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REVIEW ARTICLE

Pathophysiology of central serous chorioretinopathy: a literature review with quality assessment

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The pathogenesis of central serous chorioretinopathy (CSCR), a pachychoroid disease, is poorly understood. While choroid hyperpermeability and retinal pigment epithelium dysfunction are cornerstones for developing CSCR, the mechanisms at the retinal, vascular, retinal pigment epithelium, and cellular level continue to be an enigma. A few preclinical studies and the development of small-sized, poorly controlled clinical trials have resulted in limited insight into the disease mechanism. Effective treatments for CSCR are still lacking as current trials have produced inconsistent results for functional and structural gains. Thus, critically evaluating the literature to explore disease mechanisms and provide an up-to-date understanding of pathophysiology can provide valuable information and avenues to new treatments. In this study, a comprehensive summary of the mechanistic insight into CSCR is presented while highlighting the shortcomings of current literature. The mechanism was divided into seven sub-categories including mechanical obstruction, inflammation, oxidative stress, paracrine factors, autonomic dysfunction, mineralocorticoid receptors activation, and medications. We implemented validated tools like the JBI and CAMARADES to objectively analyze the quality of both clinical and preclinical studies, respectively. Overall, our analysis of the literature showed that no single mechanism was populated with a large number of sufficiently sized and good-quality studies. However, compiling these studies gave hints not only to CSCR pathogenesis but also pachychoroid disease in general while providing suggestions for future exploration.

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INTRODUCTION

Central serous chorioretinopathy (CSCR) is a part of the pachychoroid disease spectrum characterized by the thick choroid, serous retinal detachment at the macula, and retinal pigment epithelium (RPE) detachment with subsequent atrophy (Fig. 1) [1, 2]. CSCR affects mainly middle-aged males with a mean age of 40 years and presents with blurred vision, metamorphopsia, dyschromatopsia, central scotoma, hypermetropization and micropsia [3]. Acute CSCR is self-limiting, and 84% of cases resolve in 4–6 months with almost complete resolution of symptoms without requiring treatment [4]. Episodes lasting beyond 4–6 months are referred to as persistent, non-resolving, or chronic CSCR [5]. Chronic CSCR presents with a varying degree of RPE atrophy leading to a permanent and severe decline in visual acuity, often warranting intervention (Fig. 2) [5, 6]. CSCR symptoms are often reported in one eye but bilateral involvement can be detected in up to 40% of the cases [7, 8]. Because vision loss affects the working-age group, it can result in significant financial burden, loss of independence, and a negative impact on mental/physical health, consequently increasing the burden on the healthcare system [9]. As such, a prompt and accurate diagnosis is essential for initiating appropriate management to minimize vision loss. It is also important to rule out potential vision or life-threatening conditions that mimic CSCR such as inflammatory disease (e.g. Vogt–Koyanagi–Harada [VKH] or malignancies (e.g. leukemia) [10]. Clinicians must consider various features such as disease laterality (e.g. unlike CSCR, VKH presents as bilateral and symmetrical), presence of anterior or posterior uveitis, the status of the optic disc, presence of systemic features (e.g. alopecia and vitiligo in VKH), and findings on multimodal imaging; more details about CSCR differential diagnosis is discussed by Sahoo et al. [10].

An increase in CSCR research over the last decade, mainly clinical trials exploring treatment efficacies and oral medication, have shown inconsistent improvements in chorioretinal structure or visual acuity. Preclinical studies that explore CSCR pathophysiology are lacking in the literature and may relate to a paucity in the innovation of treatments while clinical trials have been small and uncontrolled. Advances in imaging modalities demonstrate that the hallmark of CSCR is choroid vascular hyperpermeability [11–13]. These hyperpermeable regions localize with thickened

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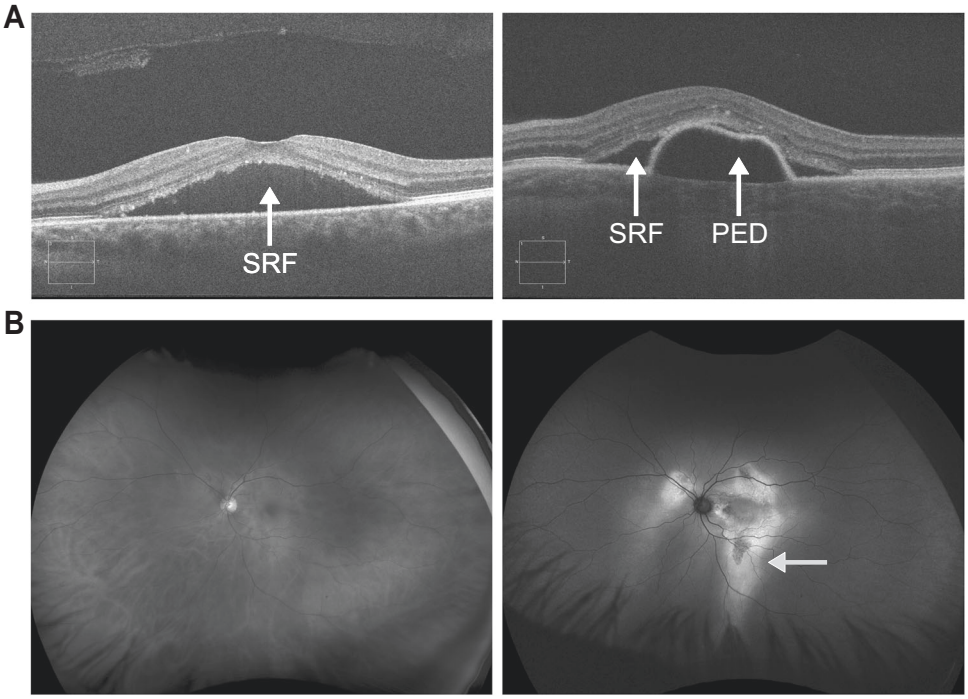

Fig. 1 CSCR phenotype. A Two different optical coherence tomography images showing subretinal fluid and pigment epithelial detachment. **B** The left panel shows a fundus photograph of a patient with chronic CSCR. The right panel is the corresponding red-free FAF image showing gravitational track region (yellow arrow) with RPE atrophy.

subfoveal choroid, also known as pachychoroid, consistent with choroidal vessel dilation and congestion [13, 14]. In addition to choroidal thickening, optical coherence tomography demonstrates thinning of the inner choroid (smaller choriocapillaris) and is likely a result of direct compression by enlarged outer choroidal vessels, hyperpermeable vessels causing increased hydrostatic pressure, and atrophy of choriocapillaris [14, 15]. Overall, it is hypothesized that ischemia from choriocapillaris compression and increased choroid parenchyma hydrostatic pressure, overwhelming the RPE barrier, causes a cascade of RPE dysfunction, detachment and micro-rips resulting in fluid accumulation in the subretinal space (Fig. 2). In general, this disease mechanism is termed the "pachychoroid-driven process" and is the hallmark of pachychoroid disease which includes CSCR, pachychoroid pigment epitheliopathy (PPE), polypoidal choroidal vasculopathy, pachychoroid neovasculopathy (PNV), pachychoroid geographic atrophy (pGA) (Fig. S1); more detailed discussion can be found here [16]. CSCR is thought to represent disease progression within the continuum of pachychoroid disease. For example, PPE is considered the "forme fruste" of CSCR as it presents with pachychoroid features and RPE changes but no exudative retinal detachment [16, 17]. Chronic CSCR is often considered the progression of acute CSCR. However, only 16% of acute CSCR patients progress to chronic CSCR and a majority of chronic cases (73%) are not preceded with an acute episode, which raises the question of whether or not they share similar pathophysiology driving pachychoroid changes [18, 19]. Eventually, prolonged ischemia from pachychoroid-driven processes can cause loss of RPE and photoreceptors resulting in pGA [20]. Unlike conventional geography atrophy, which is a drusen driven inflammatory process in age-related macular degeneration (AMD), patients with pGA are younger, have thicker choroid, lack drusen, present with a smaller area of atrophy and, the AMD risk allele (ARMS2 A69S) is less common [20]. Overall, when attempting to understand the pathophysiology of CSCR it should not be treated as an individual entity but instead should be considered part of the larger pachychoroid disease spectrum.

While the pachychoroid-driven process in CSCR is well appreciated with multimodal imaging, how this process occurs remains elusive. Emerging evidence shows that CSCR is a complex multifactorial disease likely involving venous congestion, inflammation, ischemia, and changes in hormone and the biochemical milieu involving factors such as catecholamine, corticosteroids, or inflammatory cytokines [12, 21–26]. This review has the goal of updating the current understanding of the pathophysiology of CSCR to assist founding ideas for new treatments. In addition, the plethora of publications dissecting the mechanism of CSCR will also help shed light on the etiopathology of pachychoroid disease. The authors have synthesized the literature pertaining to CSCR disease pathogenesis, and objectively assessed the quality of studies using the validated Joanna Briggs Institute (JBI), and Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) tool for clinical (observational/experimental) and preclinical studies [27].

