The spectrum of central serous chorioretinopathy: clinical characteristics, genetic associations and outcome of treatment
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The spectrum of central serous chorioretinopathy

Clinical characteristics, genetic associations and outcome of treatment

Danial Mohabati
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by

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The spectrum of central serous chorioretinopathy
Clinical characteristics, genetic associations
and outcome of treatment

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Voor Anne, Jasmin en Siebe

Voor mijn ouders
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<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>aCSC</td>
<td>acute central serous chorioretinopathy</td>
</tr>
<tr>
<td>AMD</td>
<td>age-related macular degeneration</td>
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<tr>
<td>ARMS2</td>
<td>age-related macular degeneration susceptibility 2</td>
</tr>
<tr>
<td>BCVA</td>
<td>best-corrected visual acuity</td>
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<tr>
<td>BDUMP</td>
<td>Bilateral diffuse uveal melanocytic proliferation</td>
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<td>BM</td>
<td>Bruch’s membrane</td>
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<tr>
<td>C4B</td>
<td>complement factor 4B</td>
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<tr>
<td>cCSC</td>
<td>chronic central serous chorioretinopathy</td>
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<tr>
<td>CDH5</td>
<td>cadherin 5</td>
</tr>
<tr>
<td>CFH</td>
<td>complement factor H</td>
</tr>
<tr>
<td>CFT</td>
<td>central foveal thickness</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CME</td>
<td>cystoid macular edema</td>
</tr>
<tr>
<td>CNV</td>
<td>choroidal neovascularisation</td>
</tr>
<tr>
<td>CRT</td>
<td>central retinal thickness</td>
</tr>
<tr>
<td>CSC</td>
<td>central serous chorioretinopathy</td>
</tr>
<tr>
<td>DARA</td>
<td>diffuse atrophic retinal pigment epithelium alterations</td>
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<tr>
<td>DD</td>
<td>optic disc diameter</td>
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<tr>
<td>DRPE</td>
<td>diffuse retinal pigment epitheliopathy</td>
</tr>
<tr>
<td>EDI</td>
<td>enhanced-depth imaging</td>
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<tr>
<td>ELM</td>
<td>external limiting membrane</td>
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<tr>
<td>ERG</td>
<td>electroretinography</td>
</tr>
<tr>
<td>ETDRS</td>
<td>Early Treatment Diabetic Retinopathy Study</td>
</tr>
<tr>
<td>EZ</td>
<td>ellipsoid zone</td>
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<tr>
<td>FA</td>
<td>fluorescein angiography</td>
</tr>
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<td>FAF</td>
<td>fundus autofluorescence</td>
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<tr>
<td>GCL</td>
<td>ganglion cell layer</td>
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<tr>
<td>HF</td>
<td>haplotype frequency</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>ICGA</td>
<td>indocyanine green angiography</td>
</tr>
<tr>
<td>ILM</td>
<td>internal limiting membrane</td>
</tr>
<tr>
<td>INL</td>
<td>inner nuclear layer</td>
</tr>
<tr>
<td>MAF</td>
<td>minor allele frequency</td>
</tr>
<tr>
<td>MEK</td>
<td>mitogen-activated protein kinase kinase</td>
</tr>
<tr>
<td>METC</td>
<td>Medisch Ethische Toetsingscommissie</td>
</tr>
<tr>
<td>NA</td>
<td>not annotated</td>
</tr>
<tr>
<td>nAMD</td>
<td>neovascular age-related macular degeneration</td>
</tr>
<tr>
<td>NR3C2</td>
<td>nuclear receptor subfamily 3 group C member 2</td>
</tr>
<tr>
<td>OCT</td>
<td>optical coherence tomography</td>
</tr>
<tr>
<td>OCTA</td>
<td>optical coherence tomography angiography</td>
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</tbody>
</table>
ONL  outer nuclear layer
OPL  outer plexiform layer
OR   odds ratio
PCRD posterior cystoid retinal degeneration
PCV  polypoidal choroidal vasculopathy
PD   pigment epithelial detachment
PDT  photodynamic therapy
PNV  pachychoroid neovascularopathy
PPE  pachychoroid pigment epitheliopathy
PPS  peripapillary pachychoroid syndrome
RCT  randomized controlled trial
RPE  retinal pigment epithelium
SD   standard deviation
SD-OCT spectral-domain optical coherence tomography
SMACH Serous maculopathy due to aspecific choroidopathy
SMARPE Serous maculopathy with absence of retinal pigment epithelium
SML  subthreshold micropulse laser
SNP  single nucleotide polymorphism
SRF  subretinal fluid
VA   visual acuity
VEGF vascular endothelial growth factor
VIPR2 Vasoactive Intestinal Peptide Receptor 2
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CHAPTER 1

General introduction
1. CENTRAL SEROUS CHORIORETINOPATHY

1.1. Introduction

Vision in the human eye starts with reflected light waves from an object, that reach the photosensitive cells (photoreceptors) in the neurosensory retina, and initiate a cascade of processes that create an electric signal. This electric signal is transmitted to the visual cortex of the brain by the optic nerve, and is converted into an image. The retinal photoreceptors are strongly dependent on the supportive function of the retinal pigment epithelium (RPE) cells, that form a monolayer in between the retina and underlying densely vascularized choroid. The RPE regulates movement of fluids, oxygen, and nutrients and additionally forms an important protective barrier between the choroid and the neurosensory retina, preventing excessive fluid passage, and substance accumulation underneath the neurosensory retina. This intensive interaction between the RPE, the neurosensory retina, and the choroid is crucial in the understanding of the eye disease central serous chorioretinopathy (Figure 1).

![Figure 1. Anatomy of the human eye and a simplified schematic overview of the neuroretina. Abbreviations: RPE, retinal pigment epithelium; BM, Bruch’s membrane (Ruan et al, 2021)].

The disease central serous chorioretinopathy (CSC) was presumably first observed and funduscopically described by von Graefe in 1866.1, 2 Our knowledge on CSC has increased considerably throughout the years, although many mysteries around its pathogenesis, clinical classification, and treatment remain unresolved. Over the years, CSC was referred to by different terms, mostly based on the suspected origin of the disease, such as central recurrent retinitis, idiopathic flat detachments of the macula, central angiospastic retinopathy, diffuse retinal pigment epitheliopathy, and central serous choroidopathy.1

Affected CSC patients typically complain about a sudden onset of blurred or loss of vision in one eye, with a central grayish scotoma, metamorphopsia, and disturbance of color and
contrast vision. These complaints are caused by a detachment of the neurosensory retina in the macula due to an accumulation of subretinal serous fluid (SRF). As a result of the serous detachment of the neurosensory retina, the physiological connection between the photoreceptors and the underlying RPE cells is disturbed. Since normal photoreceptor functioning is highly dependent on interaction with the RPE cells, a detachment of the neuroretina from the RPE generally causes immediate visual complaints. Furthermore, the RPE cells in CSC patients partially lose their pump function and fail to adequately remove the SRF, which causes a persistent serous detachment of the neuroretina. Vision loss may be largely reversible when the serous retinal detachment resolves and the visual cycle is restored, unless there is substantial tissue atrophy or persistent SRF.

The clinical presentation of CSC is heterogeneous and consists of a spectrum of different and overlapping clinical phenotypes. The most prevalent distinguished CSC phenotypes are the acute, and the chronic CSC (Figure 2). Different severity chronic CSC forms can also be distinguished as well as the presence or occurrence of secondary complications, as will be discussed later on.

### 1.2. Epidemiology

Currently, limited data are available on the incidence of CSC. Kitzmann and coworkers have reported an incidence rate of 9.5 per 100,000 in men, and 1.6 per 100,000 in women. The relatively high recurrence rate, variable clinical presentation, and inconsistent medical terminology makes an accurate estimation of the disease prevalence challenging.

The onset of CSC is generally at a relatively young age. Patients often experience their first CSC episode between the age of 25 and 60 years. Men are affected up to 7 times more often than women. Women with CSC tend to be older at the time of first presentation. Besides the older age of onset, CSC specific findings on multimodal imaging techniques, and disease progression show similar patterns between males and females. CSC is more prevalent in the Caucasian and Asian population and somewhat less frequent in the African populations.

### 1.3. Risk factors

In the current literature, numerous risk factors have been associated with CSC, which can be categorized in: use of certain drugs, endocrine disorders, axial length of the eye, cardiovascular diseases, sympathetic-parasympathetic imbalance, psychopathology, gastrointestinal diseases, sleep disorders, and genetic predisposition. In the following paragraphs the most important risk factors will be outlined.

**Exogenous steroids**

The use of corticosteroids, through all routes of administration, is the most important risk factor for CSC, and may increase the risk of CSC up to 37 times. Thus far, no direct dose-dependent association has been found. However, a more chronic and extensive
Figure 2. An overview of findings on multimodal imaging in a 27-year-old healthy male (A, D, G, J, M), a 41-year-old male with acute central serous chorioretinopathy (aCSC) (B, E, H, K, N), and a 59-year-old male with chronic CSC (cCSC) (C, F, I, L, O). There are barely any differences noticeable on fundus photography among the three eyes (A, B, C). Optical coherence tomography (OCT) shows a normal anatomy of the neurosensory retina in the healthy eye (D), while there is macular subretinal fluid (SRF) accumulation with subretinal hyperreflective material in the aCSC eye (E). OCT in the cCSC eye shows SRF accumulation together with multiple small retinal pigment epithelium (RPE) detachments (F). Fundus autofluorescence (FAF) imaging reveals a circumscribed area of RPE changes in the aCSC eye at the location of central SRF (H), while in the cCSC eye large areas of disturbed and damaged RPE can be seen, which is referred to as the characteristic gravitational track (I). Mid-phase (3 to 8 minutes) fluorescein angiography (FA) shows no abnormalities in the healthy eye (J). Mid-phase FA in an aCSC eye shows only a small hyperfluorescent leakage spot in the central macula (K), while on FA in the cCSC eye there are multiple small hyperfluorescent leakage spots and large areas of diffuse hyperfluorescent abnormalities corresponding with atrophic RPE changes (L). Indocyanine green angiography (ICGA) imaging shows areas of choroidal hyperpermeability, which are typically more extensive as compared to the hyperfluorescent areas on FA, both in the aCSC (N) and the cCSC eyes (O).
form of CSC was described in patients that were on chronic systemic steroids after organ transplantation. Furthermore, steroid-associated CSC is often found bilaterally. Use of corticosteroids has been suggested to influence the electrophysiological balance of the RPE cell, and by that may steroids alter the RPE pump function, which may subsequently contribute to SRF accumulation. Moreover, corticosteroids may have an effect on the choroidal structure and function. For example, chronic use of corticosteroids is shown to be significantly correlated with thickening of the choroid in CSC patients.

