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Central serous chorioretinopathy: Pathophysiology, systemic associations, and a novel etiological classification

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Abstract:

Central serous chorioretinopathy (CSC) has remained an enigmatic disease since its initial description by Von Graefe. Over the years, multiple risk factors have been recognized: these include psychological stress, behavioral traits, and corticosteroids. The basic pathophysiology of CSC involves choroidal thickening, vascular congestion, altered choroidal blood flow (ChBF), and choroidal hyperpermeability, leading to retinal pigment epithelium decompensation and subsequent neurosensory detachment. Multiple organ systems, mainly the nervous, cardiovascular, endocrinal, and renal systems participate in the control of the vascular tone and the ChBF via hypothalamus–pituitary–adrenal axis and renin–angiotensin–aldosterone system, while others such as the hepatic system regulate the enzymatic degradation of corticosteroids. Many vasoactive and psychotropic drugs also modulate the ocular perfusion. In addition, there are anatomical and genetic predispositions that determine its progression to the chronic or recurrent form, through cellular response and angiogenesis. We herein review the basic pathophysiology and immunogenetics in CSC along with the role of multiple organ systems. With this background, we propose an etiological classification that should provide a framework for customized therapeutic interventions.

Keywords:

Central serous chorioretinopathy, classification, etiology, pathophysiology, systemic associations

Introduction

Central serous chorioretinopathy (CSC) has remained an enigmatic disease since the first description by Von Graefe in 1866 as "recurrent central retinitis," in which an inflammatory component was implicit. While psychological stress and behavioral traits were recognized as potential contributing factors as early as in 1927 by Horniker, a paradoxical role of corticosteroids was not suspected until the disease was already known for a century; definitive evidence appeared another two decades later.[1,2] The next major association, the type A personality trait, was described by Yannuzzi in 1987.[3] As the diagnostic techniques such as fluorescein angiography, indocyanine green angiography, and optical coherence tomography gradually evolved, the tissue in which the disease was thought to originate shifted from retinal pigment epithelium (RPE) to the choroid.[4]

Nowadays, key events in the pathogenesis of CSC have been found to include choroidal thickening, vascular congestion, altered choroidal blood flow (ChBF), and choroidal hyperpermeability, leading to RPE decompensation and subsequent neurosensory detachment.[5] The implications of its multiple associations are manifold: first, an ideal classification of the disease has been elusive; the neuronal control of the ChBF means that eyes may just be end-organs manifesting a systemic

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condition of neurovascular origin. In addition, the disease has anatomical and genetic predispositions that determine its progression to the chronic or recurrent form, through cellular response and angiogenesis. We herein review the etiopathogenesis of CSC and propose to classify CSC as exogenous and endogenous (further subclassified as central, ocular, and peripheral) in origin with potential overlap and synergism.

Pathophysiological Mechanisms

The most salient feature of the pachychoroid spectrum is the presence of hypertrophic or congested vessels in the choroid (pachyvessels) with thinning of the overlying choriocapillaris, which is in contrast to a thickened choroid *per se*.[6] The normative value of choroidal thickness is subjected to physiological factors that may be either predetermined such as the axial length or subjected to physiological (diurnal) influences, pharmacological influences, and disease states such as end-stage renal disease.[6-11] In a recent review, Yeung *et al*. report a significant increase in choroidal thickness after intraocular pressure lowering therapies, atropine eye drops, and systemic administration of β-blockers and ethanol, while cyclopentolate, phenylephrine, caffeine, and nicotine are associated with reduced thickness.[10] Phenylephrine and sympathomimetics have also been linked with CSC,[12-14] and animal models of adrenaline-induced CSC support these observations.[15,16] Altered ChBF is a frequent mechanism that leads to increased hydrostatic pressure and increased capillary permeability. Still, it is intriguing that both vasoconstrictors such as sympathomimetics and vasopressin and vasodilators such as phosphodiesterase inhibitors (PDIs) and minoxidil are associated with CSC.[12-14,17-19]

In theory, vasoconstriction can induce hypoxia leading to RPE dysfunctions. Alternatively, the counter-regulatory mechanisms aimed at maintaining the ocular perfusion may lead to increased choroidal thickness in response to epinephrine.[16] The effects of mydriatics and cycloplegics on choroidal vasculature have been studied mostly in normal subjects.[20] It remains unclear if the autonomic dysfunction[5] would lead to a different outcome in CSC patients.