METHODS

Literature search

A thorough literature search was completed using PubMed and Medline using the terms "central serous retinopathy" and "central serous chorioretinopathy' with other key phrases including "pathophysiology," "pathogenesis," "etiology" and "animal studies" and "animal model" from 1981 to 2021 (Table S1). After the initial review of literature, the etiology of CSCR was categorized into seven subheadings: mechanical obstruction; inflammation; oxidative stress; paracrine factors; autonomic system dysfunction; mineralocorticoid receptors activation, and medication. The search criteria were further streamlined to include "mineralocorticoid receptor antagonist," "corticosteroid or steroid," "paracrine factors or biomarkers," "oxidative stress," "inflammation," "sympathetic or autonomic regulation/dysregulation," "vortex vein," "venous congestion" and "gene association" (Fig. S2). Key article references were also identified using meta-analysis or original articles that were not found using the search strategy.

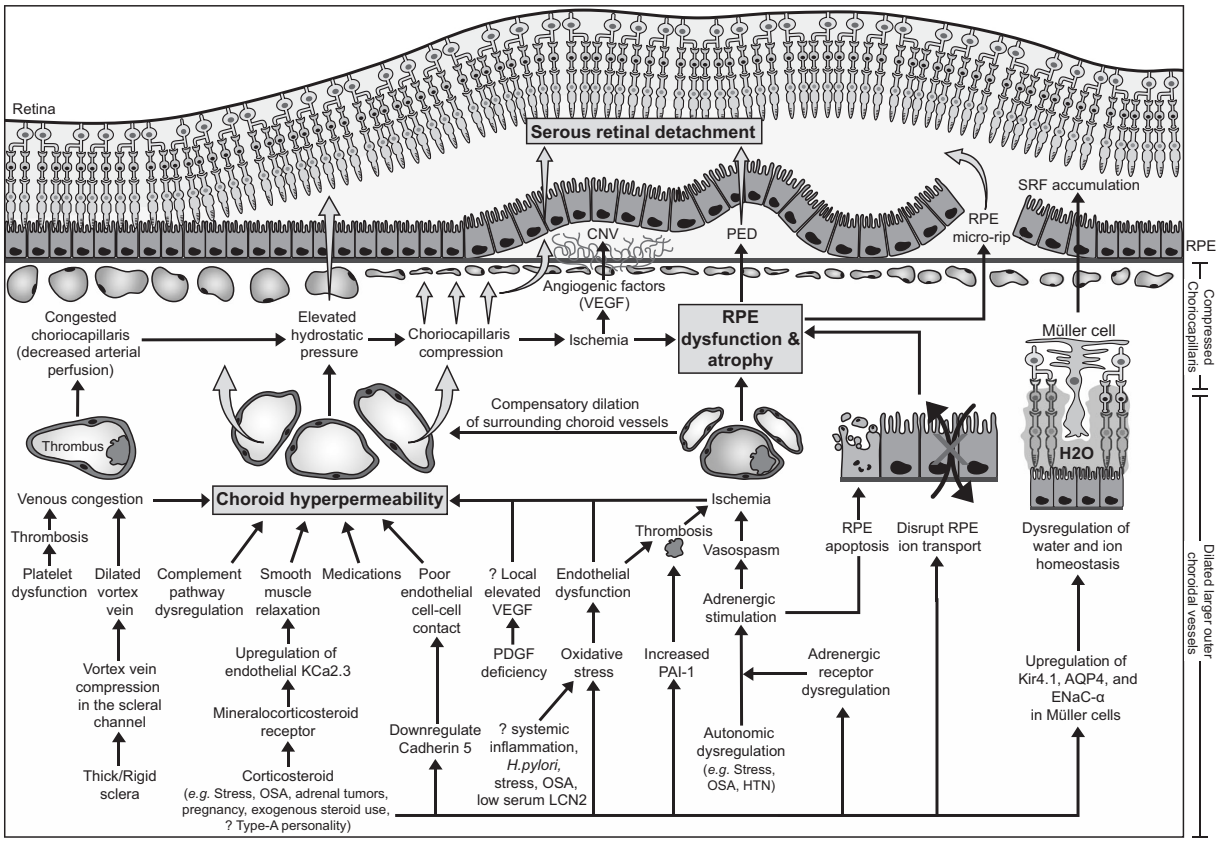

Fig. 2 CSCR pathophysiology. The schematic shows the potential mechanisms for developing CSCR. Various factors including mineralocorticoid receptor activation, vortex vein compression (venous congestion), dysregulation of complement or adrenergic pathway can result in choroidal vessel hyperpermeability or direct injury to RPE cells. Elevated hydrostatic may cause compression of choriocapillaris leading to ischemic damage to RPE cells, pigmented epithelial detachment, micro-rips or atrophy. RPE cells are overwhelmed and unable to provide adequate barrier resulting in subretinal fluid accumulation. Accumulation of subretinal fluid may be further exacerbated by changing Müller cell's water and ion homeostasis via corticosteroids. Prolonged ischemia can stimulate the release of angiogenic factors like VEGF resulting in CNV. CNV choroidal neovascularization, HTN Hypertension, LCN2 lipocalin 2, OSA obstructive sleep apnea, PAI-1 plasminogen activator inhibitor 1, PDGF platelet-derived growth factor, PED pigmented epithelial detachment, RPE retinal pigment epithelium, SRF subretinal fluid, VEGF vascular endothelial growth factor.

Quality assessment

The JBI checklist (Tables S2–S7) was used to assess the quality of all experimental, observational, and descriptive clinical studies by at least two independent authors (PK and AG) [27, 28]. To remain objective, we included studies that supported or undermined a mechanism for CSCR. The JBI could not be applied to assess the quality of genetic association studies. Studies not addressing mechanisms were not subjected to JBI quality assessment. For each individual criteria on the JBI checklist, to maintain objectivity, the following guidelines were used. If a study appropriately addressed the criteria (i.e., consistency in implementation, explained its rationale), then, it was given "yes". If a study mentioned the criteria but did not explain its rationale or did not subsequently apply it, then, it was given unclear. Otherwise, if a study omitted the criteria from its methods altogether, then, it was given "no". Each study was then given a rating score based on the number of "Yes" responses to each question in the checklist and was expressed as a percentage; very poor quality if 0–25% Yes to questions; poor quality if 26–50% and; fair quality if 51–75%; good quality if 76–100%. The scores from the two independent assessments were averaged for the final report. The search came across many studies showing potential links between corticosteroids and CSCR in either endogenous or exogenous use, however, not all studies could be discussed using quality assessment. When necessary, quality assessment of specific clinically relevant evidence was discussed, such as treatments targeting the pathway for mineralocorticoid receptors activation. Summaries of meta-analyses that discussed the association between steroids and CSCR were also included. To note, interpretation of results from interventional case series/reports (or poorly controlled trials) needed to be exercised with caution as improvement can be due to spontaneous disease resolution rather than intervention.

Similarly, the CAMARADES checklist was used to assess the quality of preclinical studies (Table S8) [29]. In general, the higher the score, the higher the quality of the publication and less likely to introduce biases.

RESULTS

The quality of clinical and preclinical studies reporting on the etiology of CSCR were assessed using the JBI and CAMARADES checklists, respectively (Tables S2–S8). Quality assessment was performed on a total of 51 clinical studies from 2003 to 2021 with 8% case controls, 12% cohort, 10% case reports, 31% case series, 16% cross-sectional analysis, and 23% RCTs (Table 1; Fig. 2 summarizes the mechanisms in a diagram). As shown in Fig. 3, most studies were observational/descriptive (predominated by case-series) and 50% of RCTs targeted the mineralocorticoid receptors (MR) pathway. Overall, 38%, 38%, and 24% of observational/descriptive studies had a JBI score range of 0–50% (very poor-to-poor quality), 51–75% (fair quality), and 76–100% (good quality), respectively (Fig. 3, Tables 1 and S2–S6). For RCTs,

Table 1. Summary of CSCR clinical studies.

Study	Proposed mechanism	Type of study	Sample size	Mean duration of CSCR symptoms	Interventional study	Findings	JBI score (%)
Mechanical obstruction							
Venkatesh P et al. [32]	Scleral thickening (increase vortex vein vascular resistance)	Case report	$n = 1$ patient	Chronic CSCR (5 years of decreasing vision)	Yes (scleral resection)	Partial thickness scleral resection with mitomycin C resulted in resolution of exudative retinal detachment after 4 months in a patient with chronic CSCR and border-line low axial length.	44% (Poor)
Imanaga N et al. [31]		Cross-sectional	$n = 87$ patients (40 CSCR and 47 age & gender matched controls)	N/A	No	Scleral thickness was statistically thicker in CSCR patients using anterior segment OCT	75% (Fair)
Kishi S et al. [23]	Vortex vein compression	Case series	$n = 32$ patients (21 acute and 11 chronic CSCR)	Acute <6 months Chronic >6 months	No	Acute CSCR patients showed greater filling delay (ICGA) in choriocapillaris that overlapped with areas of dilated vortex vein vs. chronic CSCR Acute CSCR demonstrated statistically greater central choroid thickness Asymmetry of vortex vein was not statistically different between acute and chronic CSCR	80% (Good)
Hiroe T et al. [30]		Cross-sectional	$n = 74$ patients (35 acute CSCR and 39 age-matched controls)	<6 months	No	100% of CSCR patients showed asymmetrical venous drainage by vortex veins vs. 38% in controls The dominant vortex vein was markedly dilated in CSCR patient's vs. controls	63% (Fair)
Inflammation							
Caccavale A et al. [43]	Inflammation causing hypercoagulable state resulting in choroid ischemia	Prospective cohort with historic control	$n = 198$ CSCR patients	N/A	Yes (109 treated with aspirin and 89 historic control patients)	Treated group achieved quicker visual recovery compared to control group	55% (Fair)
Mazzolani F et al. [39]	Inflammation causing oxidate damage	Case series	$n = 12$ CSCR patients	N/A	Yes (All patients treated with curcumin-phospholipid [anti-inflammatory properties])	At 12 months there was a statistically significant improvement in vision, reduction of subretinal or RPE detachment, and	70% (Fair)