**Endogenous steroids and other hormonal factors**

It has been hypothesized that CSC patients may generally have a higher level of endogenous cortisol, which could potentially make these patients more prone to developing the disease. However, the results of the clinical studies are ambiguous. Although endogenous cortisol levels may be at the higher end of normal in CSC patients, the findings are generally considered within the normal range. It is therefore unclear if there is a primary causal link between cortisol levels and the development of CSC in these patients. It is of interest that a pathological elevated endogenous cortisol level in the context of Cushing syndrome has been associated with the development of (secondary) CSC. Similar discrepancies exist on the role of intrinsic testosterone levels and the risk of CSC development. Pregnancy is another known risk factor, and pregnant women are up to 7 times more prone to CSC development in comparison to women that are not pregnant. In these women, CSC was suggested to be related to hormonal disturbances, since CSC occurred especially in the third trimester of the pregnancy. Although incidental cases have been described with a severe disease course, the majority of the pregnancy-related CSC cases resolve spontaneously after child delivery with a near complete visual recovery.

**Ocular risk factors**

The axial length of the eye has been shown to correlate with the choroidal thickness through alterations in the chorioretinal vascular structure. A thickened choroid is thought to play a significant role in CSC pathophysiology (further discussed in paragraph 1.6), and therefore patients with a thin choroid appear relatively protected. However, CSC cases have been reported in highly myopic patients with a relatively thin choroid.

**Other risk factors**

Additional risk factors have been described for CSC, including type A personality, psychological stress, shift-work, and inadequate coping mechanism in stressful situations. A relationship between the use of psychopharmaceuticals and CSC is suggested, which may also reflect the contribution of psychopathology to the risk of CSC development. Furthermore, systemic conditions such as hypertension, autoimmune disease, intestinal H. pylori infection, and sleeping disorders may also contribute to the risk of CSC development. On the other hand, there are also risk reducing factors.
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Genetics

Generally, CSC is not thought of as a disease with a significant genetic component, as most cases are isolated, and a family history of CSC is rare. However, a number of studies have reported familial occurrence of CSC, suggesting a role for genetic predisposition. 41-44

Age-related macular degeneration (AMD) and CSC, especially the chronic phenotype of CSC, show similarities in their clinical presentations. 45 The role of genetics in the pathogenesis of AMD has been previously established. 46-48 The AMD-related genetic variants are subsequently also studied in CSC patients. Few research groups established an association with a number of known AMD-related genetic variations -single-nucleotide polymorphisms (SNPs)- in the age-related macular degeneration susceptibility 2 (ARMS2) gene and the complement factor H (CFH) gene in CSC patients with chronic disease. 45, 49, 50 Interestingly, presence of an associated SNP in the ARMS2 gene (the most important risk carrying genetic factor in AMD) was found to be protective against CSC. 45, 49 Also, two SNP’s in the CFH gene (with an inhibitory role in the innate immune system) were associated with the risk of CSC development, while another SNP in this gene was protective. 45, 49 Further investigations showed that other complement pathways may be influential in CSC pathogenesis too, for example carrying three or more copies of variations in the complement factor 4B (C4B) gene was identified as a risk reducing factor in CSC disease development. 51 Schubert and coworkers were the first to suggest a genetic association with vascular abnormalities in CSC. They hypothesized on the influence of corticosteroid use on gene expression in these patients, 52 and they subsequently reported on the association of 4 SNPs in the Cadherin 5 (CDH5) gene. CDH5 protein plays a role in endothelial cell junctions, and can alter vascular permeability under influence of corticosteroids. 52, 53 Furthermore, van Dijk and coworkers reported an increased risk of chronic forms of CSC that were associated with a variant in nuclear receptor subfamily 3 group C member 2 (NR3C2), which is a mineralocorticoid receptor gene. 54, 55 Hosoda and coworkers reproduced on the risk carrying effect of CFH gene in CSC, and discovered a novel SNP in the Vasoactive Intestinal Peptide Receptor 2 (VIPR2) gene. SNPs in both CFH and VIPR2 genes were significantly associated with a thickened choroid in CSC patients. 56 The search for new genetic variants continues, and recent whole exome sequencing studies have identified multiple new candidate genes (PIGZ, DUOX1, LAMB3, RSAD1, and SLC7A5). 57, 58 The exact role of the currently known genetic characteristics in CSC pathogenesis is still under debate. 59

Most of the mentioned genetic studies are performed in CSC cohorts with limited differentiation between clinical phenotypes of CSC. 59 There are only a small number of studies, which are performed solemnly in well-defined chronic CSC patients. But, there are almost no studies available that compare mutual genetic variations between different CSC phenotypes.
1.4. Pathophysiology of CSC

There is still much unknown about the pathophysiology of CSC, despite the increasing amount of literature.\textsuperscript{60} It is currently thought that there is an elevated fluid pressure from the choroidal vasculature into the subretinal space.\textsuperscript{1,9,10,61} The mechanism may be explained as follows: An abnormally increased blood flow from the congested choroidal vessels causes serous leakage into the interstitial space.\textsuperscript{62} Especially the deep Haller’s layer vessels of the choroid are dilated, while the superficial choriocapillaris layer and medium-sized Sattler’s layer vessels are thin.\textsuperscript{62,63} The excess of interstitial fluid disturbs the pressure equilibrium existing on each side of the RPE, which normally keeps the neuroretina in place.\textsuperscript{9} An increased pressure in the choroid may lead to a local elevation of the overlying RPE, and in some cases a subsequent serous RPE detachment.\textsuperscript{9,64,65} With time, a defect in the outer blood-retina barrier of the RPE monolayer can lead to relatively sudden passage of fluid into the subretinal space, which results in a serous retinal detachment.\textsuperscript{9,66} In addition, an impaired pump function of the RPE cells is suggested to contribute to insufficient fluid drainage from the subretinal space, further contributing to the serous retinal detachment.\textsuperscript{10,67-69} Recently, an alternative visual cycle through the act of the retinal ganglion cells has been suggested to partially take over the role of the RPE-dependent photoreceptor (rods and cones) cells.\textsuperscript{70} This may explain the initial relatively preserved visual acuity in CSC patients in the acute phase of the disease, although color perception and retinal sensibility may already be impaired.\textsuperscript{71}

1.5. Characteristics on multimodal imaging

Multimodal imaging technologies have contributed to a better recognition of the disease characteristics and a better understanding of the pathophysiology of CSC. Additionally, multimodal imaging has assisted in the differentiation of CSC from other entities presenting with macular subretinal fluid. An overview of the broad differential diagnostic spectrum of diseases that may resemble CSC is given in Table 1.

Optical coherence tomography (OCT) and OCT angiography

OCT imaging can help to visualize retinal layers and its abnormalities in micrometer-level detail in a non-invasive manner.\textsuperscript{14,72} OCT is a pivotal method to study the choroid-Bruch-RPE-neuroretina interface, which plays a crucial role in the pathogenesis of CSC. In addition, OCT is very helpful as primary imaging tool to distinguish CSC from other causes of SRF accumulation in the macula. Besides the evaluation and follow-up of SRF accumulation, OCT may be used to study the configurations of individual retinal layers,\textsuperscript{72} subretinal debris accumulation as a sign of chronicity,\textsuperscript{73} the aspect of RPE detachment, detecting irregularities suspicious for sub-RPE neovascularization and choroidal thickness and structure (Figure 3A, B, C).\textsuperscript{8,74} For instance, enhanced depth imaging OCT (EDI-OCT) has shown that choroidal thickening in CSC is mostly due to dilatation of deep Haller’s layer vessels, while the superficial choriocapillaris layer and medium-sized Sattler’s layer vessels are abnormally thinned.\textsuperscript{61,62,75}
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OCT angiography combines the abilities of conventional (structural) OCT with the possibility to evaluate the choroidal and retinal vasculature in a noninvasive manner. Although vessel leakage and subretinal fluid leakage through the RPE cannot be visualized on OCT angiography, this technique may be used in CSC patients to evaluate in more detail the areas of choroidal hyperperfusion, enlarged vascular density, and vascular lumen alterations in different stages of the disease, although this needs further study. Furthermore, OCT angiography is able to detect a subtle sub-RPE neovascularization which might be overlooked on other imaging modalities, but is a relatively frequent complication of chronic CSC (Figure 4).

Fundus autofluorescence

Fundus autofluorescence (FAF) is a non-invasive imaging modality that visualizes lipofuscin and its precursor components in the RPE cells and outer retina (Figure 2G-I). This technique made it possible to visualize disturbed or damaged RPE. Different patterns of FAF abnormalities are distinguishable. Retinal areas with active leakage appear more hyper-autofluorescent on FAF imaging, while resolved leakage areas may reveal a mixture of hyper and hypo-autofluorescence. Retinal areas with a history of recurrent or persistent SRF may show predominantly hypo-autofluorescence which may reflect areas of RPE cell loss resulting in atrophy (Figure 3D-F).

Fluorescein angiography

Fluorescein angiography (FA) is an invasive technique that historically was the imaging modality used for the diagnosis and for studying the pathogenesis of CSC (Figure 2J-L).
General introduction

Dye is injected intravenously prior to making fundus photographs where focal fluorescein leakage corresponds to the site of an RPE detachment and/or a small RPE break in CSC patients. Normally, the RPE acts as the outer blood-retina barrier, and regulates the passage of fluid and nutrients from the underlying choroidal layer to the subretinal space. A disturbance in the integrity of the outer blood-retina barrier results in unregulated fluid accumulation, and eventually a serous retinal detachment (Figure 3G-L).9, 10, 66, 68

Indocyanine green angiography

With the use of indocyanine green angiography (ICGA) imaging, the choroid and its abnormalities became more visible (Figure 2M-O). In CSC, large multifocal areas of hyperpermeable choriocapillaris, and dilated larger choroidal vessels can be clearly visualized.64, 84 These findings were shown to correspond to, but were not identical to, the retinal abnormalities and the sites of RPE disturbances visualized by FA.65 The areas of vascular hyperpermeability and leakage, resulting in typical hyperfluorescent zones of leakage identifiable on FA are typically more extensive on ICGA, especially in chronic forms of the disease (Figure 3M-R).66 These observations strongly indicate that congested and hyperpermeable choroidal vessels may be the primary source of serous fluid in CSC patients.