Anatomical features such as pachysclera and a small axial length with the associated refractive states predispose to what we will term as "CSC of ocular origin" with pachychoroid itself being a consequence of rigid sclera impeding the vascular outflow.[21,22] Impedance to the vortex venous outflow in patients who have undergone scleral buckling procedures and choroidal effusion is reminiscent of CSC.[23] Spaide suggested that the vortex venous system could be a buffer compensating for the pulsatile arterial inflow within a rigid sclera and drew an analogy between CSC and varicose veins as both result from chronic venous insufficiency.[23] In a recent review, Kishi and Matsumoto concluded intervortex venous anastomoses to be among the key factors underlying the development of pachychoroid diseases.[24]

The human retina is devoid of neuronal innervation and the vascular flow across inner retina is solely determined by its metabolic need.[25] In contrast, the choroidal autoregulation depends on its cellular architecture, intrinsic choroidal neurons, and autonomic and sensory innervation.[25]

The hemodynamic changes and choroidal hyperpermeability are interrelated, and vasodilatation is a feature of CSC of diverse pathological and pharmacological origin. Nitric oxide (NO) serves regulatory function in neurotransmission and modulates vascular tone. Three different isoforms of the enzyme NO synthase exist: neuronal "n"NOS (or NOS-I), inducible "i"NOS (or NOS-II), and endothelial "e"NOS (or NOS-III).[26] Neuronal NOS-derived NO participates in central control of blood pressure. In the peripheral nervous system, it causes gastroesophageal reflux disorder (GERD) and erectile dysfunctions, both associated with CSC.

Inducible NOS is not constitutionally expressed in cells but can be induced by bacterial lipopolysaccharide and cytokines from diverse cells including macrophages leading to profound vasodilatation as in septic shock.[26]

Once expressed, iNOS is constantly active regardless of intracellular Ca^{++} levels;[26] it is unclear if this could be a feature of chronic CSC (cCSC) that have cellular and angiogenic activities.

Endothelial NOS-derived NO is a physiological vasodilator with vasoprotective roles.[26] Significant differences exist in the endothelium-dependent flow-mediated vasodilation in CSC patients but not in the endothelium-independent nitroglycerine-mediated vasodilation.[27] In addition to NO, the endothelial cells employ prostacyclin, and epoxyeicosatrienoic acids, a class of endothelial-derived hyperpolarizing factor for vasodilatation and endothelin (ET) for vasoconstriction.[27] ETs are peptides with three isoforms and at least four (ET_A, ET_{B1}, ET_{B2}, and ET_C) receptors expressed in many organs including the RPE where it is thought to regulate the ChBF; however, serum ET-1 level was normal in CSC.[28]

Adrenomedullin (AM) and calcitonin gene-related peptide are related members of the calcitonin family of peptides, sharing many biological properties and some sequence homology. Tittl *et al*. associated the exercise-induced

increased ChBF in CSC patients to AM activity and considered it as abnormal autoregulation.[29] Complement factor H (CFH) binds and interacts with AM to induce choroidal vasodilation and increase microvascular permeability. When co-infused with the NOS inhibitor NG-monomethyl-L-arginine, the vasodilatory action of AM was blunted though the effect on the ophthalmic artery was unmitigated implying different physiological characteristics of these vasculatures.[30] Karsa-Basta speculated that increased levels of pro-inflammatory cytokines lead to abnormal endothelium-dependent vasodilation.[31] In addition, bradykinin-mediated vasodilatation has been implicated in a case of CSC with idiopathic nonhistaminergic angioedema.[32]

Genetical Factors

Against a backdrop of several sporadic reports of familial CSC, a larger report that found cCSC to be familial in 52% of cases with an indetermined mode of inheritance kindled further interest in the genetics of CSC.[33] It received further impetus when the interaction between the complement system and AM was recognized. The three major pathways of the complement system, the classical, the lectin, and the alternative pathways are involved in the pathogenesis of CSC. The classical and lectin pathways modulate the production of C3b via the other C3-convertase (C4b2a) enzymes that include complement component 4 (C4) protein. The role of CFH and other genes is summarized in Table 1. In addition, the genomic copy number variations in the C4B gene are also linked to the risk with higher number of copies favoring protection.[36,50] Further, KCNT2, PIGZ, DUOX1, LAMB3, and RSAD1 have been identified as potential new candidate genes for cCSC specifically in females, the RSAD1 gene is associated with intrinsic sexual dimorphism of the cortisol response.[50]