Table 1 continued

Study	Proposed mechanism	Type of study	Sample size	Mean duration of CSCR symptoms	Interventional study	Findings	JBI score (%)
						decreased retinal thickness.	
Erol MK et al. [26]		Case-control	$n = 407$ patients (43 acute and 44 chronic CSCR and 320 age & gender matched controls)	Acute <3 months Chronic >3 months	No	Neutrophil/lymphocyte ratio (marker for inflammation) and C-reactive protein was statistically elevated in patients with acute CSCR vs chronic CSCR and control group The mean platelet volume was greater in acute CSCR patients vs. acute CSCR and control group	45% (Poor)
Sirakaya E et al. [38]		Cross-sectional	$n = 76$ patients (38 acute CSCR and 38 controls)	<3 months	No	Monocyte to high-density lipoprotein ratio (marker for inflammation) was statistically higher in CSCR group vs. control No difference between groups for, neutrophil/ lymphocyte ratio, c-reactive protein, and erythrocyte sedimentation rates	75% (Fair)
Khan NA et al. [40]		Retrospective cohort	$n = 57$ acute CSCR patients	N/A	Yes (13, 13, 16 treated with oral, topical or combination of diclofenac, respectively. 15 control patients)	No *p*-values reported Patients in all group were reported to show decreased macular thickness and improve visual acuity	35% (Poor)
Bahadorani S et al. [41]		Retrospective cohort	$n = 27$ eyes of acute CSCR patients	Acute <3 months	Yes (14 treated with topical bromfenac or nepafenac and 13 control)	Treatment group demonstrated statistically significant reduction in CMT	45% (Poor)
Paracrine mechanism							
Matet A et al. [48]	Decreased LCN2 alters RPE blood-retinal barrier and make it more susceptible to oxidative damage.	Case control	$n = 277$ patients (71 acute/recurrent and 76 chronic CSCR. 130 age and gender matched controls)	Acute/recurrent = no epitheliopathy Chronic = epitheliopathy	No (Measuring serum protein biomarkers)	Serum LCN2 alone or complexed with MMP-9 were statistically lower in CSCR patients vs. control. These levels were lower in the chronic vs. acute/ recurrent group	45% (Poor)

Table 1 continued

Study	Proposed mechanism	Type of study	Sample size	Mean duration of CSCR symptoms	Interventional study	Findings	JBI score (%)
Shin MC et al. [45]	PDGF deficiency promotes RPE dysfunction, decrease protection from oxidative stress, and promotes pericyte loss with local VEGF elevation resulting in choroid vascular dysfunction	Case series	$n = 40$ patients (20 CSCR and 20 control patients)	>3 months	Yes (proteomic analysis of aqueous humour before treatment with bevacizumab injection)	Significant decreased in PDGF in CSCR vs. control and no difference between IL-6, IL-8, MCP-1, and VEGF	75% (Fair)
Terao N et al. [24]	Pro-inflammatory milieu causing immune cell recruitment, oxidate damage and choroid vessel dilation.	Case series	$n = 58$ patients (18 acute and 20 chronic CSCR. 20 patients with PNV)	Acute <6 months Chronic >6 months	No (proteomic analysis of aqueous humour)	IL-6 and IL-8 in chronic CSCR were significantly elevated vs. acute and PNV, respectively.	75% (Fair)
Kimura T et al. [47]	Unclear mechanism (low serotonin levels may result in systemic vascular dysregulation)	Case series	$n = 93$ CSCR patients	Acute <6 months Chronic >6 months	No (measured blood serotonin levels)	The patients with lower serotonin level were more likely to have multiple (5 or more) leakage sites seen on fluorescein angiography, more recurrence of SRF, and worse visual recovery	90% (Good)
Sakai T et al. [46]		Case control	$n = 79$ patients (49 CSCR, 30 age matched controls)	Acute <6 months Chronic ≥6 months	No (measured blood serotonin levels)	Patients with chronic CSCR showed statistically significant decrease in blood serotonin levels compared to acute CSCR and control group	60% (Fair)
Jung SH et al. [25]	Unclear mechanism	Case series	$n = 57$ patients (10 acute, 22 chronic/ recurrent CSCR and 25 control patients)	Acute <3 months Chronic >3 months or recurrent (all CSCR patients had previously received bevacizumab treatment)	No (Proteomic analysis of aqueous humour collected during cataract surgery)	Only IP-10 significantly elevated in CSCR group vs control No significant elevation of MCP-1, VEGF, PDGF-AA, IL-6, IL-8, FGF-2 and TNF-α vs. control	70% (Fair)
Lim JW et al. [44]	VEGF and IL8 does not appear to play a role in choroid vessel hyperpermeability	Case series	$n = 20$ patients (8 acute and 4 chronic CSCR. 10 control patients for comparing cytokine)	Acute <3 months Chronic >3 months	Yes (Proteomic analysis of aqueous humour and plasma before treatment with bevacizumab injection)	No significant difference in VEGF and IL8 concentration in CSCR vs. control	75% (Fair)

Table 1 continued

Study	Proposed mechanism	Type of study	Sample size	Mean duration of CSCR symptoms	Interventional study	Findings	JBI score (%)
Karska-Basta I et al. [54]	Imbalance in proangiogenic and antiangiogenic factors may influence choroid vessel hyperpermeability. Lower levels of VEGF in CSCR suggests that CNV may result from arteriogenesis rather than angiogenesis	Case control	$n = 80$ patients (30 chronic CSCR, 30 acute CSCR, 20 controls)	Acute <6 months Chronic ≥6 months	No (Measured blood cytokine levels)	Significant decrease in the VEGF, PlGF, and PDGF-AA plasma concentration in (acute + chronic CSCR vs controls). Significant decrease in angiopoietin-1 levels in chronic CSCR vs. control. Significant decrease in PDGF-AA in acute CSCR vs control.	55% (Fair)
Bae SH et al. [51]	VEGF promotes choroid vessel hyperpermeability	RCT	$n = 32$ patients with CSCR	Chronic CSCR > 6 months Recurrent CSCR (symptom free period not defined)	Yes (18 patients received intravitreal ranibizumab, 16 patients received low-fluence PDT)	PDT treatment was superior to ranibizumab injection in maintaining complete resolution of SRF at month 12. Both groups showed improvements in visual acuity and central retinal thickness compared to baseline but no statistical difference between groups. PDT was significantly better at reducing choroid hyperpermeability.	66% (Fair)
Chung YR et al. [52]		Case series	$n = 71$ patients with CSCR	Chronic CSCR > 4 months Atypical CSCR (bullous retinal detachment, neurosensory detachment with tracts, multifocal disease) Recurrent CSCR (at least 3 months of complete resolution)	Yes (All patients received intravitreal bevacizumab injection)	Bevacizumab injection resulted in improved visual acuity vs baseline in the chronic and recurrent group but not atypical CSCR. Improvements in central retinal thickness was observed in all groups.	85% (Good)
Lim JW et al. [53]		RCT	$n = 24$ eyes of patients with CSCR	Acute <3 months	Yes (12 eyes received intravitreal bevacizumab injection, 12 eyes were observational control)	No significant functional or anatomical improvements were seen in CSCR patients receiving bevacizumab injection vs. observational control group.	19% (Very poor)

Table 1 continued

Study	Proposed mechanism	Type of study	Sample size	Mean duration of CSCR symptoms	Interventional study	Findings	JBI score (%)
Oxidative stress							
Turkcu FM et al. [69]	Oxidative damage causing RPE and choroid endothelial cell dysfunction	Cross-sectional	$n = 86$ patients (46 acute CSCR and 40 age and gender matched controls)	N/A	No (Measuring plasma antioxidant capacity)	Plasma total plasma total antioxidant capacity was significantly lower in CSCR compared to control group	75% (Fair)
Altinkaynak H et al. 2017		Cross-sectional	$n = 116$ patients (51 acute CSCR and 65 control patients)	<6 weeks	No (Measuring serum antioxidant capacity by quantifying thiol/disulfide homeostasis)	Antioxidative capacity (total thiol, thiol/disulfide ratio) was significantly lower in CSCR vs. control group	82% (Good)
Turkoglu EB et al. [70]		Cross-sectional	$n = 71$ patients (34 chronic CSCR and 37 age and gender matched controls)	>3 months	No (Measuring plasma antioxidant capacity by quantifying disulfide/thiol homeostasis)	Significantly elevated plasma disulfide/thiol ratio indicated lower antioxidant capacity in CSCR patients vs. control	75% (Fair)
Kunikata H et al. [68]		Cross-sectional	$n = 36$ patients (20 CSCR and 16 control patients)	N/A	No (Measured serum biological antioxidative capacity)	Significantly decreased serum biological antioxidant potential in CSCR vs. control group	38% (Poor)
Ratanasukon M et al. [75]	No benefits with antioxidant therapy	RCT	$n = 58$ acute CSCR patients	Acute <6 weeks	Yes (29 patients received treatment with high-dose antioxidant tablets and 29 served as control)	High-dose antioxidant tablets did not achieve significant visual or structural gains in acute CSCR patients	62% (Fair)
Autonomic dysregulation							
Michael JC et al. [77]	Adrenergic dysregulation causes vasospasm resulting in choroid ischemia and promote RPE dysfunction/apoptosis.	Case series	$n = 4$ acute CSCR patients	Few days to 2 months	No (Patients taking sympathomimetic medications like pseudoephedrine, oxymetazoline, or 3,4-methylenedioxymethamphetamine)	Resolution of CSCR coincided with stopping medication	39% (Poor)
Pierce KK et al. [79]		Case series	$n = 3$ patients with chronic CSCR	For one patient 7 months	No (Patients had history of taking ephedra	2 out of 3 patients showed resolution of CSCR after stopping ephedra	78% (Good)
Tewari HK et al. [78]		Cross-sectional study	$n = 73$(45 CSCR and 28 age matched controls)	N/A	No (sympathetic and parasympathetic activity was evaluated by measuring heart rate variability and changes in blood pressure at rest and with stressor stimuli)	CSCR patients showed significantly decreased parasympathetic and increased sympathetic activity	50% (Poor)