1.6. Pachychoroid disease spectrum

Besides a serous retinal detachment, a thickened choroid is one of the most characteristic features of CSC.87, 88 Warrow and coworkers have introduced the term ‘pachychoroid’ to describe this observation which seems to be the linking characteristic finding among multiple diseases, which are referred to as the pachychoroid disease spectrum.89 Besides CSC, this spectrum also includes pachychoroid pigment epitheliopathy (PPE), polypoidal choroidal vasculopathy (PCV), peripapillary pachychoroid syndrome (PPS), and pachychoroid neovasculopathy (PNV).90-92 In PPE, there are visible atrophic alterations of the RPE cells in the absence of serous subretinal fluid. The RPE is presumably still able to cope with the underlying choroidal dysfunction, whereas in CSC the outer blood-retina barrier is disrupted, and the pump function of RPE cells fails which results in a focal serous retinal detachment. With time, choroidal neovascularization (CNV) and/or PCV may develop secondary to the abnormal subretinal environment, where there may be...
Chapter 1

an ischemic component due to choriocapillaris thinning, Bruch’s membrane damage, and an increased level of vascular endothelial growth factor.\textsuperscript{90, 93} Observing a pachychoroid, with enlarged Haller’s layer vessels and attenuated inner choroidal vasculature, is the key finding in distinguishing CSC from other causes of macular SRF and CNV/PCV.\textsuperscript{94} This important clinical distinction may have therapeutic consequences, on the treatment of first choice, the treatment frequency, and the expected treatment effect and outcome.

2. CLINICAL SPECTRUM OF CSC

There is currently no consensus on the clinical classification of CSC.\textsuperscript{12, 60} The clinical presentation of CSC is highly variable, and the different terminology used to classify CSC is subject of controversy.\textsuperscript{95} Historically, CSC is classified in either an acute or a chronic form, often depending on the duration of ocular complaints or the duration of observed SRF.\textsuperscript{60, 96} Alternative classifications have been suggested that also include non-resolving CSC, recurrent CSC, multifocal CSC, and inactive CSC.\textsuperscript{12, 60} The extent of abnormalities on multimodal imaging within the spectrum of chronic CSC may vary considerably and are not considered in these classifications. While all chronic CSC patients presumably have prolonged disease, some may present with limited atrophic RPE alterations where others display multifocal and large atrophic RPE areas, covering almost the entire posterior pole.\textsuperscript{4, 97-99} This severe presentation is observed when SRF is persistent or waxes and wanes over years. This may for instance be observed in some patients with chronic corticosteroid use.\textsuperscript{19, 99, 100} In the past, the term diffuse retinal pigment epitheliopathy (DRPE) was also used to address a more severe form of the disease that has affected the RPE extensively.\textsuperscript{22, 101}

A recent publication by an international expert panel introduced a diagnostic flow chart in an attempt to cover all clinical presentations of CSC. In their method, they used multimodal imaging findings identifiable on OCT, FA, ICGA, and FAF, to divide CSC phenotypes into simple or complex disease, and subcategorized in primary, recurrent, or resolved CSC.\textsuperscript{102} Future studies should implement this method in order to assess the reliability and the level of agreement among international retina experts.

Although there is no consensus on the terminology of different CSC phenotypes, it is widely accepted that different forms of CSC exist. It is however unclear, whether CSC phenotypes form different disease entities, or if they are part of a spectrum of diseases and may transition from one to another. An accurate classification of CSC is clinically relevant, not only for example to determine whether a spontaneous recovery is likely, but also whether treatment should be considered. Furthermore may disease prognosis and visual outcome differ strongly between these phenotypes. A worldwide accepted and uniform classification will greatly aid in future studies to make outcomes comparable.
General introduction

For the remainder of this introduction, the focus will be on the two major and most widely accepted CSC phenotypes; acute and chronic CSC.

2.1 Acute CSC

General clinical characteristics

Acute CSC (aCSC) is characterized by a sudden onset of central vision loss. This CSC phenotype is more frequent among younger patients during their professionally active age (between 35 and 55 years), and rare among the elderly. The clinical presentation of aCSC includes a unilateral dome-shaped serous retinal detachment in the macula as observed fundoscopically and on OCT imaging (Figure 3A). In previous studies it was shown that the height of the serous detachment was correlated with the severity of patients' complaints and it was shown that this was a suitable parameter for clinical follow-up until recovery. Besides the presence of SRF, disturbance of retinal structures at the level of the external limiting membrane (ELM), the ellipsoid zone, and the outer nuclear layer (ONL) may also be observed and monitored on OCT imaging. Gradual restructuring of these layers after SRF resolution was shown to be followed by visual recovery. When FA imaging is performed in aCSC cases, only one, or a few focal leakage spots are observed, which correspond to a focal defect at the level of the RPE (Figure 3G, J). This leakage may appear as a so called "smokestack" when fluorescein dye leaves the RPE break at the early-phase of FA (up to 3 minutes), then gradually ascends during the mid-phase (3 to 8 minutes), and ultimately fills the space under the neurosensory detachment in the late-phase FA (more than 8 minutes) (Figure 5F, H). Other patterns of leakage are also frequently observed in aCSC, such as a well circumscribed leakage spot (hot spot), which gradually increases in size during early to late phase FA; a so called "inkblot" (Figure 5E, G). FA may also show minimal focal RPE alterations, sometimes even in the non-symptomatic contralateral eye, but in absence of significant atrophy of the RPE, the latter being indicative of chronic disease. FAF imaging in aCSC may reveal a hypo-autofluorescent spot at the area of an RPE break, while the area of the neurosensory retinal detachment may either stay iso-autofluorescent due to its acute nature, or slightly hyper-autofluorescent (Figure 3D). ICGA imaging is occasionally performed in aCSC and may show an area of hyperfluorescence, which is slightly larger than the corresponding circumscribed leakage spot on FA (Figure 3M, P). The area of hyperfluorescence on ICGA originates from the underlying hyperpermeable and leaking choroid, which in some cases may also reveal early changes in a non-symptomatic fellow eye.

Prognosis

Acute CSC is generally self-limiting with a (near) complete visual recovery. It has been estimated however, that between 20% to 50% of aCSC patients have disease recurrence. Others will only experience one disease episode. The exact percentage of typical aCSC cases that transition to a recurrent disease is unknown, and the factors that contribute to this process are yet to be found. Studies have reported on patient's characteristics such
Chapter 1
General introduction

as choroidal thickness, non-intense aspect of fluorescein leakage on FA, and a history of shift-work to correlate to an increased risk of disease recurrence. It is currently unknown whether, and to what extent, aCSC cases can convert into chronic CSC cases. On estimation, 8-16% of patients with chronic CSC may have a recorded history of aCSC. However, Wong and coworkers reported in a cohort of 25 aCSC patients, that up to 61% of cases showed progressive RPE alterations during at least 5 years of follow-up. These progressive RPE changes may be considered a sign of a chronic disease development. This knowledge gap in the percentage of aCSCs that convert to chronic CSCs, and the risk factors contributing to this process are also issues we address in this thesis.

Treatment

It is generally thought that an expectant management is recommended in the majority of aCSC patients experiencing their first disease episode, since the disease may be self-limiting. When SRF persists, treatment can be considered to avoid ongoing and (partly) irreversible photoreceptor damage and vision loss. A prolonged disease episode was correlated to patients age at first CSC presentation, the choroidal thickness, and the size of the RPE detachment. Currently, a spontaneous disease resolution is awaited for at least 3 months before treatment is considered. Some clinicians may postpone treatment up to 6 months after onset, especially when gradual resolution of SRF is observed. Prolonged macular SRF is however associated with irreversible vision loss and decreased quality of life, although there is no clear cut-off value for this duration. Also, earlier treatment may be considered in patients with a recurrent episode of aCSC.

When treatment for aCSC is considered, there should be persistent fluid detectable on OCT and a clear leaking spot on FA imaging, with corresponding typical hyperfluorescent ‘ink blot’ choroidal leakage on ICGA. A range of treatment modalities may then be considered. It is of note that most of the treatment strategies in CSC are intended to treat non-resolving and chronic cases, and few studies are available which assess treatment efficacy in the supposedly typical aCSC. Traditionally, conventional thermal laser is used to consolidate the leakage spot. Photocoagulation caused by a (krypton, xenon, or argon) laser beam attempts to close the focal defect in the blood-retina barrier at the level of the choroidal lamina.
Chapter 1

RPE, and stop subretinal leakage. This method may still be used when other treatments are not available. However, conventional thermal laser is not safe when the leakage spot is close to the fovea, due to the risk of foveal burn, progressive (secondary occurring) atrophy towards the fovea, and central scotomas. Also, functional outcome in terms of gain of visual acuity and reduced recurrence rate after this treatment modality is inconsistent. Of course, in cases where there is evidence of steroid-associated CSC, discontinuation of corticosteroid use might be the first step prior to other forms of treatment.

Photodynamic therapy (PDT), is increasingly considered as treatment of first choice in all CSC phenotypes. In PDT treatment, verteporfin is admitted intravenously, and activated by a laser beam at the level of the leaky choroid. As a result, remodeling of choriocapillaris, and to some extent the larger choroidal vessels may occur. This remodeling leads to a reduction of choroidal congestion and leakage, and a reduction of choroidal thickness. Subretinal leakage may stop when choroidal congestion is decreased, resulting in resorption of SRF, and eventually improvement of visual acuity. PDT treatment efficacy is mostly established in chronic CSC, and studied to a lesser extent in aCSC. A randomized controlled trial (RCT) advocated the superiority of half-dose PDT treatment above placebo in aCSC (existing for less than 3 months). However, a recent RCT reported no significant difference in complete SRF resolution and improvement of visual acuity in aCSC after early PDT treatment versus a watchful waiting policy.

Another treatment option includes subthreshold micropulse laser, in which the RPE pump function is supposedly stimulated when RPE cells have been exposed to multiple ultrashort diode laser pulses. This type of laser treatment causes no visible laser burns as the heat produced by the laser dissipates between the pulses, and the temperature stays below the threshold for denaturing cellular proteins. However, the exact mechanism of action is unknown. Multiple studies investigated treatment efficacy of micropulse laser with various laser settings including the wavelength (between 810 and 527 nm), duty cycle, power, spot size, and pulse duration. Micropulse laser in aCSC is shown to be equally effective when compared to conventional thermal laser in terms of SRF resolution and visual improvement, but it results in a better contrast sensitivity.