Immune Mechanisms in Central Serous Chorioretinopathy

The association between CSC and single-nucleotide polymorphisms in the CFH gene implies a potential role of the immune system in CSC. Downregulation of vascular endothelial growth factor (VEGF) as shown in some studies on CSC suggested that the choroidal abnormalities in CSC may be driven by arteriogenesis and not angiogenesis.[51,52] While angiogenesis is induced by hypoxia and results in new capillaries, arteriogenesis is induced by physical forces, most importantly fluid shear stress. Other studies reported elevated levels of interferon-γ-induced protein-10 (IP-10) that induces apoptosis, cell growth, and angiostasis.[51] In contrast, Terao *et al*. demonstrated an increase in the levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-8, monocyte chemoattractant protein-1 (MCP-1/CCL-2), and IP-10 in aqueous humor with a progression from aCSC to cCSC;[53] They showed a strong association between the area of choroidal vascular hyperpermeability and MCP-1 concentration in aCSC. MCP-1 is one of the key chemokines that regulate the migration and infiltration of monocytes/macrophages. In a recent study involving an animal model of CSC induced by intravitreal aldosterone, pretreatment with melatonin reduced choroidal thickening and vasodilation as well as macrophage/microglial infiltration,[54] supporting the view that inflammatory component may appear as the disease evolves.[53] Sirakaya *et al*. considered a high monocyte to high-density lipoprotein (HDL) ratio to be a biomarker of CSC where the monocyte–macrophage system is pro-inflammatory while the HDL is protective.[55]

Karska-Basta *et al*. considered IL-6 to be a key factor in the pathophysiology of CSC as it was found to be upregulated in both aCSC and cCSC.[31] IL-5, IL-6, and IL-12 levels correlated with mean choroidal thickness in aCSC while IL-6, IL-8, and tumor necrosis factor-alpha plasma levels correlated with hypertension in cCSC.[31,56,57] IL-6 and VEGF alter the junctional integrity of RPE and downregulate occludin and zonula occludens-1. Therefore, the authors speculated that increased levels of pro-inflammatory cytokines could lead to abnormal endothelium-dependent vasodilation, increased vascular permeability, and angiogenesis, which all have been found to be characteristic of CSC.[31] Based on varied levels of cytokines, especially angiogenic MCP-1 and angiostatic IP-10, Liu *et al*. suggested the ratio MCP-1/IP-10, the "angiogenesis index" to be a biological determinant of angiogenesis in CSC.[39]

Autoimmunity has been implicated in the pathogenesis of CSC.[58,59] Ten Berge *et al*. considered the presence of anti-retinal antibodies an epiphenomenon resulting from induction of autoimmunity following the exposure of otherwise sequestered antigens or molecular mimicry.[58] The reported risk (odds ratio: 6.2) of CSC with previous antibiotic use could signify the presence of infectious agents exhibiting molecular mimicry.[60] The presence of anti-endothelial cell antibodies possibly signifies endothelial dysfunction and hyperpermeability in CSC.[59]

Etiological Classification of Central Serous Chorioretinopathy

While the data from recent imaging studies strongly favor the predisposing role of ocular anatomical factors, it is clear that the etiopathogenesis of CSC is far more diverse. It is likely that a subsequent second hit leads to CSC. Table 2 sums up our proposed etiological