Table 1 continued

Study	Proposed mechanism	Type of study	Sample size	Mean duration of CSCR symptoms	Interventional study	Findings	JBI score (%)
Chen LC et al. [80]		RCT	$n = 120$ patients with acute CSCR	N/A	Yes (60 patients treated with oral propranolol and 60 received placebo	CSCR patient treated with propranolol demonstrated significantly quicker resolution, improved visual and structural gains, and decreased recurrence rate	15% (Very Poor)
Kianersi F et al. [82]		RCT	$n = 60$	N/A	Yes (30 treated with propranolol and 30 placebo)	Duration of disease was decreased in propranolol group (62 ± 29 days vs placebo (89 ± 44 days)	42% (Poor)
Chrapek O et al. [81]	Beta-blocker treatment showed no benefits	RCT	$n = 48$	Acute <2 weeks	Yes (23 treated with oral metipranolol and 25 placebo)	There was no statistical difference in the duration of CSCR symptoms between metipranolol and placebo group	54% (Fair)
Mineralocorticosteroid receptor activation							
Golshahi A et al. 2010	Ketoconazole inhibits steroid synthesis (decrease endogenous cortisol)	Retrospective cohort	$n = 30$ acute CSCR patients	N/A	Yes (15 Ketoconazole and 15 no treatment)	Treatment did not result in functional or anatomical benefits vs. control	35% (Poor)
Abrishami M et al. 2015	Methotrexate inhibits glucocorticoid response and has anti-inflammatory effects	Case series	$n = 23$ chronic CSCR patients	>3 months	Yes (Treated with oral methotrexate)	Treatment resulted statistically significant functional and anatomical gains compared to baseline	70% (Fair)
Gergely R et al. 2017	MR activation effects RPE ion transport, Muller cell water homeostasis, and causes choroid endothelial smooth muscle cell relaxation	Case series	$n = 28$ patients with chronic CSCR	>4 months	Yes (Treatment with eplerenone)	Statistically significant improvement in visual acuity and decreased SRF from baseline	85% (Good)
Herold TR et al. 2017		Case series	$n = 21$ eyes with persistent CSCR	>3 months	Yes (Treatment with spironolactone)	Statistically significant improvement in visual acuity and decreased SRF from baseline	80% (Good)
Kapoor KG et al. 2016		Retrospective Cohort	$n = 32$ CSCR patients	N/A	Yes (12 eplerenone, 12 spironolactone and 8 no treatment)	MRA resulted in statistically significant improvement in visual acuity and decreased SRF in all group vs. baseline. The 2 MRA were equal in efficacy No statistical difference between treatment group vs. control group.	50% (Poor)

Table 1 continued

Study	Proposed mechanism	Type of study	Sample size	Mean duration of CSCR symptoms	Interventional study	Findings	JBI score (%)
Zucchiatti I et al. 2018		Retrospective Cohort	$n = 27$ acute CSCR patients	<12 weeks	Yes (15 eplerenone, 12 no-treatment)	MRA resulted in Statistically significant improvement in visual acuity and decreased SRF/CMT vs baseline; no significant change vs. control. MRA resulted in statistically greater number of patients with SRF resolution vs. control	75% (Fair)
Pichi F et al. [99]		RCT	$n = 60$ patients with persistent CSCR	>3 months	Yes (20 treated with spironolactone, 20 eplerenone and 20 placebo)	Significant increase in visual acuity and decreased CMT with spironolactone. For eplerenone, functional and structural benefits only after switching to spironolactone. (note, significance was only compared to baseline not placebo)	62% (Fair)
Rahimy E et al. 2018		RCT	$n = 15$ chronic CSCR patients	>3 months	Yes (10 eplerenone and 5 placebo patients)	MRA resulted in statistically significant improvement in vision and decreased SRF/CMT vs. baseline; No significant change compared to placebo	73% (Fair)
Bousquet E et al. [57]		RCT crossover study	$n = 15$ CSCR patients	>3 months	Yes (8 spironolactone, 7 placebo. There was a 1-week washout period followed by crossover of treatment)	Spironolactone treatment resulted in statistically decreased SRF during initial treatment and crossover	77% (Good)
Sun Z et al. 2018		RCT	$n = 30$ chronic CSCR patients	>3 months	Yes (18 spironolactone, 12 observation)	Treatment resulted in faster resolution of SRF vs. control.	19% (Very poor)
Lotery A et al. [96] (VICI trial)		RCT	$n = 114$ chronic CSCR patients	≥4 months	Yes (57 eplerenone and 57 Placebo)	No statistical difference in functional and anatomical changes between groups	89% (Good)
Schwartz R et al. 2017		RCT	$n = 17$ CSCR patients	≥4 months	Yes (12 eplerenone and 5 placebo)	No statistical difference in functional and anatomical changes between groups	69% (Fair)
Shulman S et al. 2016	Oral Rifampin increases metabolic clearance of steroids	Case series	$n = 12$ chronic CSCR patients	≥3 months	Yes (treated with oral Rifampin)	Statistically significant functional and structural gains vs. baseline	80% (Good)

Table 1 continued

Study	Proposed mechanism	Type of study	Sample size	Mean duration of CSCR symptoms	Interventional study	Findings	JBI score (%)
Medications associated with CSCR							
Jain M et al. [103]	Altering neuroendocrine factors like dopamine and serotonin may effect choroid vessel tone	Case report	$n = 1$ patient	N/A (Presenting with new onset of symptoms)	No (Patient taking quetiapine)	SRF reduction 9 days after stopping quetiapine. Symptoms recurred after inadvertent use of medication after 10 of remission	20% (Poor)
Jain M et al. [102]	Disruption of gap junction protein (connexin 43) protein result in RPE and choroid vessel dysfunction	Case report	$n = 1$ patient	Acute (4 days)	No (Patient taking mefloquine)	Functional and structural improvement about 11 weeks after discontinuing medication	20% (Poor)
Gordon-Bennett P et al. [100]	Phosphodiesterase inhibitor result in vasodilation causing choroid hyperpermeability	Case report	$n = 1$ acute CSCR patient	Acute (presented after 10 days of symptoms)	No (Patient reported to taking tadalafil 5 days prior to symptom onset)	Functional and structural improvement seen 1 month after stopping tadalafil	20% (Very poor)
Mohammadpour M et al. 2019		Case report	$n = 1$ CSCR patient	Acute (presented 3 day of symptoms)	No (Patient reported to take sildenafil	Functional and structural improvement seen 4 weeks after stopping sildenafil	40% (Poor)
Fraunfelder FW et al. [101]		Case series	$n = 11$ CSCR patients	N/A	No (Patient reported to take sildenafil)	8 of the 11 cases stopped sildenafil therapy. 6 of the 8 patients that stopped therapy showed resolution of CSCR. In 3 resolved cases, CSCR reoccurred with resumption of sildenafil	0% (Very poor)
Breazzano MP et al. [105]	Unclear mechanism of how sildenafil decreased choroid thickness (? improved blood flow decreases ischemia resulting in better choroid vessel and RPE function)	Case series	$n = 4$ chronic CSCR patients	>6 months	Yes (Received Sildenafil)	3 of 4 patients demonstrated improvement in visual acuity. 2 patients showed resolving SRF associated with choroid thinning	75% (Fair)

CMT central macular thickness, *CNV* choroidal neovascularization, *CSCR* central serous chorioretinopathy, *FGF* fibroblast growth factors, *ICGA* Indocyanine green angiography, *IL* Interleukin, *LCN2* Lipocalin 2, *MCP-1* monocyte chemoattractant protein-1, *MMP* matrix metalloproteinases, *MRA* mineralocorticosteroid receptor antagonist, *OCT* optical coherence tomography, *PDGF* platelet-derived growth factor, *PDT* photodynamic therapy, *PlGF* placental growth factor, *PNV* pachychoroid neovasculopathy, *RCT* randomized controlled trial, *RPE* retinal pigment epithelium, *SRF* subretinal fluid, *TNF-α* tumor necrosis factor-alpha, *VEGF* vascular endothelial growth factor.