Occasionally, treatment with an intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents is reported, although there is no evidence of an underlying VEGF-driven mechanism in CSC pathogenesis. Therefore, anti-VEGF agents should not be applied in CSC unless there is evidence of a (secondary) CNV. Additionally, meta-analysis studies have shown no convincing evidence for anti-VEGF agents as an effective treatment for CSC in general, and particularly for aCSC.

Currently, a few comparative RCT studies are available, discussing different treatments in aCSC. However, it is still unclear whether treating a typical aCSC patient is necessary, when to initiate treatment, and what is the treatment of first choice, given the self-limiting character of the disease in a high number of cases.
2.2. Chronic CSC

**General clinical characteristics**
In contrast to aCSC, there is usually no spontaneous recovery in chronic CSC (cCSC), which is characterized by prolonged and/or recurrent SRF leakage in the macula, atrophic RPE changes, and a decreased vision-related quality of life. In these cases, treatment is recommended to accelerate SRF reabsorption and to preserve vision.

Patients with chronic CSC tend to manifest with more widespread abnormalities on multimodal imaging as compared to aCSC (Figure 3). In cCSC the OCT may show persistent central or peripheral SRF, but also disruption of the outer retinal layers, RPE irregularity, RPE detachment, and/or RPE atrophy. Chronic CSC is more prone to be complicated by secondary CNV due to these RPE abnormalities, although detection of small CNVs on OCT may be challenging. The presence of a so called ‘double-layer sign’ on OCT, which is a flat empty space formed between the hyper-reflective irregularly elevated RPE and the inner layer of the Bruch’s membrane, may ease this diagnosis (Figure 4A). OCT angiography is, besides having the ability to reveal areas of choroidal hyperpermeability or hypoperfusion, also a sophisticated method to detect subtle secondary CNVs (Figure 4). Interpreting FAF findings in cCSC may be challenging. FAF in cCSC shows extensive hyper-autofluorescent and hypo-autofluorescent changes, together with a characteristic gravitational track as a result of RPE damage due to persistent, and descending fluid (Figure 3E, F).

In cCSC, active disease is characterized by multiple pin point and/or diffuse hyperfluorescent areas on the early phase (up to 3 minutes) of the FA indicating fluorescein leakage through damaged RPE. However, the most characteristic findings in cCSC are hyperfluorescent areas on intermediate phase (3-8 minutes) FA due to window defects, and hyperfluorescent areas on late phase (more than 8 minutes) FA due to dye pooling, which both correspond with widespread areas of chronic atrophic RPE alteration (Figure 3H, I, K, L). As mentioned earlier is FA used to study retinal vascular abnormalities, whereas ICGA is used to illustrate deeper choroidal abnormalities in cCSC. Early phase (1-3 minutes) ICGA shows a reduced flow in the choriocapillaris in cCSC patients, appearing as hypofluorescent areas. Intermediate phase (3-15 minutes) ICGA shows multifocal areas of choroidal congestion and dilated veins, while late phase (15-40 minutes) ICGA may reveal the areas of hyperpermeability and leakage, which may be larger than abnormalities on FA (Figure 3N, O, Q, R). In fact, ICGA visualizes the origin of the leakage, while FA visualizes the consequence damage of the leakage. Also, ICGA can be useful in detection of secondary CNV or polypoidal changes in the choroid, having an important role in directing treatment, as will be discussed in the following paragraphs.
Chapter 1

Prognosis

Disease prognosis in cCSC may vary depending on the extent of the chorioretinal abnormalities, especially the amount of RPE cell loss due to atrophy. Although treatment can result in an anatomical recovery and a complete SRF resolution, even among the most severely affected cases, the final visual acuity may remain poor in cCSC due to extended RPE atrophy. However, treatment may not only be focused on improving vision but also on preserving the remaining vision. An extension of hypo-autofluorescence areas has been proven to be an important determinant of worse visual outcome in cCSC patients, which may be informative in evaluating disease prognosis.

Treatment

The treatment approach for cCSC is not globally uniformed. Several relatively large prospective RCTs and retrospective studies have shed more light on the efficacy of the most commonly performed treatment options for cCSC. The most frequently used treatments include PDT, subthreshold micropulse laser, oral mineralocorticoid receptor antagonists (eplerenone and spironolactone), and conventional laser photocoagulation. Also, treatments such as intravitreal injections of anti-VEGF agents, or systemic treatments with carbonic anhydrase inhibitors, Aspirin, beta-blockers, finasteride, and ketoconazole have been reported.

The role of cortisol and endogenous mineralocorticoid in CSC risk has been established. As a consequence the efficacy and safety of mineralocorticoid and glucocorticoid receptor antagonists are extensively investigated, since these currently available oral medications make a noninvasive and accessible treatment option. The VICI trial studied long-term effect of eplerenone treatment as compared to sham in cCSC patients, and reported that only 10% of cCSC patients had a complete SRF resolution in the group treated with oral eplerenone. The SPECTRA trial compared the outcome of oral eplerenone treatment during three months with half-dose PDT. In this trial, the SRF resolved completely in a significantly larger number of cCSC treated cases with PDT (78% versus 17% in the eplerenone group). Also, patients treated with PDT showed a higher retinal sensitivity on microperimetry compared to patients who received eplerenone. However, no statistically significant difference in visual outcome was reported between the two treatment groups. There were also no major adverse events reported in both treatment groups, making PDT evenly safe as eplerenone treatment. Besides visual improvement, a complete resolution of SRF is the most important treatment purpose in order to prevent future photoreceptor degeneration due to persisting fluid. Hence, mineralocorticoid receptor antagonists, despite the accessibility, may not be the treatment of first choice in cCSC, because of the inferior effect on SRF resolution.
The treatment efficacy of subthreshold micropulse laser with various treatment settings has been investigated, not only in aCSC patient as described in earlier paragraphs, but also in cCSC patients.\textsuperscript{155, 156} This relatively safe treatment is reported to be successful in 36-100\% of the treated cCSC patients, in terms of complete SRF resolution.\textsuperscript{96, 155} Subthreshold micropulse laser seems particularly effective in studies on cCSC eyes with focal leakage rather than diffuse leakage.\textsuperscript{156, 157} In the PLACE trial, treatment outcome of high-density subthreshold micropulse laser was compared to half-dose PDT in cCSC patients. This trial confirmed PDT’s safety and treatment efficacy, but also showed the supremacy of half-dose PDT, both in the proportion of cases with complete post-treatment SRF resolution (67\% in the PDT group as compared to 29\% in the micropulse group), as well as functional improvement (retinal sensitivity and short-term visual outcome).\textsuperscript{128} Therefore, micropulse laser may not be considered the treatment of first choice in cCSC patient when PDT treatment is also an available option.

Yannuzzi and coworkers were one of the first authors to report on successful use of ICGA-guided PDT with full-settings (6 mg/m\textsuperscript{2} verteporfin, 50 j/cm\textsuperscript{2} energy for a duration of 83 seconds) in treatment of cCSC.\textsuperscript{85, 158, 159} Despite the safety of this treatment, multiple studies followed to assess treatment efficacy of PDT with reduced settings (half-dose (3 mg/m\textsuperscript{2}), half-fluency (25 j/cm\textsuperscript{2}), or half-time (40 seconds)) in cCSC patient.\textsuperscript{160-164} So far, no significant differences in treatment outcome has been established between different PDT settings. These studies have repeatedly shown that PDT is a safe treatment and may result in complete resolution of SRF in 41\% to 100\% of the treated patients, and most importantly, improve visual acuity.\textsuperscript{128, 154, 161-163, 165} In general, ICGA-guided PDT with reduced settings is increasingly considered as treatment of first choice in cCSC, based on currently available literature (among others the PLACE, the REPLACE, and the SPECTRA trials).\textsuperscript{128, 154, 166, 167} Due to the large heterogeneity of clinical presentation in cCSC, PDT efficacy also needs to be evaluated separately in these different phenotypes, which include steroid-associated cCSC, complicated and severe cCSC, and recurrent cCSC. This subject will be discussed in the next chapters of this thesis.

2.3. Complications of CSC

*Posterior cystoid retinal degeneration*

Intraretinal cystoid changes are a common feature in patients with advanced cCSC (Figure 3C), and were shown to exist in up to 35\% of cCSC patients, depending on the extent and severity of the disease.\textsuperscript{168-171} This so-called posterior cystoid retinal degeneration (PCRD) may have a macular, and/or a juxtapapillary presentation, and differs pathophysiologically from regular cystic macular oedema in retinal vascular diseases such as diabetic retinopathy.\textsuperscript{171} In the case of PCRD, there are no signs of retinal, or choroidal neovascularization, or any other VEGF-driven processes which may explain these intraretinal cystoid changes.\textsuperscript{172} To date, little is known about the etiology of PCRD secondary to cCSC. It has been suggested that a prolonged disease over 5 years, and
subretinal fibrosis may increase the chance of PCRD formation. Recently the term peripapillary pachychoroid syndrome (PPS) was introduced to address a new entity within the pachychoroid disease spectrum, which also includes CSC. In PPS, there is a noticeable thickened peripapillary choroid, which is relatively thicker than the more temporally located choroid. Patients with PPS also show intraretinal and/or subretinal fluid extending from the temporal disc margin into the macula along with the thickened choroid. It is hypothesized that in PPS high hydrostatic pressure under the RPE, caused by a focal congested and leaky choroid, may lead to RPE dysfunction and fluid leakage into the retina. PPS is closely related to CSC, as the mechanism of fluid leakage seems comparable. However, it is difficult to distinguish PPS form cCSC with secondary PCRD as in 13-84% of PPS patients juxtapapillary intraretinal fluid is also observed. Better understanding of the disease mechanism may be achieved by studying cCSC patients with secondary PCRD more closely.