Table 1: Genes associated with central serous chorioretinopathy

Gene	Action	Proposed mechanism for CSC development	Additional comments	References
CFH	Negative regulator of the alternative pathways of the complement system: Blocks the formation of C3-convertases Protects host cells from complement-mediated damage Blocks C3-convertases	Vasodilatation by binding to adrenomedullin Alters choroidal hemodynamics Increased vascular permeability	CFH haplotype H1: Protective for both aCSC and cCSC; H3 protective for cCSC Haplotype H2, H4, H5 conferred increased risk SNPs in the CFH variants rs1065489 and rs3753394 are protective Variants in rs1329428 and rs2284664 increased risk Variant rs3753394: Spontaneous resolution Variant rs800292: Increased choroidal thickness	Dorner *et al*.[30] de Córdoba and de Jorge[34] Schellevis *et al*.[35] Mohabati *et al*.[36] Kiraly *et al*.[37] de Jong *et al*.[38]
CD46 (encodes MCP-1)	Blocks all pathways of the complement through inactivation of C3b and C4b	Maintains epithelial integrity through cadherins and integrins	Proangiogenic	Liu *et al*.[39]
NR3C2	Encodes mineralocorticoid receptor, causes aldosterone activation	Choroidal thickening Vasodilation Increased vascular permeability	Variant rs2070951 and the GA haplotype associated with an increased risk for cCSC; importantly, these haplotypes have previously been associated with perceived stress, this study linked CSC risk factors to underlying genetic associations	Mohabati *et al*.[36] van Dijk *et al*.[40]
KCNT2	Located at CFH locus Unknown function	Unknown	Associated with CSC	Schellevis *et al*.[35] Hosoda *et al*.[41]
VIPR2	Controls corticosteroid secretion Vasodilatory effects + control of corticosteroid secretion Cutaneous vasodilatation	A neurotransmitter and part of gut-brain axis Alters ChBF	rs3793217 associated with choroidal thickness Upregulated by *H. pylori*: potential link with CSC	Kellogg *et al*.[42] Hosoda *et al*.[41] Sticlaru *et al*.[43] Told *et al*.[44]
ARMS2	Found in the placenta and the RPE-choroidal complex Component of the choroidal extracellular matrix		Protective effect on CSC and PCV Predisposes to AMD	de Jong *et al*.[38]
PTPRB	Angiogenesis Endothelial barrier functions	Vascular leakage	Encodes VEPTP	Schellevis *et al*.[35]
ADAMTS9	Cleavage of proteoglycans Inhibition of angiogenesis	Regulates ECM in choroid Angiogenesis	-	Schellevis *et al*.[35]
COL8A1	Endothelial cell and vascular smooth muscle proliferation and migration	Regulates ECM in choroid Angiogenesis	Expressed in endothelium and blood vessels	Schellevis *et al*.[35]
TNFRSF10	Induction of apoptosis, vascular smooth muscle proliferation, regulation of angiogenesis	Regulates ECM in choroid Angiogenesis Modulates hormone secretion from adrenal glands	TNF receptor superfamily member 10a	Schellevis *et al*.[35] Hosoda *et al*.[41]
GATA5	Cardiac and vascular development Inactivation results in vascular endothelial dysfunction	Vascular endothelial dysfunction in choriocapillaris	rs13278062: Susceptibility locus upregulated in *H. pylori* infection	Hosoda *et al*.[41] Giannopoulos *et al*.[45]
CDH5	Vascular homeostasis Endothelial cell cohesion and organization of intercellular junctions	Increased vascular permeability	Regulated by corticosteroids	Schubert *et al*.[46]
CYP21A2	Steroid metabolism		Encodes the enzyme 21-hydroxylase In linkage disequilibrium with C4B gene Putative	Bánlaki *et al*.[47]
LCN2/NGAL	Prognosticator of renal injury Increased expression of antioxidant enzymes	Low levels associated with increased oxidative stress and outer blood-retinal barrier dysfunctions	Upregulated by corticosteroids	Matet *et al*.[48]

Contd...

Table 1: Contd...

Gene	Action	Proposed mechanism for CSC development	Additional comments	References
CRH	Involved in HPA axis response system	Susceptibility gene for CSC	CRH-deficient mice have higher pro-inflammatory cytokines IL-6 and TNF-α, both lead to vascular hyperpermeability	Jin *et al.*[49]

KCNT2=Potassium sodium-activated channel subfamily T member 2, PIGZ=Phosphatidylinositol glycan anchor biosynthesis class Z, DUOX1=Dual oxidase 1, LAMB3=Laminin subunit beta 3, RSAD1=Radical S-adenosyl methionine domain containing 1, CD46=Encodes MCP-1, NR3C2=Nuclear receptor subfamily Group 3 C member 2, VIPR2=Vasoactive intestinal peptide receptor 2, ARMS2=Age-related maculopathy susceptibility 2 protein, ADAMTS9=A disintegrin and metalloproteinase with thrombospondin motifs 9, COL8A1=Collagen, type VIII, alpha 1, GATA5=GATA-binding protein 5 transcription factor, CDH5=Cadherin 5, LCN2=Lipocalin 2, IL-6=Interleukin-6, NGAL=Neutrophil gelatinase-associated lipocalin, CFH=Complement factor H, ChBF=Choroidal blood flow, ECM=Extracellular matrix, MCP=Membrane co-factor protein, SNP=Single-nucleotide polymorphism, VEPTP=Vascular endothelial protein tyrosine phosphatase, PTPRB=Protein tyrosine phosphatase receptor type B, CRH=Corticotropin-releasing hormone, CSC=Central serous chorioretinopathy, cCSC=Chronic CSC, RPE=Retinal pigment epithelium, HPA=Hypothalamus-pituitary-adrenal, TNF-α=Tumor necrosis factor-alpha, AMD=Age-related macular degeneration, *H. pylori*=*Helicobacter pylori*, aCSC=Acute CSC, PCV=Polypoidal Choroidal Vasculopathy

