. Values were expressed as nanogram/mL for renalase and picogram/mL for cerebellin. The intra-assay coefficient of variance (CV), inter-assay CV, detection range and sensitivity of the renalase kit were reported as <10%, <12%, and 3-700 ng/mL and 2.156 ng/mL, respectively. The intra-assay CV, inter-assay CV, detection range and sensitivity of the cerebellin-1 kit were reported as <10%, <12%, and 5-1500 pg/mL and 4.385 pg/mL, respectively.

### *Statistical Analysis*

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS ver. 20) and p value <0.05 was considered statistically significant. Previously normality was evaluated by using the Kolmogorov Simirnov and Shapiro-Wilk tests. Independent samples t test was used for comparison of normally distributed data and Mann-Whitney U test was used for comparison of non-normally distributed data.

## Results

In CSC group 11 patients were female and 22 patients were male. In control group 10 participants were female and 20 were male. The sex was similar between groups *(p=1.00)*. Mean age was 41.04±5.94 (32-55) years in CSC group and 40.67±6.53 (30-53) years in the control group, respectively. Mean ages were similar between groups *(p=0.829)*. Mean renalase level was 27.19±14.01 (4.36-61.60) ng/ml in CSC group and 19.12±15.57 (2.30-56.13) ng/mL in the control group. Mean renalase level was higher in CSC group *(p=0.039)*. Mean cerebellin-1 levels were 57.76±29.72 (15.18-138.76) pg/mL and 52.50±29.25 (12.18-162.94) pg/mL in CSC and in control groups, respectively. Mean cerebellin-1 levels were similar in groups *(p=0.776)*.

## Discussion

Central serous chorioretinopathy is more frequently seen with personality prone to stress and these people were reported to have higher levels of serum and urinary cortisol and catecholamines than healthy subjects [10]. Corticosteroids have been hypothesized to inhibit collagen synthesis (a main component of Bruch's membrane), and to increase choriocapillaris permeability by altering ion transport across RPE [11]. Cortisol may also directly damage the RPE cells or their tight junctions [11]. Several studies investigated the association between cortisol levels and CSC. Zakir et al found statistically significant higher mean serum cortisol levels in CSC cases than controls [12]. Endogenous hypercortisolism named Cushing's syndrome is found to be associated with CSC [11]. Central serous chorioretinopathy is also reported to be related with use of both systemic and local glucocorticoids [13]. Exposure to elevated levels of epinephrine induces apoptosis to RPE cells in vitro. Epinephrine metabolites, 3,4-dihydroxyphenylglycolaldehyde and hydrogen peroxide that originated by monoamine oxidase can induce apoptosis in RPE cells. Evidence suggests that monoamine oxidase is present in RPE cells [14]. Norepinephrine can increase choroidal blood flow that may contribute the development or exacerbation of CSC [15]. Michael et al reported CSC patients with

excessive use of sympathomimetic drugs. Visual symptoms of the patients alleviated after discontinuation of the sympathomimetics [15].

As previously mentioned, renelase and cerebellin exert opposite effects. Cerebellin has a stimulating effect on the secretion of aldosterone, cortisol and catecholamines while renalase directly degrades circulating catecholamines. Cerebellin-1 levels were similar in CSC and control patients in this study. Corticosteroids have alternative metabolisms that occurs primarily in the liver. Presumably circulating corticosteroid levels might be regulated by alternative metabolic pathways without affecting serum cerebellin-1 levels in CSC patients. Recent studies suggest that renalase plays an important role in blood pressure regulation via decreasing the levels of circulating catecholamines [16]. Increased renalase levels might be due to increased catecholamine levels in our CSC patients. On the other hand, all of our patients were normotensive. Increased renalase levels may have contributed to the prevention of hypertension in CSC patients. Since the literature information is limited, this mentioned association is speculative and we cannot make any precise scientific conclusion about the increment of serum renalase levels in CSC patients. One limitation of our study is we did not measure the aforementioned molecules aldosterone, cortisol and catecholamines that contribute to the pathogenesis of CSC. If we measured the levels of these molecules we could make more detailed discussion about biochemical relationships.

To the best of our knowledge it is the first study about the serum renalase and cerebellin-1 levels in CSC patients according to medline search. Comparing with healthy subjects serum renalase levels were higher and cerebellin-1 levels were similar in CSC patients. More detailed studies with higher number of participants are needed to prove the exact pathophysiologic roles of these proteins in CSC.

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***ORCID ID of Authors***

*Mete Guler / 0000-0002-6232-8445*
*Burak Bilgin / 0000-0001-6332-2371*
*Filiz Alkan Baylan / 0000-0003-3117-7768*
*Selma Urfalioglu / 0000-0002-3709-6988*
*Gamze Gizem Duman / 0000-0001-8690-7436*

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