Choroidal neovascularization
Any damage to Bruch’s membrane increases the risk of CNV formation. CSC patients, in whom the RPE-Bruch’s membrane-choriocapillaris interface is affected, are therefore also prone to develop a secondary CNV (Figure 4). Different types of CNV’s exist. In CSC a type 1 macular neovascularization is most frequently seen. A CNV may be detected on OCT as a flat and irregular RPE detachment with accumulation of sub-RPE hyperreflective debris, which is in contrast to the frequently encountered dome shaped RPE detachments with hyporeflective sub-RPE space in typical CSC without CNV. FA imaging remains the gold standard in detection of CNVs. Although, OCT angiography is shown to be an accurate and non-invasive method to detect even subtle secondary CNV’s in cCSC. It is estimated that secondary CNV formation may occur in approximately 2-15% of CSC patients, mostly in chronic cases, but occasionally in acute cases too. Secondary CNV in patients with a history of CSC may be distinguished from pachychoroid neovasculopathy, in which a CNV is the primary presentation (without a previous history of CSC) in association with an underlying pachychoroid. A timely diagnosis of secondary CNV is of great importance as it may, when left untreated, damage the vision dramatically and permanently. Combination therapy with PDT using the original (full) settings, monotherapy with intravitreal Anti-VEGF agents, or a combination therapy of PDT and anti-VEGF agents have been suggested to be evenly successful in these cCSC cases complicated by the development of a CNV. However, combination therapy seems the most sensible choice, as it deals with both thenon-VEGF driven cCSC, and the VEGF-driven CNV.

Polypoidal choroidal vasculopathy
Polypoidal choroidal vasculopathy (PCV) is considered a variant of type 1 macular CNV. PCV is an aneurysmal neovascular dilation at the border of a CNV, that may be relatively solitary or associated as polyp-like terminal dilations to a sub-RPE branching vascular network. PCV is more common in Asians than in the European population, and may present as an idiopathic entity without a drusenoid AMD background, in association with
AMD, or secondary to cCSC. Our research group has previously described a spectrum of AMD in Caucasian patients who had no drusen in the fellow eye. In 10% of these patients there was evidence of PCV in the affected eye. There is also overlap in the clinical presentation of CSC and PCV, including SRF, RPE abnormalities and RPE detachments, as well as focal choroidal hyperpermeability on ICGA. PCVs show specific characteristics such as reddish-orange nodules in the posterior pole, retinal hemorrhages, and neovascular tissue that may help to distinguish PCV from CSC. Secondary PCV may occasionally complicate cCSC, and PCV may even present as a masquerader of CSC. PCV may also independently of the occurrence of CSC be considered part of the pachychoroid disease spectrum, just like CSC, as a thickened choroid (thickness above 395 µm) was also shown to be a frequent finding in PCV. PCV, regardless of its background, always needs to be treated, just like any other type of subretinal neovascularization. In PCV, full-settings PDT, usually in combination with intravitreal anti-VEGF medications, appears the most successful treatment. This is in contrast to uncomplicated cCSC, in which PDT with reduced settings as monotherapy is effective and sufficient.

**Other complications**

Subretinal accumulation of fibrin, although uncommon, is among other complications of CSC. Schatz and coworkers previously reported that subretinal fibrin in the macula in six cCSC cases causing fibrotic scars, and severe vision loss. Yannuzzi suggested that the presence of subretinal fibrin may exaggerate the response to PDT, and therefore PDT must be used with caution in cCSC with subretinal fibrin accumulation. Contrary, Liang and coworkers have reported that PDT efficacy and visual outcome were not negatively influenced by central subretinal fibrin accumulation in 48 patients with CSC as compared to 125 controls with CSC but without the presence of subretinal fibrin.

Inferior bullous retinal detachments may be observed in rare cases of extensive and severe cCSC. These patients may also show multiple RPE detachments, RPE tears, and areas of non-perfusion on FA. So far, no clear patient characteristics or other findings on multimodal imaging have been associated with the risk and development of a bullous cCSC variant. However, it is hypothesized that marked fibrinous exudation from a leaky choroid in cCSC may initiate a cascade of morphological changes in the choroid, RPE, and the retina, which may lead to a bullous retinal detachment. Future prospective studies are necessary to prove this theory.
Chapter 1

3. AIMS AND OUTLINES OF THIS THESIS

This thesis attempts to provide new insights in the understanding of CSC in all its aspects. The aims of this thesis can be summarized in three main subjects. Firstly, to provide an overview of the heterogeneous clinical presentations in CSC, their overlaps, and the major differences. Secondly, to report genetic predispositions in all phenotypes of CSC, and to assess whether these genetic predispositions explain the different clinical presentations. Thirdly, to evaluate treatment efficacy and post-treatment visual outcome, especially for PDT treatment, in a wide range of CSC phenotypes, including the most excessive and complicated CSC cases.

Chapter 1 is the general introduction of this thesis. The reader is provided with information on our current understanding and knowledge of CSC’s pathophysiology, present clinical classification, current treatment options, and treatment outcomes. The gaps in our current knowledge are also outlined in this chapter.

Chapter 2 includes studies on different clinical presentations of CSC. Chapter 2.1 describes patient characteristics in a large cohort of typical acute CSC (aCSC), and the long-term outcome of early treatment and the risk of aCSC recurrence are assessed. In addition, this chapter attempts to identify the clinical characteristics that may be used to predict the transition of aCSC to a chronic CSC (cCSC). In chapter 2.2 a subgroup of cCSC is presented, which shows a severe form of the disease with extensive anatomical abnormalities, and profound vision loss. This chapter introduces a definition for this severe phenotype of cCSC. Moreover, it assesses to what extent these severe cCSC cases are preceded by a typical aCSC. Chapter 2.3 also focuses on the severe cCSC phenotype, and specifically those cases characterized by the presence of posterior cystoid macular degeneration. The clinical characteristics on multimodal imaging techniques are described in these patients, together with the treatment (especially PDT) outcome in terms of anatomical recovery and the final visual acuity.

Chapter 3 includes two studies focusing on the genetic predisposition in CSC. In chapter 3.1, for the first time, the genetic risk factors in aCSC patients are studied. Possible genetic associations in four previously identified genes (the ARMS2, CFH, NR3C2, and C4B genes) are investigated. Furthermore, the presence of a possible genetic overlap between aCSC and cCSC patients is assessed. Chapter 3.2 looks in a broader scale at the mutual genetic similarities and differences in three assumingly clinically separate phenotypes of CSC, including aCSC, non-severe cCSC, and severe cCSC. This chapter attempts to substantiate different clinical presentations of CSC based on their genetic predispositions.

Chapter 4 encompasses studies on the efficacy of photodynamic therapy in different CSC phenotypes. In chapter 4.1, PDT treatment outcome is investigated in steroid-associated cCSC cases, and compared to treatment outcome in non-steroid-associated cCSCs.
Additionally, PDT treatment outcome is evaluated in a subgroup of steroid-associated cCSC patients who could not omit steroids use. Chapter 4.2 presents the outcome of treatment, specifically PDT treatment, in the severe phenotype of cCSC, both in terms of SRF resolution and final visual outcome. Moreover, in this chapter patient characteristics as well as clinical features are studied, which may assist to predict post-treatment visual improvement.

Chapter 5 is devoted to the general discussion. Here, the most important findings in this thesis come together, and will be discussed in a broad perspective, as well as in the context of the current literature.

Chapter 6 includes an English, and Dutch summary of this thesis, a list of publications, the authors acknowledgments, and a short biography of the author.
Table 1 Differential diagnosis of central serous chorioretinopathy (This table is adapted from *van Dijk and Boon, 2021, Prog Retin Eye Res.*).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical characteristics and differential diagnostic aspects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular neovascular disease</td>
<td>Subretinal neovascularization in context of pachychoroid neovasculopathy. Older age, presence of neovascular network on ICGA (sometimes FA), and OCTA, neovascularization over areas of choroidal thickening and thickened Haller’s layer vessels (‘pachyvessels’)</td>
<td>174, 206</td>
</tr>
<tr>
<td>Polypoidal choroidal vasculopathy</td>
<td>Older age; presence of polypoidal dilatations on OCT and ICGA, sometimes with concurrent non-polypoidal neovascularization on ICGA and OCT</td>
<td>207-211</td>
</tr>
<tr>
<td>Neovascular age-related macular degeneration</td>
<td>Presence of drusen in combination with or without vitelliform lesion, neovascular lesion on OCT, OCTA, FA (and ICGA)</td>
<td>212, 213</td>
</tr>
</tbody>
</table>
| Other conditions with subretinal neovascularization | - Pachydrusen: Thickened choroid (on average 419 µm), well defined large (>125 µm) drusenoid accumulations under the RPE, distributed throughout the posterior pole  
- High myopia: chorioretinal atrophy adjacent to optic disc, oblique insertion of optic disc, macular pigment abnormalities, thin choroid  
- Angioid streaks (often in pseudoxanthoma elasticum): early onset, bilateral deep retinal red-brown bands, optic disc drusen, peripheral round atrophic scars  
- Multifocal choroiditis: yellow-white punched-out round spots deep to the retina, women < 50 years  
- Choroidal rupture: yellow-white subretinal streak, history of blunt eye trauma | 214-220    |
Table 1 Continued

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical characteristics and differential diagnostic aspects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitelliform lesions</td>
<td><strong>Autosomal dominant Best vitelliform macular dystrophy</strong> and <strong>autosomal recessive bestrophinopathy due to BEST1 gene mutations</strong> Positive family history, bilateral disease, vitelliform lesion on fundoscopy, serous detachment on OCT, filled with hyperreflective material on OCT; hyperautofluorescence on FAF; no focal leakage on FA, no choroidal hyperpermeability on ICGA, absent or markedly decreased light rise on electro-oculography, mutations in the BEST1 gene</td>
<td>221, 222</td>
</tr>
<tr>
<td>Acute exudative polymorphous vitelliform maculopathy</td>
<td>Multiple, bilateral well-defined serous macular detachments, subretinal accumulation of yellow-white material; hyperautofluorescence on FAF; no focal leakage on FA/ICGA</td>
<td>223, 224</td>
</tr>
<tr>
<td>Adult-onset foveomacular vitelliform dystrophy</td>
<td>Either unilateral or bilateral small (&lt; 1 disc diameter) round foveal yellowish subretinal lesions; hyperautofluorescence on FAF; central hypofluorescence with a hyperfluorescent ring on FA (with late staining of vitelliform lesion), either non- or hypofluorescent changes on ICGA</td>
<td>225-228</td>
</tr>
<tr>
<td>Vitelliform lesions secondary to age-related macular degeneration</td>
<td>Presence of drusen in combination with surrounding vitelliform detachment, underlying confluent drusen</td>
<td>212, 213</td>
</tr>
</tbody>
</table>
| Vitelliform lesions in the context of other diseases                  | - Epiretinal membrane  
  - Vitreomacular traction  
  - Persistent SRF after retinal reattachment surgery                                                                                                                                                              | 229, 230   |
Table 1 Continued