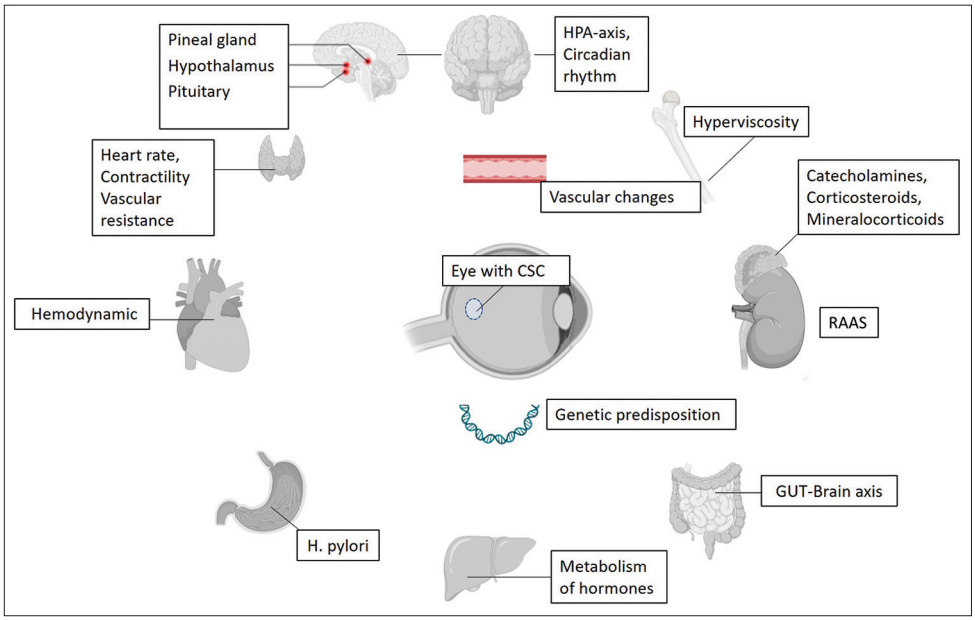

Figure 1: Systemic influences on eye with CSC. The influence of brain (HPA axis and the circadian rhythm), cardiovascular system (heart along with its innervation and vascular and hematological alterations), thyroid, kidneys, and gastrointestinal tract on eventual progression to CSC is shown here. The effects of *H. pylori* via the gut–brain axis are speculative at the moment. In addition, there are anatomical and genetic predispositions as well. CSC = Central serous chorioretinopathy, HPA = Hypothalamus–pituitary–adrenal, *H. pylori* = *Helicobacter pylori* (created with BioRender.com)

classification, while Figure 1 highlights the important organs that regulate the vascular tone or contribute to CSC pathogenesis indirectly. In the proposed scheme, trauma represents a rare exogenous cause. It is unclear if some of these cases especially those associated with bony fracture or throbbing headache had a loss of cerebrospinal fluid making way for a compensatory cerebral vasodilatation as per the Monro-Kellie hypothesis.[61,62] The hypothesis states that any decrease in volume of craniospinal content must be compensated by an increase in volume of another constituent or vice versa.[63]

Central Serous Chorioretinopathy of Central Origin

According to our proposed classification, CSC seen with psychological stress, personality disorders, circadian rhythm disturbances, and obstructive sleep apnea (OSA) seems to have a central origin. Endogenous Cushing's syndrome includes two major subtypes: adrenocorticotropic hormone (ACTH) dependent and ACTH independent; the ACTH dependent would qualify as having a central origin.

The classic fight-or-flight reaction is mostly due to the three major players: cortisol, adrenaline, and noradrenaline. However, estrogen and testosterone also affect the way we respond to stress. Anatomically, the hypothalamus–pituitary–adrenal axis (HPA) is closely integrated with the limbic system, a group of brain structures that regulate behavioral and emotional responses. It comprises hippocampus, medial prefrontal cortex, and amygdala. The hippocampus and anterior cingulate/prelimbic cortex inhibit stress-induced HPA activation, whereas the amygdala and perhaps the infralimbic cortex may enhance glucocorticoid secretion

Table 2: Etiological classification of central serous chorioretinopathy

CSC
Exogenous
Stress
Drug induced
Corticosteroids in autoimmune disorders
Sympathomimetic drugs
Other drugs
Psychotropic and vasoactive drugs
Hormonal replacement therapies
Drugs affecting the hepatic clearance of endogenous hormones
Trauma
Infection and/or vaccinations leading to pro-inflammatory cytokines
Endogenous
Ocular factors*
Pachysclera, vortex vein stasis
Central mechanisms
Stress, psychiatric and psychosomatic disorders
Type A personality
HPA axis derangements
ACTH-dependent endogenous Cushing's syndrome
Circadian rhythm disturbance
OSA
Autonomic dysfunctions#
Diabetes
Dysautonomia
POTS
Peripheral mechanisms
Cardiovascular
Hemodynamic
Coagulopathy and/or hyperviscosity states
Renal
Other endocrinal disorders
Adrenal tumors
ACTH-independent endogenous Cushing's syndrome
Thyroid disorders
Pregnancy
Hepatic dysfunctions leading to hormonal alterations
Gastrointestinal
GERD
Inflammatory bowel disorders
Helicobacter pylori infection
Other systemic associations