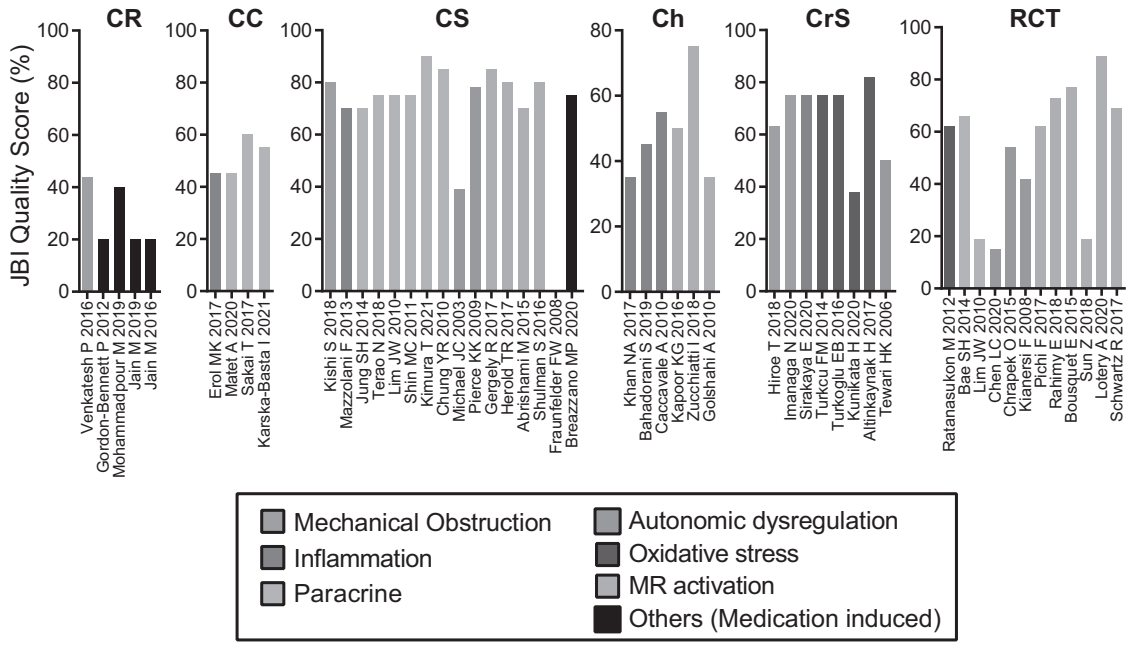

Fig. 3 JBI quality score for clinical studies. The graph shows the quality assessment score in percentage for case reports (CR), case-control (CC), case series (CS), cohort (Ch) studies, cross-sectional (CrS) studies, and randomized controlled trial (RCT). The mechanism of each study is colour coded as shown in the figure legend. MR mineralocorticoid receptors, JBI Joanna Briggs Institute.

34% of studies were very poor-to-poor quality, 58% fair quality, and 8% good quality (Fig. 3, Tables 1 and S7).

CAMARADES quality assessment was performed on 12 animal studies of which 58%, 42%, 0% rated very poor-to-poor, fair, and good, respectively (Tables 2 and S8).

Mechanism for developing CSCR

Mechanical obstruction. Mechanical obstruction of the dominant vortex vein, which drains the macula, may contribute to the pathogenesis of CSCR (Table 1) [23, 30]. Two studies demonstrated that patients with CSCR had asymmetrical dilatation of the vortex vein [23, 30]. Vortex veins transverse the sclera at an oblique angle and the narrowing of the scleral channel from thickened or rigid sclera is thought to result in venous congestion thereby increasing the permeability of choriocapillaris. A recent study showed that patients with CSCR had significantly thicker sclera compared to normal eyes [31]. Applying the JBI criteria across these studies (1 case series, 2 cross-sectional) revealed fair-to-good quality research but were limited by small sample sizes, did not identify or control for confounding factors, and had inherent inability of cross-sectional studies to assert a temporal relationship between exposure and outcome. In support of this hypothesis, a single interventional case report ($n = 1$ patient; JBI 44%) showed effective management of chronic CSCR after partial-thickness scleral resection but larger studies are needed to confirm these findings [32].

Acquired focal choroidal excavation (FCE) is described by a concavity in the choroid (mostly in the macula) and may belong to the pachychoroid disease spectrum as it shares many clinical features including thickened choroid and choroid vessel hyperpermeability [33]. It has been proposed that FCE may contribute to the pathogenesis of CSCR by mechanical compression of the choriocapillaris and Sattler layer under the concavity lesion thereby exacerbate ischemia-induced RPE/Bruch membrane damage [33, 34]. However, FCE may also be considered a sequela of CSCR thus, its role in pachychoroid disease progression remains unclear and requires further elucidation [35].

Lastly, mechanical compression of choriocapillaris by the pachyvessels in the Haller's layer is an important pathophysiological finding that guides the use of photodynamic therapy (PDT) in CSCR [36, 37]. Specifically, PDT exerts its therapeutic effect by damaging endothelial cells via radical formation which promotes large choroid vessel remodeling and shrinkage [36]. Ultimately, the shrinkage of large choroid vessels improves choriocapillaris blood flow by increasing pressures in the large vessels and/or alleviating the mechanical compression on capillaries [36].

INFLAMMATION

Although there is no sufficient data linking CSCR to systemic inflammatory disease, two studies demonstrated elevated systemic inflammatory markers (neutrophil-to-lymphocyte ratio and monocyte-to-high-density lipoprotein ratio) in patients with acute CSCR (Table 1) [26, 38]. These two studies demonstrated poor-to-fair quality scores (JBI 45%, 75%) and were limited by small-to-moderate sample sizes ($n = 76$, 407 patients), insufficient identification/control for confounding factors, and not using multimodal imaging to diagnose CSCR. It was proposed that the pro-inflammatory milieu may result in the generation of reactive oxidative species causing oxidative damage to RPE and choroid endothelial cells. One case series ($n = 12$ patients; JBI 70%) demonstrated that the use of curcumin-phospholipid (anti-inflammatory properties) provided structural and functional benefits but overall, the results are inconclusive as there was no control group [39]. Two small-sized ($n = 27$, 57 patients) retrospective cohort studies reported structural gains with the use of topical or oral nonsteroidal anti-inflammatory drugs but the quality of the study was poor (JBI 35%, 45%) due to insufficient control for confounding factors, short follow-up time, inadequate data presentation, and lack of statistical analysis [40, 41].

Choroidal endothelial dysfunction and local inflammation have been hypothesized to activate platelets resulting in thrombogenesis and ischemia in the choroid vessels [26, 42]. One study ($n = 198$ patients) that treated patients with aspirin for anti-thrombotic effects demonstrated quicker resolution of CSCR but no functional benefits [43]. This was a fair quality study

Table 2. Summary of preclinical studies.

Author and year	Preclinical model	Proposed mechanism	Notes	Peer-reviewed publication	Sample size	Reported animal age	Report animal gender	Reported Animal housing conditions	Randomization of treatment	Blinded treatment and/or data analyses	Validated by another independent group
In vivo studies											
Matsumoto H et al. [117]	In vivo Mice with sutured vortex veins	Vortex vein congestion results in choroid vessel dilation	Suture vortex vein induced thickening of choroid as seen on OCT (not quantified) and histology Gene expression from RPE–choroid–sclera complex demonstrated upregulation of inflammatory factors vs. control (no *p*-value) Macrophages (CD11b cells) not quantified over multiple histological sections. No negative control staining (showing background non-specific antibody binding) or confocal microscopy to confirm if positive CD11b signal is localized to a cell.	✓	$n = 6$ per group reported for measuring choroid thickness based on histological sections No replicates reported for OCT measuring choroid thickness, microarray data, and immunohistochemical staining of macrophages and RPE morphology	✓	✓	X	Not applicable	X	X
Zhao M et al. 2012	In vivo Rats with intravitreous injection of aldosterone and high dose corticosterone	MR activation caused upregulation of choroid endothelial potassium channels (KCa2.3) causing vasodilation resulting in choroid hyperpermeability	MR antagonist but not GR antagonist caused reversal of aldosterone-induced choroid thickening Increased expression of KCa2.3 in eyes with aldosterone injection was prevented by MR antagonist Negative control showed background KCa2.3 and endothelial cell (CD31) immunohistochemical staining but nuclear staining appears less bright compared to other samples (No mention if brightness/contrast setting are similar amount different images). No confocal microscopy to show colocalization between KCa2.3 and CD31 Did not provide lower magnification or serial histological images to show choroidal changes across a larger cross-sectional area Although protein expression of KCa2.3 was measured (western blot), gene (miRNA) expression was not quantified	✓	$n = 4$–8 animals per group	✓	✓	✓	X	X	X