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical characteristics and differential diagnostic aspects</th>
<th>References</th>
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<tr>
<td>Inflammatory diseases</td>
<td><strong>(Vogt-Koyanagi-)Harada disease</strong></td>
<td>231-233</td>
</tr>
<tr>
<td></td>
<td>Harada disease: only ocular signs, including vitritis and optic disc oedema Rapid onset, young age, bilateral in 95% of cases; cystoid outer retinal fluid on OCT, numerous central leakage points on FA, in some cases with serous inferior retinal detachment; early hyperfluorescence on ICGA, markedly thickened choroid, which decreases quickly with corticosteroid treatment At least 3 of the following findings to establish the diagnosis Vogt-Koyanagi-Harada disease: bilateral chronic iridocyclitis, posterior uveitis, neurologic signs, cutaneous signs</td>
<td></td>
</tr>
<tr>
<td>White dot syndromes (e.g., acute</td>
<td><strong>posterior multifocal placoid pigment epitheliopathy</strong></td>
<td>234</td>
</tr>
<tr>
<td></td>
<td>Rapid onset with progressive marked vision loss and often slow recovery, female predominance, relatively young age, (placoid) subretinal (yellow-white) lesions on fundoscopy, OCT, and FA, hypofluorescent changes on late-phase ICGA</td>
<td></td>
</tr>
<tr>
<td>Posterior scleritis</td>
<td>Middle-aged women; presentation with deep pain, hyperemia of the conjunctiva and large scleral vessels, painful eye movements, choroidal folds, serous retinal detachment, and optic disc oedema on examination; fluid in the sub-Tenon space around the optic disc (T-sign) on ultrasonography, no leakage on FA/ICGA</td>
<td>235, 236</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Nodules on conjunctiva and anterior, intermediate or posterior uveitis on examination, retinal vasculitis, small round atrophic granuloma lesions in inferior peripheral fundus Systemic disease: granulomas in different organs, mainly lungs, skin, and lymphatic system</td>
<td>237, 238</td>
</tr>
<tr>
<td>Unilateral acute idiopathic maculopathy</td>
<td>Presentation soon after a flu-like illness, young age, swelling of outer retina with elevated and disrupted ellipsoid zone on OCT, spontaneous and quite rapid resolution of SRF, vitritis on examination, no leakage on FA and no hyperfluorescence on ICGA</td>
<td>239-242</td>
</tr>
<tr>
<td>Disease</td>
<td>Clinical characteristics and differential diagnostic aspects</td>
<td>References</td>
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<tr>
<td>Ocular tumors</td>
<td></td>
<td>243, 244</td>
</tr>
<tr>
<td><strong>Choroidal nevus and melanoma</strong></td>
<td>Hyperpigmented (sometimes amelanotic) and elevated choroidal mass on fundoscopy, low internal reflectivity on ultrasonography, solid choroidal mass on OCT, multiple areas of pinpoint leakage on FA, blockage of fluorescence on ICGA Focal leakage on FA may be seen in case of neovascularization</td>
<td></td>
</tr>
<tr>
<td><strong>Choroidal metastasis</strong></td>
<td>Yellow-white elevated choroidal lesions, sometimes multifocal and bilateral, minority of patients is not known with a primary tumor at the moment of ocular presentation, high internal reflectivity on B-scan ultrasonography, irregular hyperreflective spots in the photoreceptor layer and RPE layer, in combination with choroidal mass on OCT, early hypofluorescence and late leakage on FA, blockage of choroidal fluorescence on ICGA at the location of the tumor</td>
<td>245-247</td>
</tr>
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<td><strong>Circumscribed cavernous choroidal hemangioma</strong></td>
<td>Elevated orange-red mass on fundoscopy, elevated choroidal lesion with mixed reflectivity characteristics on OCT that fit within the vascular nature of the tumor, mild diffuse hyperfluorescence on early-phase FA with increasing diffuse leakage throughout the later phases, rapid filling of tumor vessels and late ‘wash-out’ phenomenon on ICGA, high internal reflectivity on B-scan ultrasonography</td>
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<td><strong>Choroidal osteoma</strong></td>
<td>Young women; well-defined bone structure in papillary or macular region; hyperreflective horizontal lamellar lines on OCT between choroid and tumor tissue; hyperfluorescent changes on late-phase FA and ICGA</td>
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<td>Hematological malignancies</td>
<td>Bilateral macular serous retinal detachments; no focal leakage on FA, no choroidal hyperpermeability on ICGA, hyperviscosity-related retinopathy on fundoscopy (in some cases) Overproduction of the monoclonal immunoglobulin type M, blood hyperviscosity</td>
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<td>Choroidal lymphoma</td>
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<td>Leukemia</td>
<td>In majority of patients: cotton wool spots, hemorrhages, vascular tortuosity In minority of patients: bilateral foveal SRF; multifocal granular hyperfluorescence on FA, dot-like choroidal hyperfluorescence without leakage on ICGA Thrombocytopenia, anemia, and leukocytopenia, leukemic blasts in the bone marrow</td>
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<td>Paraneoplastic syndromes</td>
<td>Several elevated pigmented bilateral uveal lesions and progressive cataract, association with (usually) non-ocular tumors; RPE atrophy and irregularity on examination, early hyperfluorescence on FA, corresponding to the RPE changes and RPE detachments, granular hyperfluorescent changes on ICGA</td>
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<td>Paraneoplastic vitelliform maculopathy</td>
<td>Relationship with cutaneous and uveal melanoma; vitelliform lesions; anti-RPE and anti-retinal auto-antibodies in serum</td>
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<td><strong>Best vitelliform macular dystrophy and autosomal recessive bestrophinopathy due to BEST1 gene mutations</strong>&lt;br&gt;<strong>RP1L1-associated occult macular dystrophy</strong>&lt;br&gt;<strong>Central areolar choroidal dystrophy (CACD) due to PRPH2 gene mutations</strong>&lt;br&gt;<strong>Pseudoxanthoma elasticum and serous fluid</strong></td>
<td>see ‘Vitelliform diseases’&lt;br&gt;<strong>RP1L1 gene mutation, autosomal dominant inheritance</strong>&lt;br&gt;<strong>PRPH2 gene mutation, autosomal dominant inheritance</strong>&lt;br&gt;<strong>ABCC6 gene mutation, autosomal recessive inheritance</strong></td>
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<td></td>
<td>Poor visual acuity despite very few abnormalities on fundoscopy, thickened and blurry ellipsoid line on OCT in the early stage of disease, which is disrupted and absent in the late phase; few abnormalities on FAF, no focal leakage on FA/ICGA&lt;br&gt;Moderate atrophic RPE changes in the stage 1 and 2, geographic atrophy in the stage 3 and 4, highly symmetrical FAF abnormalities, no leakage on FA, no hyperfluorescent changes on ICGA&lt;br&gt;Angioid streaks (bilateral deep retinal red-brown bands radiating from optic disc), thin choroid on OCT, no focal leakage on FA (unless in case of subretinal neovascularization), no CSC-like hyperfluorescent zones on ICGA&lt;br&gt;Localized skin changes (‘plucked chicken’ appearance), premature atherosclerosis, gastrointestinal and cardiovascular complications</td>
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<td>Ocular developmental anomalies</td>
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<td>Dome-shaped macula</td>
<td>Inward macular deviation with a thickened underlying sclera, together with relatively thin choroid, especially on vertical OCT scan</td>
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<td>Tilted disc with inferior staphyloma</td>
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<td>Optic disc pit</td>
<td>Congenital unilateral abnormality of the optic disc (grey ‘pit’) on fundoscopy; no focal leakage on FA, no choroidal hyperpermeability on ICGA; connection of SRF to optic disc and retinoschisis-like intraretinal fluid on OCT</td>
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<td>Uveal effusion syndrome</td>
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<td>Concavity in the choroid, with normal overlying retinal architecture</td>
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<td>secondary serous subretinal fluid</td>
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<td>Macular choroidal macrovessel</td>
<td>Large tortuous choroidal vessel temporally in the macula; no leakage on FA, early filling on ICGA</td>
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<td>Torpedo maculopathy</td>
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<td>MEK inhibitor associated serous retinopathy (MEKAR)</td>
<td>Onset of SRF associated with MEK inhibitor treatment (targeted treatment for metastatic tumors); bilateral and symmetrical, sometimes multifocal serous retinal detachments, no pachychoroid or RPE detachments on OCT; no leakage on FA; no light rise on electro-oculography</td>
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<td>Checkpoint inhibitors causing birdshot-like chorioretinopathy (e.g. pembrolizumab)</td>
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<td>Hair dyes containing aromatic amines (para-phenylenediamine and 5-diamine sulphate) causing serous retinopathy</td>
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<td>Poppers maculopathy</td>
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<tr>
<td>Rhegmatogenous and tractional retinal detachment</td>
<td>Acute (or in rare cases gradual) onset of symptoms, such as visual field loss, central vision loss when macula is affected; history of flashes, floaters, and vision loss; pigment in the vitreous, peripheral retinal breaks, and peripheral extension of retinal detachment on examination</td>
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<td>Retinal vein occlusion</td>
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<td>Pregnancy-related serous maculopathy</td>
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<td>Atrophic RPE changes and hyperpigmentations on fundoscopy, irregular and thickened RPE on OCT, elevated by a thickened and irregular and structurally altered choroid, early blockage of fluorescein on FA with staining and leakage on mid- to late-phase, variable fluorescence changes on ICGA</td>
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**Abbreviations:** AREDS, Age-related Eye Disease Study; CSC, central serous chorioretinopathy; FA, fluorescein angiography; FAF, fundus autofluorescence; ICGA, indocyanine green angiography; MEK, mitogen-activated protein kinase kinase; MEKAR, MEK inhibitor treatment serous retinopathy; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; RPE, retinal pigment epithelium; SMACH, serous maculopathy due to aspecific choroidopathy; SMARPE, serous maculopathy with absence of retinal pigment epithelium; SRF, subretinal fluid; VEGF, vascular endothelial growth factor
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Chapter 1


General introduction


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CHAPTER 2
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CHAPTER 2.1

Risk of recurrence and transition to chronic disease in acute central serous chorioretinopathy

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ABSTRACT

Purpose: To study the risk of recurrence in acute central serous chorioretinopathy (aCSC) and to evaluate the risk of transitioning to chronic CSC.