*Ocular factor and genetic predispositions may need additional mechanisms or synergistic factors, #These autonomic dysfunctions need further studies and validation. CSC=Central serous chorioretinopathy, HPA=Hypothalamus-pituitary-adrenal, ACTH=Adrenocorticotropic hormone, OSA=Obstructive sleep apnea, POTS=Postural orthostatic tachycardia syndrome, GERD=Gastroesophageal reflux disorder

through corticotrophin-releasing hormone from the hypothalamus which then stimulates the secretion of ACTH from the pituitary gland eventually leading to cortisol surge.[64-66]

Yannuzzi observed an association between CSCR and type A personality pattern;[3] such patients had a higher emotional distress index.[67] In addition, CSC is found to be associated with multiple psychiatric conditions such as anxiety, stress, depression, aggression, and sleep disorders.[68,69]

The circadian rhythm disturbances, including the diurnal variations in catecholamines and cortisol, are controlled by pineal glands which secrete melatonin according to the amount of light a person is exposed to. Shift work is associated with autonomic and metabolic dysfunctions.[70-72] OSA may be seen to be closely related to circadian rhythm alterations due to multiple spells of apnea that disrupt physiological sleep; the association between OSA and CSC is favored by recent studies, with odds ratios in the range of 1.05–4.67.[73,74] Untreated OSA patients exhibit higher ACTH and cortisol secretion suggestive of HPA axis activation in response to apneic events.[75]

The role of epinephrine in CSC has been demonstrated in an animal model.[15] Unlike similar experiment from the pre-OCT era, Cheong *et al*. demonstrated an increase in the subfoveal choroidal thickness following systemic administration of adrenaline.[16] In addition, adrenaline was shown to contribute to RPE dysfunction by induction of apoptosis.[76] Both catecholamines and cortisol levels are elevated in CSC.[77]

In subsequent sections, we describe the peripheral mechanisms.

Cardiovascular Diseases and Central Serous Chorioretinopathy

Apart from the nervous and the cardiovascular systems, the sympathetic nervous system brings together the HPA axis and the closely related renin–angiotensin–aldosterone system (RAAS), thereby integrating the kidneys in the multisystemic control of vascular tone. Prehypertension/hypertension and autonomic dysfunctions are recognized risk factors for CSC.[61,78-80] Conversely, some researchers have identified CSC as a risk factor for hypertension, hyperlipidemia, coronary artery disease, and ischemic stroke, which was most evident in middle-aged men.[81-83] Boonarpha *et al*. reported the thickest choroid in CSC patients with hypertension and hypothesized that the choroidal vascular bed of hypertensive CSC patients is more vulnerable to systemic changes than those with normal blood pressure.[84] Interestingly, Nasrollahi *et al*. recently proposed the intima–media thickness of the common carotid arteries as a biomarker of subclinical atherosclerosis in CSC.[85]

Normally, overperfusion of vascular beds is prevented by vasoconstriction induced by sympathetic stimulation. In CSC patients, autonomic dysfunction[5,86] has been

thought to result in choroidal hyperperfusion and secondary RPE dysfunction. Heart rate variability is a marker of sympathetic activity noted in CSC patients; decreased variability indicates an increase in sympathetic tone and a decrease in parasympathetic tone.[5,86] In addition, blood pressure variability and significantly reduced spontaneous baroreflex function are described in CSC.[87,88] The arterial wall of blood vessels is more susceptible to intermittent stress than to continuous stress as may be brought about by multiple risk factors working synergistically or sequentially.[88]

Increased risk of CSC among the patients with heart failure could be attributed to the activation of RAAS, which has been hypothesized based on an animal model study that exhibited aldosterone-mediated upregulation of the endothelial vasodilatory potassium channel (KCa2.3).[89,90]

It is intriguing that despite multiple studies reporting an association between CSC and hypertension, there are no reports of hypertensive retinopathy, accelerated hypertension, or choroidal infarction in CSC. A possible explanation could be the two-tier vascular arrangement of the retinochoroid with differential autoregulatory abilities. Autonomic dysfunctions could predispose patients with dysautonomia and postural orthostatic tachycardia syndrome to CSC. However, this has not been published yet. The aviators' CSC, usually attributed to stress, could also be closely related to physical factors such as hypoxia, low atmospheric pressure, altered acceleration due to gravity, and postural variation.[91] In that respect, CSC following organ transplant is another interesting scenario. It is thought to result from the use of corticosteroids as part of immunosuppressive regimen. However, additional factors could also play a role and these include complete autonomic denervation of organs such as the heart and kidney with heart contracting at its intrinsic rate, and kidney losing the control over the RAAS.