Table 2 continued

Author and year	Preclinical model	Proposed mechanism	Notes	Peer-reviewed publication	Sample size	Reported animal age	Report animal gender	Reported Animal housing conditions	Randomization of treatment	Blinded treatment and/or data analyses	Validated by another independent group
Zhao M et al. 2010	In vivo Rats with intravitreous injection of aldosterone	MR activation caused retinal swelling by altering ion/water homeostasis. This was likely caused by upregulation of Müller glial cell sodium (ENaC-α), potassium (Kir4.1) and aquaporin 4 (AQP4) channels while promoting Kir4.1 and AQP4 localization to the outer limiting membrane	Aldosterone induced Kir4.1, and AQP4 expression was prevented with co-injection of MR antagonist	✓	$n = 3$ animals per group	✓	✓	X	X	X	X
Daruich A et al. 2015	In vivo Transgenic mouse with human MR over-expression restricted to the endothelium	Endothelial cell have increased contractile response to vasoconstrictors (e.g. phenylephrine) possibly causing local vasospasm and/or local elevated hydrostatic pressure resulting in ischemia, choroid vessel dilation and RPE disruption.	Transgenic mice were shown to have thickened choroid, dilated choroid vessels, and disruption of RPE tight junction.	X (preliminary results only)	Not mentioned	X	X	X	Not applicable	?	X
Schubert C et al. 2014	In vivo Mice injected (sub-retinal space) with triamcinolone	Corticosteroids reduced cadherin 5 (cell adhesion protein) expression in the eye. Altered cell-cell adhesion in choroid vessel or RPE may result in CSCR phenotype	After 24 h, corticosteroid injection reduced cadherin 5 mRNA expression level in eyes and increased claudin-1 expression; tissue localization of RNA expression is unclear ie., RNA collected from RPE/choroid/sclera Protein expression and histology showing RPE/choroid morphology and structural proteins was not investigated	✓	$n = 5$ per group	✓	✓	✓	X	X	✓
Ji X et al. 2016	In vivo nm3342, or called rpea1 mice with nonsense mutation in the *Prkcq* gene	Disruption of the protein kinase Cθ function results in RPE dysfunction, atrophy and abnormalities in the formation of tight junction proteins	Did no investigate the direct effect of mutated kinase C θ in the choroid No replicate images shown for most histology images No mention of blinding/masked to data analysis	✓	$n = 3$ animal explant for protein expression quantification for mutant vs. wild type	✓	unclear	✓	Not applicable	X	✓
Luna G et al. 2016	In vivo nm3342, or called rpea1 mice with nonsense mutation in the *Prkcq* gene	Down regulation of cell polarity genes (*Prkcq* and *Pard3)* likely causes abnormal RPE function, disruption of tight junction protein formation, dysregulation of aquaporin-1 channel expression result in serous retinal detachment	Demonstrated abnormally large choroid vessels with thickened wall and abnormal expression of cytoskeleton protein (ezrin) under areas of retinal detachment Thickening of choroid vessel maybe result of increased expression of extracellular matrix protein (collagen type III) No replicate images shown for most histology images	✓	$n = 2$ and 3 animal explants for quantifying gene expression (microarray) and protein, respectively for mutant vs. control mice	✓	X	X	Not applicable	X	✓

Table 2 continued

Author and year	Preclinical model	Proposed mechanism	Notes	Peer-reviewed publication	Sample size	Reported animal age	Report animal gender	Reported Animal housing conditions	Randomization of treatment	Blinded treatment and/or data analyses	Validated by another independent group
Lewis GP et al.v2011	In vivo nm3342, or called rpea1 mice with nonsense mutation in the *Prkcq* gene	Serous retinal detachments in mutant mice strain secondary to changes in intraphotoreceptor matrix, alterations in RPE mitochondrial morphology, cytoskeleton and aquaporin 1 protein expression.		X (abstract only)	Not mentioned	X	X	X	Not applicable	?	?
Matsumoto H et al. [119]	In vivo Mice subretinal space injected with hyaluronate to create retinal detachment	Mechanical separation of RPE from retinal layer	No mechanism explored Mechanically formed serous retinal detachment may not represent an appropriate model for studying CSCR etiology.	✓	$n = 1$	unclear	unclear	unclear	X	X	X (in the context of CSCR)
Park HK et al. [116]	In vivo cynomolgus monkeys with repeat oral administration of MAPK/ERK kinase (MEK) inhibitors	Unknown	No mechanism explored 6 monkeys each treated with 6 different MEK inhibitors. Only 4 of 6 developed SRD seen on OCT. OCT findings were compared to histology but they excluded 2 animals without providing reason. Unable to detect SRF on histology due to tissue processing artifact No multimodal imaging such as fundus photos, or FA. No ocular exam (to asses for inflammation)	✓	$n = 6$ animals	✓	✓	✓	X	X	X
Negi A et al. [118]	In vivo Rabbit subretinal space injected with buffered solution to produce retinal detachment	Possible exudate inflow causing SRF from inflammatory foci or focal vasculature RPE dysfunction prevention SRF resolution	Mechanically induced serous retinal detachment may not represent an appropriate model for studying CSCR etiology. RPE blebs formed over laser damaged RPE showed quicker SRF resolution vs blebs over normal RPE; proposed that RPE damage lead to architectural microdisruption allowing for fluid to freely flow to choroid via oncotic pressure	✓	$n = 7$-11 eyes per group (one control group was reported to have 42 blebs)	X	X	X	Not applicable	X	X
Yoshioka H et al. [114]	In vivo Macaca irus monkey with repeated intravenous adrenaline and intramuscular prednisolone injections	Treated animals formed phenotype similar to CSCR seen on Fluorescein angiography	No mechanism investigated No control animals receiving vehicle	✓	$n = 1$ animal	✓	✓	X	X	X	X

Table 2 continued

Author and year	Preclinical model	Proposed mechanism	Notes	Peer-reviewed publication	Sample size	Reported animal age	Report animal gender	Reported Animal housing conditions	Randomization of treatment	Blinded treatment and/or data analyses	Validated by another independent group
In vitro studies											
Sibayan SA et al. [83]	in vitro Culture of porcine RPE cells treated with epinephrine or dexamethasone	Treatment with epinephrine but not dexamethasone resulted in increased RPE cell apoptosis	No in vivo validation No mechanism explored	✓	$n = 4$ independent experiments	Not applicable	Not applicable	Not applicable	Not applicable	X	X
Arndt C et al. [91]	in vitro Electrophysiological parameters measured in porcine and bovine RPE and choroid tissue explant treated with hydrocortisone	Corticosteroid induced imbalance of ion transport across RPE may result serous retinal detachment	Did not explore mechanisms by which corticosteroid altered electrophysiological parameters Whether these electrophysiological changes result in subretinal serous fluid accumulation remains to be determined	✓	$n = 5–8$ animal tissue explant preparations	Not applicable	Not applicable	Not applicable	Not applicable	X	X

CSCR central serous chorioretinopathy, *MR* mineralocorticosteroid receptor, GR glucocorticoid receptor, OCT optical coherence tomography, *RPE* retinal pigment epithelium, *SRF* subretinal fluid.

(JBI 55%) with its conclusion limited by the use of a historical control group.

The link between systemic inflammation and CSCR is intriguing given that elevated glucocorticoid, which is an associated risk factor for CSCR, has anti-inflammatory effects. The relation between these two opposing mechanisms and their role in CSCR development needs further evaluation.

PARACRINE MEDIATORS

Studies looking at the expression profile of cytokines and growth factors (e.g. interleukins 6, 8, interferon gamma-induced protein-10, vascular endothelial growth factor) within the aqueous humor of CSCR patients have produced mixed results (Table 1) [24, 25, 44, 45]. For example, while one report showed elevated interleukin 6 and 8 in chronic CSCR [24], others showed no difference with the control group [45]. One study reported decreased platelet-derived growth factor (PDGF) levels in patients with CSCR [45]. PDGF deficiency was thought to contribute to CSCR pathogenesis by promoting RPE dysfunction, pericyte loss, and a local increase in VEGF resulting in choroid hyperpermeability [45]. These studies are limited by (1) lack of independent assessment by other research groups; (2) small sample size ($n =$ 20–57 patients); (3) poor control of confounding factors; (4) cross-sectional analysis of paracrine factors making temporal association to CSCR difficult and; (5) sampling error since the secretome within the aqueous humor may not reflect the local concentration within the choroid. As such, the role of cytokines/growth factors in the pathogenesis of CSCR remains elusive and investigations are ongoing.

Two studies demonstrated a relationship between blood serotonin levels and CSCR (Table 1) [46, 47]. One reported that patients with lower serotonin levels were more likely to develop chronic CSCR while no difference was seen between acute CSCR and the control group (case-control, JBI 60%) [46]. While the second study (case series; JBI 90%) did not find a relationship between chronic and acute CSCR, it showed that patients with lower serotonin levels were more likely to develop multiple leakage sites, show recurrence, and have worsening recovery of vision at follow up [47]. It is thought that lower serotonin levels may result in vascular dysregulation which may influence choroid permeability but its direct effect on choroid vessels and RPE is lacking.

Lipocalin 2 (LCN2) is an acute-phase protein with both anti- and pro-inflammatory effects and is secreted by various cell types including RPE and retina Müller cells [48]. One case-control study ($n = 277$ patients; JBI 45%; Table 1) demonstrated a significantly lower levels of serum LCN2 in CSCR patients [48]. Moreover, a stepwise decrease in LCN2 levels was correlated with worsening CSCR severity. It was proposed that decreased serum LCN2 makes RPE susceptible to oxidative damage and alters its blood–retinal barrier function. Unfortunately, the study focused only on serum LCN2 levels which may not be reflective in ocular tissue and lacked complete identification of confounding factors such as baseline blood pressure, other medical comorbidities, or prior use of steroids. Interestingly, glucocorticoid which is associated with increased risk for CSCR is shown to upregulate LCN2 secretion in various non-ocular cells [49]. This contradictory effect highlights the complexity of CSCR pathogenesis and questions the role of glucocorticoids in CSCR pathogenesis. It is possible that glucocorticoids may have a differential effect on ocular tissue LCN2 expression, but this remains to be proven.