Patients and methods: The medical records and multimodal imaging data of 295 aCSC cases were reviewed. Typical aCSC was defined as the presence of serous subretinal fluid (SRF), one focal leakage spot on fluorescein angiography (FA), retinal pigment epithelium (RPE) alterations limited in area to less than one optic disc diameter, and complete recovery from this first CSC episode. An increase in RPE alterations combined with persistent SRF was considered a sign of chronicity, which was determined in cases with >12 months follow-up. The main outcome measures includes final visual acuity, percentage of disease recurrence, and percentage of cases moving toward a chronic phenotype. Treatment strategies and their efficacy were also reviewed.

Results: A total of 295 eyes in 291 patients with aCSC were included. Spontaneous recovery was awaited in 154 eyes (52%), whereas 141 eyes (48%) recovered following treatment. SRF recurrence occurred in 24% of untreated cases and in 4% of treated cases (p<0.001). An analysis of 61 eyes that underwent a FA after ≥12 months of follow-up revealed increased RPE alterations in 22 eyes (36%), and 14 eyes (23%) had both an increase in RPE alterations and SRF recurrence.

Conclusions: All aCSC cases recovered from the first disease episode, and none of the cases developed persistent SRF leakage. Among the cases for which long-term follow-up information was available, 36% showed a tendency toward chronicity in terms of increased RPE alterations, whereas 23% showed both an increase in RPE alterations and recurrent SRF. Early PDT treatment may decrease the risk of recurrences.
INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by an accumulation of serous fluid under the retina. This subretinal fluid (SRF) is believed to accumulate as the result of a dysfunctional, hyperpermeable choroid together with a disruption in the retinal pigment epithelium (RPE), which compromises the outer blood-retinal barrier.

Generally, CSC can present as either an acute or chronic form. Acute CSC (aCSC) is usually self-limiting, with a good visual prognosis. In contrast, in chronic CSC, the SFR usually does not resolve spontaneously, and may result in irreversible photoreceptor damage, vision loss and a decreased vison-related quality of life. Therefore, treatment is generally recommended for chronic CSC.

It is unclear whether aCSC and cCSC are different entities or if they are part of a spectrum of diseases and whether aCSC can transition to cCSC, and if so, what factors may contribute to this process. Also, there is no consensus regarding the exact period after which CSC should be considered chronic; some authors suggest that typical aCSC resolves spontaneously within 2-4 months, whereas others suggest a duration of 6 months. It is also unclear whether chronic CSC is usually preceded by aCSC.

There are clinical features in addition to disease duration that can help distinguish between acute CSC and chronic CSC. Chronic CSC tends to manifest with more widespread abnormalities on multimodal imaging compared to aCSC. In cCSC, optical coherence tomography (OCT) shows disruption of the outer retinal layers, RPE irregularities and/or detachment, and posterior cystoid retinal degeneration. Fluorescein angiography (FA) shows gravitational tracks, multiple “pin points” or diffuse RPE leakage, and/or widespread areas of atrophic RPE alterations. Indocyanine green angiography (ICGA) shows signs of multifocal hyperpermeable choroidal congestion and hyperpermeability. Fundus autofluorescence (FAF) imaging shows extensive hyper-autofluorescent and hypo-autofluorescent changes. Unlike chronic CSC, an episode of aCSC is generally defined as only a single leak on FA with minimal focal changes in the RPE.

Little is known about which aCSC patients are at risk for developing recurrent and/or chronic CSC. Therefore, better insight into the clinical course, risk factors, and long-term outcome of aCSC can be helpful in determining whether these diseases largely overlap or are pathophysiologically and clinically distinct. Here, we reviewed a large number of patients who presented with their first episode of typical aCSC based on multimodal imaging characteristics. These patients were followed over time in order to evaluate the prevalence of recurrence and to identify the clinical features that can be used to predict the transition of aCSC to chronic CSC.
Chapter 2.1

PATIENTS AND METHODS

**Patient selection**

This study was approved by the respective institutional review boards at the participating centers and was performed in accordance with the tenets of the Declaration of Helsinki. No written consent had to be collected for reviewing the medical records, as all data were anonymized upon collection. In this retrospective multicenter study, subjects were identified from a large cohort of CSC patients seen from January 2005 until December 2017 at two Dutch tertiary referral centers: The Department of Ophthalmology at Leiden University Medical Center (Leiden, the Netherlands) and the Rotterdam Eye Hospital (Rotterdam, the Netherlands). Patients who met the clinical definition of aCSC, had at least one follow-up visit, and had evidence of complete resolution of the first CSC episode were included. Acute CSC was defined as: 1. documented presence of SRF on OCT; 2. only one focal leakage (“hot spot”) on FA; 3. limited RPE alterations, including RPE detachment, less than one optic disc diameter. Patients were excluded when there was a suspicion of other possible causes of SRF accumulation, such as choroidal neovascularization, or polypoidal choroidal vasculopathy. In this study, previous steroid use was not an exclusion criterion.

**Clinical examinations**

Patients underwent a range of ophthalmological and multimodal imaging examinations both at the time of diagnosis and during follow-up visits. These examinations included best-corrected visual acuity (BCVA, measured with a Snellen chart, then converted to ETDRS letters for statistical comparison); slit-lamp examination and/or color fundus photography (Topcon Corp., Tokyo, Japan or Carl Zeiss Meditec AG, Jena, Germany); spectral-domain OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Jena, Germany, OCT-HS100, Canon Inc., Tokyo, Japan, or Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany); fundus autofluorescence imaging (FAF) (Heidelberg Spectralis HRA+OCT or Topcon Corp.); FA (Topcon Corp., Spectralis HRA+OCT, or Carl Zeiss Meditec); and ICGA (Topcon Corp., Heidelberg Spectralis HRA+OCT, or Carl Zeiss Meditec).

**Clinical outcome measures**

For this study, patients were subdivided into the following two groups based on available follow-up data: patients with ≥12 months follow-up, and patients with <12 months of follow-up. Only patients with ≥12 months of follow-up data were included in our analysis of disease progression over time. Follow-up began at the first episode of CSC confirmed by an ophthalmologist and ended with the last available visit. The following clinical characteristics were obtained: presence and location of SRF on OCT; abnormalities on FAF; RPE alterations on FA; SRF leakage on FA; and the aspect of the hyperpermeable choroid areas on ICGA. In addition, the presence of RPE alterations in the unaffected contralateral eye was assessed. RPE alterations were defined as patches of granular hyperfluorescence as seen on mid-phase FA. The amount of RPE alterations, and the extension of the area of RPE alterations, were evaluated by two experienced retina specialists (SY and CJFB). All clinical management strategies were also reviewed and included photodynamic therapy.
(PDT), conventional thermal laser, subthreshold micropulse diode laser (SML), and a “wait-and-see” policy. CSC was considered to be recurrent when SRF returned at least once following complete resolution. Signs of chronic CSC were defined as the persistence and/or recurrence of SRF together with an increased area of cumulative RPE alterations based on follow-up FA imaging. Patients with aCSC who were followed for less than 12 months were contacted by telephone and questioned regarding any complaints suggestive of recurrent CSC (either with or without consulting an ophthalmologist) since their final follow-up visit.

**Statistical analysis**

Statistical analyses were performed using IBM SPSS software for Windows, version 23 (IBM Corp., Armonk, NY, USA). Continuous numerical data were compared using either a or an unpaired samples Student’s \( t \)-test. Categorical data were analyzed using a chi-square test. A univariate analysis was performed using Pearson’s correlation in order to evaluate the correlation between relevant clinical findings. For all tests, a \( p \)-value of <0.05 was considered significant.

**RESULTS**

**Demographic characteristics**

The clinical records of 1378 patients with a diagnosis of CSC were reviewed. A total of 295 eyes in 291 patients met our strict definition of aCSC and were included in our analysis. For 201 eyes (68%), ≥12 months of follow-up data were available (mean: 37 months; range: 12-247 months); the mean follow-up time for the remaining 94 eyes was 5 months (range: 1-11 months). The demographic characteristics of these cases are summarized in Table 1. Four of the included patients had a history of bilateral aCSC with an average interval of 28 months (range: 6-63 months) between disease onset in the first affected eye and the second affected eye. Of the 73 female patients, five had a unilateral case of aCSC during pregnancy, and all five cases recovered spontaneously after delivery.

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<td>Patients (eyes)</td>
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<td>Male gender, N (%)</td>
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<td>Caucasian, N (%)</td>
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<td>Recent steroid use, N (%)</td>
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<td>Pregnancy-associated CSC, N (%)</td>
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<td>BCVA at diagnosis, in ETDRS letters, mean ± SD (Snellen equivalent)</td>
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<td>Mean follow-up duration (range)</td>
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**Abbreviations:** BCVA, best corrected visual acuity; CSC, central serous chorioretinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study
Chapter 2.1

**Optical coherence tomography**
OCT imaging was available for all 295 eyes at diagnosis and for 292 eyes (99%) at the final follow-up visit. SRF on OCT at disease onset was subfoveal in 286 eyes (97%) and extrafoveal in 7 eyes (2%); in the remaining 2 eyes (1%), SRF resolved in the period between the fundus examination and the first imaging examination. Unresolved SRF was present at the final available OCT examination in 7 out of 292 eyes (2%) (Table 2).

**Fundus autofluorescence imaging**
FAF imaging was available for 199 eyes (67%) at the time of diagnosis and for 77 eyes (26%) at the final follow-up visit. At diagnosis, CSC-associated FAF changes at the site of serous neuroretinal detachment could be categorized as: focal hyper-autofluorescent lesion (21 eyes, 10%), hypo-autofluorescent lesions (54 eyes, 27%), a combination of both lesions (33 eyes, 17%), and speckled (i.e., granular) hyper-autofluorescent lesion with mottled hyper-autofluorescent dots (63 eyes, 32%) (Table 2, and Figure 1).

**Fluorescein angiography**
FA imaging was available at the time of diagnosis for 232 eyes (79%). Long-term follow-up FA data were available for 61 eyes (21%) with a mean interval of 37±33 months between the initial diagnosis and the final follow-up visit. At diagnosis, no RPE alterations were present in 91 eyes (39%), whereas minimal RPE alterations were observed in the remaining 141 eyes (61%). These RPE changes were located in the fovea in 24 of these 141 eyes (10%), 1 disc diameter (DD) round but excluding the fovea in 41 eyes (18%), and 1 DD away from the fovea in 60 eyes (26%). Minimal RPE alterations and RPE detachment were present in more than one area in 16 eyes (7%) (Table 2).