Coagulation imbalances in cardiovascular diseases and CSC may be pathogenic for both diseases. In both patient groups, elevated plasminogen activator inhibitor 1 may inhibit fibrinolysis and abnormal fibrin deposition,[92] which may be in line with the risk of retinal vein occlusion in CSC.[93] Recently, few cases of CSC following either COVID-19 or vaccinations such as Pfizer-BioNTech mRNA vaccine, Vaxzevria, and AstraZeneca have been reported.[94-97] With the global magnitude of the pandemic, these cases may be incidental, or psychological stress and consequent cortisol surge could be contributory factors. Alternatively, the associated cytokine storm, especially IL-6 surge and coagulopathy, could account for the occurrence of CSC in COVID-19. The AstraZeneca vaccine is known to induce inflammatory states that include vasculitis and immune-mediated thrombotic thrombocytopenia, while the Pfizer-BioNTech vaccine activates the monocyte–macrophage system with macrophages possibly representing the hyperreflective foci in the outer retinal layers in several published cases.

Renal Disease and Central Serous Chorioretinopathy

Consistent with the role of activation of RAAS, both glucocorticoids (as in endogenous Cushing's syndrome) and mineralocorticoids (primary hyperaldosteronism) are associated with CSC.[98,99] CSC and end-stage renal disease associated with hypertension, proteinuria, and renal fibrosis secondary to vascular injury[100] share the mineralocorticoid receptor (MR) pathway activation and vascular endothelial dysfunction.[101] Further, CFH binding to AM causes vasodilatation in both glomerular and choroidal capillaries.[100] Inflammatory processes implicated include release of pro-inflammatory cytokines secondary to oxidative stress.[101-103] CSC occurring in renal transplant patients is related to the usage of high-dose corticosteroids,[104] but hemodynamic derangements due to autonomic denervation, associated arterial hypertension, microangiopathy, and previous exposure to hemodialysis and surgery-related stress may be cofactors.[105]

Endocrinal Influences in Central Serous Chorioretinopathy

Corticosteroids are the major endocrinal influences in CSC. It was paradoxical that their anti-inflammatory effect offered no protection against CSC.[106] The broad categories of steroid receptors are the nuclear receptors to which glucocorticoid, mineralocorticoid, and sex hormone receptors belong, and the other classes are the G-protein-coupled receptors and the ion channels. Hippocampal MRs are involved in human HPA axis regulation.[107] Recently, Behar-Cohen's group demonstrated in a rat model that aldosterone upregulated the endothelial vasodilatory K channel KCa2.3 and its blockade prevented aldosterone-induced choroidal thickening.[90] The same group further suggested that chronic systemic dexamethasone treatment sets in an "HPA brake" that suppresses the glucocorticoid pathway and overactivates the mineralocorticoid pathway, specifically in the RPE/choroid complex.[108] The authors explain that local instillation of corticosteroids does possibly not lead to the "HPA brake," which is a systemic phenomenon.

Aldosterone has contrasting vasoactive roles: it has an endothelial vasodilator effect mediated by phosphatidylinositol 3-kinase-dependent activation of NOS, as well as a G-protein estrogen receptor-mediated vasodilator effect, and its direct action on smooth

muscles causes a vasoconstrictor effect.[109] Aldosterone also liberates ET-1 from endothelial cells, which elicits ET_A receptor-mediated vasoconstriction by inhibiting endothelial NO synthesis.[99,110] Chronic exposure to aldosterone results in impairment of endothelial dysfunction consistent with the observation of CSC in patients with primary hyperaldosteronism.[99,110]

Sex steroid hormone receptors are widely distributed in eye and several neurosteroids are synthesized in retina.[111] The female sex hormones, progesterone and estrogen, and decreasing levels of testosterone with advancing age are thought to have a protective effect in CSC.[112] Estrogen causes vasodilatation while progesterone has opposite effects. Estrogen modulator diindolylmethane for treating acne was reported to cause CSC.[113] Pregnancy-associated CSC usually occurs during the third trimester and resolves spontaneously after delivery,[114,115] consistent with the pattern of cortisol in the same period.[113,116] Bouzas *et al*. believed it to be associated with raised levels of endogenous cortisol leading to alteration in outer blood–retinal barrier.[98]

Human RPE cells have androgen receptors, and subjects with polycystic ovarian disease and type A personalities have high levels of testosterone.[112,117] Although isolated reports of patients with exogenous testosterones developing CSC exist,[118] elevated serum testosterone is rarely reported in patients with normal levels of cortisol, renin, and aldosterone.[119] Zhao *et al*. reported significantly increased androgen concentrations, including testosterone, free testosterone, and sex hormone-binding globulin in CSC patients, especially in the nonresolved CSC group.[120]