The role of VEGF in the pathogenesis of CSCR is unclear but local VEGF production due to choroidal ischemia may contribute to vascular hyperpermeability [45]. Despite the poor correlation between VEGF levels and the development of CSCR, some investigators believe that intravitreal injection of anti-VEGF

agents (e.g. bevacizumab, ranibizumab) would benefit patients by reducing choroid hyperpermeability [50]. Unfortunately, given the lack of large-scale RCTs, the efficacy of anti-VEGF therapy remains controversial [50–53]; the JBI score of these studies (2 RCTs, 1 case series) ranged from very poor to good quality (Table 1). A meta-analysis (enrolled 14 studies, 266 eyes) revealed that anti-VEGF treatment for acute CSCR is not superior to observation alone [50]. Similarly, no visual gains were observed in patients with chronic CSCR (symptoms ≥ 3 months) [50]. Imbalance in proangiogenic and antiangiogenic factors may also contribute to the development of CSCR. For example, serum levels of angiopoietin-1 (promotes the formation of endothelial tight junctions) were decreased in chronic CSCR and is thought to contribute to disease progression by promoting leaky choroid vessels ($n = 80$ patients; JBI = 55%; Table 1) [54].

Angiogenic factors also play a role in the formation of type 1 choroidal neovascularization (CNV) which complicates chronic CSCR in 16–36% of cases [55–57]. CSCR-associated CNV is considered a subset of a disease spectrum called pachychoroid neovascularization (Fig. 3) [16]. The mechanism of PNV is unclear but is thought to result from a pachychoroid-driven process i.e., a combination of choroid congestion and choriocapillaris compression resulting in ischemia and RPE damage that promotes the production of angiogenic factors (Fig. 2) [16, 58]. This is supported by imaging modalities which have allowed researchers to understand choroid hemodynamics in a patient with CSCR [59–62]. Hypoperfusion causing ischemia can be seen with indocyanine green angiography (ICGA) as areas of delayed choroid arterial filling [59]. Saito et al. used laser speckle flowgraphy to characterize choroid hemodynamics and proposed that regions corresponding to delayed ICGA likely reflect areas of increased vascular resistance (decreasing blood flow to choriocapillaris) with compensatory passive blood overflow into surrounding choroid veins [61]. Detailed anatomical and functional assessment of vascular network using OCTA also revealed flow impairment in choriocapillaris in regions corresponding hypoperfusion on ICGA along with decreased deep retinal capillary perfusion and density in areas of subretinal fluid [60].

Choroid ischemia promoting VEGF secretion may play an important role in the development of CNV. This is supported by studies showing clinical benefits of using anti-VEGF treatment in patients with CSCR-associated CNV [63, 64]. Anti-VEGF also demonstrated similar efficacy to full-fluence PDT for treating CNV in chronic CSCR patients [64]. Intriguingly, a few studies characterizing the aqueous humor cytokine profile demonstrated lower concentrations of VEGF in patients with PNV compared to neovascular-age-related macular degeneration (nAMD) suggesting that these two diseases entities have a different mechanism for initiating neovascularization [65, 66]. The difference in VEFG levels may explain why PNV required fewer anti-VEGF injections compared to nAMD [67]. For nAMD, drusen play a crucial role in driving chronic inflammation which promotes the production of VEGF [66]. In contrast, CSCR associated CNV (or in general PNV) is likely the result of pachychoroid-driven changes resulting in chronic choroid/RPE ischemia that stimulates the production of angiogenic factors. Lower levels of VEGF in PNV compared to nAMD may be a result of: (1) Angiogenic factors other than VEGF playing a larger role in PNV; (2) PNV may have a lower threshold response to VEGF due to differences in genetics, mechanical forces (dilated and congested choroid vessels) or biochemical/cellular milieu (inflammatory vs. ischemia); (3) The concentration of VEGF in aqueous humor may not be reflective of the disease process as VEGF in CSCR maybe more confined within the choroid compared to nAMD [65]. Interestingly, another study found that the levels of plasma VEGF were significantly lower in patients with acute/chronic CSCR [54]. They hypothesized that vessel hyperpermeability and CNV formation may be secondary to a VEGF-independent process called arteriogenesis (transformation of existing vessels causing increased lumen size and thickness) rather than angiogenesis (formation of new vessels in a VEGF-dependent process) but this remains to be confirmed. Overall, further work is required to characterize the role of various angiogenic factors in the formation of CNV in pachychoroid diseases like CSCR.

OXIDATIVE STRESS

A few small-sized cross-sectional studies ($n = 36$–116 patients) have shown a link between systemic oxidative stress and CSCR (Table 1) [68–71]. Patients with CSCR demonstrated greater blood disulfide-to-thiol ratio (a measure of elevated oxidative stress) and decreased antioxidant activity compared to healthy controls [69, 70]. This imbalance of oxidative and anti-oxidative homeostasis may lead to reactive oxygen species-mediated damage of choroid vessels and the RPE. Risk factors that are associated with CSCR like elevated cortisol, obstructive sleep apnea, stress, and *H. pylori* infection are also linked to increased oxidative stress suggesting a potential common pathway for disease pathogenesis [72–74]. While these cross-sectional studies demonstrated poor-to-good quality assessment, confounding factors were poorly controlled and they are inherently limited to make temporal associations. An attempt to treat CSCR with high-dose antioxidants in a single RCT ($n = 58$ patients, JBI 62%, Tables 1 and S7) did not show any functional or structural benefits [75].

AUTONOMIC DYSFUNCTION

Given that choroid vessels are regulated by the autonomic nervous system [76], it is unsurprising to consider that CSCR was associated with autonomic nervous activity imbalances [77, 78]. Increased sympathetic tone and decreased parasympathetic activity may cause autonomic dysfunction induced vasospasm leading to choroid ischemia and subsequent choroid hyperpermeability [77, 78]. Likewise, the use of sympathomimetic drugs has been implicated in the formation of CSCR [77, 79]. Unfortunately, the role of sympathetic dysregulation in CSCR remains unclear as many of these studies were small-sized case series ($n = 3$–4 patients) or cross-sectional studies with poor-to-good quality assessment scores (Table 1). One RCT showed support for beta-blocker in resolving CSCR (JBI 15%) [80], while two demonstrated no benefits (JBI 54%, 42%, Tables 1 and S7) [81, 82]. These RCTs lacked methodology to sufficiently control for bias, i.e. not reporting randomization of protocol, lacking allocation concealment, methods not accounting for loss-to-follow up, lacking patient demographics. or suffered from imprecision.

Another mechanism by which sympathomimetic drugs and adrenergic hormones may cause CSCR is by inducing cell apoptosis (Table 2) [83]. Corticosteroids may further augment this effect by increasing the expression of adrenergic receptors on cells [84]. As such, patients with conditions with increased catecholamines and corticosteroids (i.e. obstructive sleep apnea, elevated stress) are associated risk factors for developing CSCR [85–88]. Likewise, Type-A personality has been associated to CSCR, but this link remains controversial [89].

MINERALOCORTICOID RECEPTOR ACTIVATION

A meta-analysis by Liu et al. identified exogenous glucocorticoid use to have a strong association with developing CSCR ($n =$ 7 studies, odds ratio = 4.29; 95% confidence interval 2.01–9.15) but showed large data heterogeneity ($I^2 = 84\%$) [86]. Another reported a relationship between endogenous cortisol levels and

CSCR ($n = 5$ case-control studies; standard mean deviation = 0.77; 95% confidence interval 0.55–0.99) [90]. Animal studies suggested that corticosteroids interact with mineralocorticoid receptors to upregulate choroid endothelial calcium-activated potassium channel ($K_{Ca}2.3$) causing smooth muscle relaxation resulting in increased choroidal permeability (Fig. 2, Table 2); limitations of animal studies is discussed below [21]. Furthermore, corticosteroids may disrupt the RPE barrier by interrupting ion transport and dysregulating choroid hemodynamics by upregulating adrenergic receptors [84, 91]. Studies in rats demonstrated that intravitreal injection of aldosterone induced a mineralocorticoid/glucocorticoid receptor-dependent upregulation of epithelial sodium channel-α (ENaC-α), potassium (Kir4.1), and aquaporin-4 (AQP4) channels in retinal Müller cells resulting in retinal swelling (Fig. 2, Table 2) [92]. Others have proposed that hypercortisolism can also lead to increased levels of plasminogen activator inhibitor-1 resulting in a hypercoagulable state secondary to platelet dysfunction causing transient obstruction of choroid circulation [43, 93, 94].

Cortisol has also been shown to decrease the expression of cadherin 5 (CDH5) on choroidal vessels, a major cell–cell adhesion protein, thereby increasing vessel permeability (Table 2) [95]. Genomic studies suggest that certain CDH5 gene variants may predispose the male patient to develop CSCR when exposed to both exogenous and endogenous corticosteroids [95]. As such, mineralocorticosteroid receptor (MR) antagonists have been proposed to treat CSCR by abrogating the interaction between corticosteroid and its receptor.

The role of corticosteroid in human CSCR pathogenesis remains uncertain as clinical studies using MR antagonist (e.g. eplerenone and spironolactone) have failed to consistently provide functional and anatomical gains. Tables 1 and S4, 5 summarizes 7 observational/descriptive studies (3 cohort, 4 case series; JBI poor-to-good) which were limited by small size ($n = 12$–114 patients), little control for confounding factors, and inherent bias from no blinding to treatment/analysis. Without a control in interventional case series, it is a challenge to discern if the resolution of symptoms was the result of the treatment or spontaneous disease resolution. The quality of 6 RCTs (Tables 1 and S7) ranged from poor-to-good and were limited by small sample sizes ($n = 15$–144), some inadequately powered, poor control for confounding factors, missing placebo control, for example using observational control, and cross-over studies did not have adequate washout periods. Also, few studies reported statistically significant improvements only compared to the baseline but not to the placebo group. The largest randomized controlled trial to date (VICI trial; $n = 144$) was good quality (JBI 89%) and demonstrated no benefit of using oral eplerenone in treating chronic CSCR [96]. Why MR antagonist failed to treat CSCR despite the evidence showing its potential role in disease pathogenesis is perplexing but, perhaps not all patients respond to MR antagonist equally. Different haplotypes of MR gene (NR3C2) have been associated with increased risk for chronic CSCR and these genetic variants may result in different treatment efficacy by MR antagonist [97]. This may explain why patients with phenotypic differences in choroid thickness responded differently with treatment in some studies (better treatment response with thicker baseline choroid >515 µm) [98]. In addition, patients that do not respond to eplerenone may benefit from spironolactone which has a greater binding affinity to mineralocorticosteroid receptor [99]. Further studies are required to assess whether MR haplotyping will allow clinicians to predict which patients will benefit most from MR antagonist therapy.

MEDICATIONS ASSOCIATED WITH CSCR

Various medications including sympathomimetic drugs [77, 79], phosphodiesterase inhibitors (e.g. tadalafil [100] and sildenafil [101]), quinoline (i.e. antimalarial drug like mefloquine [102]), and neuroleptics [103] have shown possible associations with developing CSCR (Table 1).

Neuroleptics like quetiapine are thought to cause dysregulation of choroid perfusion by altering neuroendocrine factors like dopamine and serotonin [103]. Indeed, low serum serotonin has been reported in patients with chronic CSCR [46].

Phosphodiesterase inhibitors are thought to cause choroid hyperpermeability as a result of nitric oxide-mediated venous dilation [104]. Although this notion has been challenged by a case series study showing functional and anatomical benefits in chronic CSCR [105].

Quinolines may exert their effects by disrupting connexin 43 within the gap junctions of choroid vessels resulting in hyperpermeability [102].

These studies were mainly limited to case reports/series and quality assessment predominantly ranged from very poor-to-fair due to bias arising from the lack of control groups, randomization, and blinding to treatment/analysis. Larger adequately controlled studies are required to confirm the association between these medications and CSCR.

GENOMIC ANALYSIS

Certain gene variants (complement factor H [CFH], age-related maculopathy susceptibility 2 [ARMS2], nuclear receptor subfamily 3 group C member 2 [NR3C2; mineralocorticoid receptor], and CDH5) have also been associated with increased risk for CSCR [95, 97, 106, 107].

CFH is a major regulatory protein that inactivates the complement system [108]. Genomic and proteomic analysis hint that CFH is upregulated in CSCR patients suggesting that dysregulation of complement system may play a role in pathogenesis [106, 109, 110]. Additionally, CFH can bind and stabilize adrenomedullin, a member of the calcitonin peptides family which has vasodilatory effects on choroid vessels [108, 111]. Other genes involved in the complement pathway are also linked to the development of CSCR including a cluster of differentiation 46 (CD46) and complement component 4B (C4B) [106, 112].

Lastly, allele variants of transcription factor GATA-5 and tumor necrosis factor receptor superfamily member-10A are associated with CSCR where the former may play a role in choroidal endothelial cell dysfunction and the latter is thought to create an imbalance in hormone secretion by the adrenal glands [113]. Regardless of the associations predicted by the genome-wide analysis, direct evidence such as proteomic/miRNA expression profile, co-localization and functional analysis of proteins at specific tissue, and morphological features using immunohistochemistry are needed to confirm their role in the development of CSCR.

PRECLINICAL STUDIES

Progress in understanding CSCR pathogenesis has not accelerated and some preclinical studies have attempted to shed light on this topic. Preclinical studies date back to 1981 with a significant gap until the last decade (9 studies since 2010). Although many were exploratory studies, the CAMARADES tool demonstrated diminished quality due to high risk for bias (no randomization to treatment and lacked blinding to treatment/data analysis), small sample size, some lacking exploration of cellular mechanisms, and few limited to abstracts or preliminary reports (Tables 2 and S8).

The earliest animal model was developed about four decades ago in which administration of adrenaline in monkeys produced CSCR phenotype seen on fluorescein angiography [114]. While this was an essential step forward in understanding CSCR, the overall

quality of the study was poor with small sample size, high risk for bias, no detailed exploration of molecular mechanism, and the model has not been explored since its conception. As such, the role of autonomic dysregulation in CSCR relied primarily on indirect evidence from in vitro studies [83] and a small number of human case series showing association between disease and the use of sympathetic medications as discussed above.

Only two preclinical studies (by the same research group) have produced CSCR phenotype in rats with intraocular injection of corticosteroids [21, 92]. They showed that MR activation could produce CSCR phenotype and was ameliorated with MR antagonist but, they were small sized ($n = 3$–8 per group), subject to performance and detection bias (not blinded to treatment/analysis), and have not been validated by other independent research groups. In support of this mechanism, mice over-expressing MR produced a phenotype similar to CSCR but was only reported as a preliminary result without further investigation [5]. While exciting, larger and more stringently controlled pre-clinical studies are need to dissect the role of MR in CSCR [95]. It should also be noted that findings in pre-clinical studies, especially small animal models, may not necessarily translate to humans due to anatomical and physiological differences. For example, mice lack macula and foveal pit (an important area of CSCR development), have thinner Bruch's membrane and show many differences in RPE gene expression controlling processes like oxidative stress, immunoregulation, structural proteins, and cell-signaling pathways [115]. As such, larger animal models more closely modeling human eyes, such as non-human primates, are likely more appropriate for studying CSCR disease [116].

To support the hypothesis of mechanical obstruction, one study produced CSCR phenotype in mice after ligating the vortex vein [117]. However, this study was subject to detection bias, small-sized ($n = 6$ per group), did not report replicates for various experiments (e.g. choroid thickness measured by optical coherence tomography or gene expression analysis by microarray), and lacked appropriate immunohistochemistry staining controls. Nonetheless, this model has the potential to allow researchers to explore the role of venous congestion on choroidal circulation, RPE function, and structural alterations in the blood-retinal barrier.

Other animal models that mechanically induce retinal detachment (i.e., injecting solutions into the sub-retinal space) are likely not appropriate models for CSCR as they do not address underlying etiology [118, 119]. However, they may have application in exploring laser treatment modalities to aid with earlier fluid reabsorption.

Lastly, the new mutant mouse strain (nm3342, or also known as retinal pigment epithelium atrophy 1 [rpea1]), develops early central exudative retinal detachment followed by late-onset of RPE atrophy mimicking chronic CSCR [120, 121]. The rpea1 mice contain a mutation in the in the Prkcq gene producing an aberrant protein kinase Cθ (PKCθ; expressed mostly in RPE/choroid tissue). Aberrant PKCθ disrupts RPE cytoskeletal structure and metabolism and may also disturb choroid endothelial cell barrier function [120]. Unfortunately, the role of protein kinase C isoforms in the development of CSCR in humans remains unknown but, it provides an intriguing avenue for future research.

CONCLUSION

Evidence is building that CSCR is a complex and multifactorial disease with varying phenotypic presentations influenced by genetic, environmental, exogenous, and endogenous hormonal and paracrine factors. Our analysis of the literature showed that many studies are inadequately powered, missing appropriate controls, lack long-term follow up, and have methodology prone to various biases thus, the etiology of CSCR remains elusive. However, preclinical and clinical studies have provided useful insight to begin understanding the disease mechanism. Activation of mineralocorticoid receptors is postulated to play a central role in formation of CSCR but targeting this pathway for treatment has produced inconsistent results. Investigations in the future may explore other mechanisms including inflammation, oxidative stress, and venous congestion. A newer focus on vortex veins compression caused by thickened/ridged sclera is promising for understanding disease and developing future therapies. Still, a unified model is lacking to explain the formation of choroid hyperpermeability and RPE dysfunction seen in CSCR. While we explored over two decades of work investigating the etiology of CSCR, intuitively the pathogenic mechanisms causing choroid thickness, choriocapillaris ischemia, and RPE dysfunction likely overlap with the new and exciting concept of pachychoroid disease spectrum. The development of well-controlled and rigorously designed studies is needed to dissect the mechanisms leading to pachychoroid disease while opening avenues for new interventions.

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AUTHOR CONTRIBUTIONS

PK, AG and MSB were responsible for designing the study protocol. PK and AG were responsible for screening studies, data acquisition, analysis, organizing tables/figures and drafting the manuscript. MSB, CG, RK, and SGC were involved in editing the manuscript, helping revise the protocol and providing feedback. The final version was of the manuscript was approved by all authors.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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