Adrenal tumors such as adrenal myelolipoma, carcinoma and adenoma lead to ACTH-independent endogenous Cushing's syndrome and resolve after surgical resection of tumors.[121-123]

Thyroid dysfunctions have multiple actions on the heart and cardiovascular system, such as changes in cardiac output, cardiac contractility, blood pressure, vascular resistance, and rhythm disturbances; conversely, restoration of normal thyroid function most often reverses the abnormal cardiovascular hemodynamics.[124] This is consistent with the observation of an inverse relationship between cCSC and thyroid replacement therapy, as this treatment may enhance the cortisol clearance.[125] Thyroid hormones modulate eNOS functions, regulate AM, and activate RAAS.[124] A positive correlation exists between serum TSH levels and cortisol levels.[126] Ulas explained these plausible associations by norepinephrine surge in hypothyroidism,[127,128] whereas Takkar *et al*. suggested roles of autoimmunity and extracellular matrix comprising glycosaminoglycans.[129]

Although no association of CSC with parathyroid glands is currently known, recent clinical and molecular research has shown that direct and indirect actions of these glands also affect the heart and vasculature through downstream actions of G-protein-coupled receptors in the myocardium and endothelial cells.[130]

Gastrointestinal System and Central Serous Chorioretinopathy

Many gastrointestinal disease states such as gastroesophageal reflux disease (GERD), *Helicobacter pylori* infection, and inflammatory bowel disease have been linked with CSC.[131,132] However, it may very well be the case that this association is indirect, as inflammatory bowel diseases (ulcerative colitis and Crohn's disease) are often treated with corticosteroids. Alternatively, the associated ocular inflammation may provide a milieu conducive to choroidal hemodynamic alteration.[132]

The psychosomatic nature of gastrointestinal disorders and CSC provides an alternative perspective: both GERD and CSC are associated with stress and have similar adaptive response to stress. A significant association was found between GERD and CSC by Manseutta *et al*., especially in the use of antacids/anti-reflux agents and development of CSC.[131] Another study in Taiwan identified peptic ulcer as an independent risk factor for CSC. These authors also noted that patients had a significantly higher chance of developing peptic ulcer after diagnosis of CSC.[133]

H. pylori is a possible etiological factor for occlusive arterial diseases in stressed young people,[134] and this disorder shares the characteristic type A personality with CSC. Further studies are needed to establish a significant association, also taking into account that Van Haalen *et al.* did not find an increased perception of psychosocial stress in their prospective study.[135]

Liver cirrhosis has been reported as an independent indicator of CSC in a population-based cohort study that reported a higher risk of CSC among cirrhotic patients with ascites and other complications.[136] Hepatic dysfunctions can modulate the plasma levels of corticosteroids. Indeed, rifampicin and ketoconazole have been used to promote the hepatic metabolism of cortisol. Further, the positive effect of discontinuing the drugs metabolized by the cytochrome 450 3A4 enzymes also supports the potential hepatic influences in CSC.[137]

Other Systems and Central Serous Chorioretinopathy

CSC has been reported after dermal, nasal, inhalational, intra-articular, and epidural steroids.[138] In addition, dermal application of minoxidil and nasal desmopressin also led to CSC.[17,18] CSC seen in autoimmune disorders is likely manifestation of the concurrent corticosteroids. Balkarli *et al*. recently reported a significant association with fibromyalgia syndrome, which is often associated with other risk factors of CSC such as anxiety disorder, depression, sleep disorders, and gastrointestinal symptoms.[139] PDIs have been long considered to have an association with CSC; apart from the pharmacological role of drugs such as sildenafil, an important feature is the underlying autonomic erectile dysfunctions in these subjects.[140] Hematological disorders such as cryoglobulinemia, Waldenstrom's macroglobulinemia, and purpura often receive corticosteroids, though hyperviscosity could be a contributory factor.[141]

Conclusion

Multiple organ systems, mainly the nervous, cardiovascular, endocrinal, and renal systems, participate in the control of the vascular tone via HPA axis, RAAS, and other mechanisms that include immunogenetic factors. Some patients may also have an anatomical predisposition to CSC. In addition, some disorders are associated with CSC indirectly through their respective medications. Currently, some CSC patients are difficult to treat, despite the availability of photodynamic therapy, which could be caused by the diverse mechanisms that are important in its pathogenesis. The proposed etiological classification may provide a framework for customized therapeutic interventions, although in many instances, mixed mechanisms may be possible. Virtually, any physician may come across a CSC predisposing condition. Hence, wide awareness among nonophthalmologists is crucial in pinning down a possible CSC cause.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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