**Indocyanine green angiography**
ICGA imaging was available for 54 eyes (18%) at diagnosis and 23 eyes (8%) at the final visit, which was on average 11±15 months after the first ICGA. On mid-phase ICGA (i.e., 10 minutes), a monofocal hyperfluorescent and hyperpermeable region in the choroid was visible in 34 eyes (63%). Multifocal hyperfluorescent lesions were seen in 20 eyes (37%), even though all of the patients included in this study had only one leakage spot on FA imaging (Table 2, Figure 2). At the time of diagnosis, 30 eyes (56%) had a hyperfluorescent ICGA lesion that exceeded the size of the RPE alteration shown on FA imaging; in the remaining 24 eyes (44%), the extent of the hyperfluorescent choroidal abnormalities was equal to the extent of the RPE alterations on FA (Table 2, Figure 2).
| Table 2 | Clinical findings on multimodal imaging at diagnosis and during follow-up |
|------------------|------------------|------------------|------------------|------------------|------------------|
|                | Imaging at baseline |                 | Last available imaging |                 |                 |
|                | Entire cohort (n=295 eyes) | Cases with < 12 months follow-up (n=94 eyes) | Cases with ≥ 12 months follow-up (n=201 eyes) | Entire cohort (n=295 eyes) |
| OCT Eyes with available OCT | Location SRF (%) | 295 eyes | 94 eyes | 198 eyes | 292 eyes |
|                | No SRF | 2 (1) | 89 (95) | 196 (99) | 285 (97) |
|                | Central | 286 (97) | 3 (3) | 2 (1) | 2 (2) |
|                | Peripheral | 7 (2) | 2 (2) | 0 | 2 (1) |
| FAF Eyes with available FAF | Abnormalities (%) | 199 eyes | 10 eyes | 67 eyes | 77 eyes |
|                | No abnormalities | 28 (14) | 3 (30) | 11 (16) | 14 (18) |
|                | Hyper-autofluorescent lesions | 21 (10) | 5 (50) | 12 (18) | 17 (22) |
|                | Hypo-autofluorescent lesions | 54 (27) | 1 (10) | 25 (37) | 26 (34) |
|                | Both lesions | 33 (17) | 1 (10) | 19 (29) | 20 (26) |
|                | Speckled hyper-autofluorescent lesion | 63 (32) | 0 | 0 | 0 |
| FA Eyes with available FA | Location RPE alterations (%) | 232 eyes | 3 eyes | 61 eyes | 64 eyes |
|                | No RPE alterations | 91 (39) | 0 | 10 (16) | 10 (15) |
|                | Foveal | 24 (10) | 1 (33) | 6 (10) | 7 (11) |
|                | <1 DD from fovea | 41 (18) | 1 (33) | 13 (21) | 14 (22) |
|                | >1 DD from fovea | 60 (26) | 1 (33) | 27 (44) | 28 (44) |
|                | Multiple locations | 16 (7) | 0 | 5 (9) | 5 (8) |
|                | Composition RPE alterations (%) |  |  |  |  |
|                | Monofocal | 75 (53) | 2 (66) | 28 (55) | 30 (56) |
|                | Multifocal | 66 (47) | 1 (33) | 23 (45) | 24 (44) |
|                | RPE alterations in contralateral eye (%) |  |  |  |  |
|                | No RPE alterations | 135 (58) | 0 | 33 (54) | 33 (52) |
|                | Minimal RPE alterations | 90 (39) | 0 | 23 (38) | 23 (36) |
|                | Bilateral CSC | 6 (2) | 3 (100) | 5 (8) | 8 (12) |
|                | Missing image | 1 (1) | 0 | 0 | 0 |
### Table 2 continued

<table>
<thead>
<tr>
<th>FA Location of ‘hot spot’ of leakage on FA (%)</th>
<th>Imaging at baseline</th>
<th>Last available imaging</th>
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<tr>
<td>Foveal</td>
<td>39 (17)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>&lt;1 DD from fovea</td>
<td>89 (38)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>&gt;1 DD from fovea</td>
<td>104 (45)</td>
<td>15 (24)</td>
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<tr>
<td>Entire cohort (n=295 eyes)</td>
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<tr>
<td>Cases with &lt; 12 months follow-up (n=94 eyes)</td>
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<td>Cases with ≥ 12 months follow-up (n=201 eyes)</td>
<td></td>
<td></td>
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<tr>
<td>Entire cohort (n=295 eyes)</td>
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<table>
<thead>
<tr>
<th>Hot spot morphology (%)</th>
<th>Imaging at baseline</th>
<th>Last available imaging</th>
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</thead>
<tbody>
<tr>
<td>Smoke stack</td>
<td>47 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Ink blot</td>
<td>185 (80)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Entire cohort (n=295 eyes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases with &lt; 12 months follow-up (n=94 eyes)</td>
<td></td>
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<tr>
<td>Cases with ≥ 12 months follow-up (n=201 eyes)</td>
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<tr>
<td>Entire cohort (n=295 eyes)</td>
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<tr>
<th>ICGA Eyes with available ICGA</th>
<th>Imaging at baseline</th>
<th>Last available imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monofocal</td>
<td>34 (63)</td>
<td>24 (44)</td>
</tr>
<tr>
<td>Multifocal</td>
<td>20 (37)</td>
<td>0</td>
</tr>
<tr>
<td>Entire cohort (n=295 eyes)</td>
<td></td>
<td></td>
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<tr>
<td>Cases with &lt; 12 months follow-up (n=94 eyes)</td>
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<tr>
<td>Entire cohort (n=295 eyes)</td>
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| Abbreviations: | CSC, central serous chorioretinopathy; DD, optical disc diameter; FA, fluorescein angiography; FAF, fundus autofluorescence; ICGA, indocyanine green angiography; OCT, optical coherence tomography; RPE, retinal pigment epithelium; SRF, subretinal fluid

Abbreviations:
- CSC, central serous chorioretinopathy
- DD, optical disc diameter
- FA, fluorescein angiography
- FAF, fundus autofluorescence
- ICGA, indocyanine green angiography
- OCT, optical coherence tomography
- RPE, retinal pigment epithelium
- SRF, subretinal fluid
Figure 1. Clinical features visible on multimodal imaging of the left eye of a 37-year-old male patient with aCSC. (A) Color fundus photograph showing small pigment clustering in the macula and a silhouette of the serous retinal detachment. The arrow indicates the scanning plane, which is depicted on the SD-OCT. (B) FAF image at diagnosis showing a speckled (i.e., granular) hyper-autofluorescent lesion at the site of the serous neuroretinal detachment. (C) FA imaging revealed a single “hot spot” of leakage and a typical small detachment of the RPE above the inferior retinal arcade (arrow). (D) An SD-OCT scan at diagnosis revealed SRF accumulation, a thickened choroid, and subretinal debris, presumably consisting of non-phagocytized photoreceptor outer segments. (E) SRF resolved spontaneously within a few weeks. (F) The areas of hyper-fluorescence on mid-phase ICGA revealed diffuse choroidal hyperpermeability that was larger than the leakage site visible on FA. A recurrent episode 1.5 years later was treated with two subthreshold micropulse diode laser but did not result in resolution of the SRF. Eventually, half-dose photodynamic therapy resulted in resolution of the SRF (G and H). At the patient’s final visit 11 months later, hyper-autofluorescent and hypo-autofluorescent abnormalities were visible (G), and FA imaging revealed a slightly enlarged area of RPE alterations (H). Abbreviations: aCSC, acute central serous chorioretinopathy; ICGA, indocyanine green angiography; FA, Fluorescein angiography; FAF, Fundus autofluorescence; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal serous fluid; RPE, retinal pigment epithelium.
Figure 2. Clinical features visible on multimodal imaging of the right eye of a 37-year-old female patient (A-D) and a 34-year-old male patient (E-H) with aCSC. (A and E) FA revealed one focal “hot spot” of leakage and no changes in the retinal pigment epithelium. (B and F) Despite these circumscribed lesions on FA, ICGA revealed a more widespread area of hyper-fluorescence, which corresponded with multifocal (B) or monofocal (F) choroidal leakage. (C and G) FAF imaging revealed speckled (i.e., granular) hyper-autofluorescent changes at the site of serous neuroretinal detachment in both patients, which corresponded with serous retinal detachment visualized on OCT (D, H).

Abbreviations: aCSC, acute central serous chorioretinopathy; ICGA, indocyanine green angiography; FA, Fluorescein angiography; FAF, Fundus autofluorescence; OCT, optical coherence tomography; SRF, subretinal serous fluid; RPE, retinal pigment epithelium.
**Treatment, resolution of SRF, and visual outcome**

In total, 154 eyes (52%) had spontaneous resolution of the first aCSC episode (the wait-and-see group) 14.8±11.6 weeks after diagnosis; the remaining 141 eyes (48%) received treatment (applied on average 13.7±12.7 weeks after diagnosis) and all resolved, on average in 9.6±10.2 weeks after this treatment. SRF resolution occurred significantly faster after treatment compared to resolution after a wait-and-see strategy (p<0.001). The choice of treatment modalities, which was at the discretion of the treating physician, is summarized in Table 3.

**Table 3** Treatment modalities and specifications during follow-up in patients with acute CSC

<table>
<thead>
<tr>
<th>Study eyes</th>
<th>Entire cohort</th>
<th>Cases with &lt;12 months follow-up</th>
<th>Cases with ≥12 months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes not treated at first episode [wait-and-see approach] (%)</td>
<td>154 (52)</td>
<td>47 (50)</td>
<td>107 (51)</td>
</tr>
<tr>
<td>Eyes treated at first episode [early-treatment group] (%)</td>
<td>141 (48)</td>
<td>47 (50)</td>
<td>94 (49)</td>
</tr>
<tr>
<td>Treatment specifications at first episode (%)</td>
<td>PDT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>134 (95)</td>
<td>43 (92)</td>
</tr>
<tr>
<td></td>
<td>Conventional laser</td>
<td>3 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td>SML</td>
<td>4 (3)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Eyes with additional treatments after first episode (%)</td>
<td>23 (8)</td>
<td>1 (1)</td>
<td>22 (11)</td>
</tr>
<tr>
<td>Average number of retreatments (range)</td>
<td>1 (1-2)</td>
<td>2 (2-2)</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>Re-treatment specifications (%)</td>
<td>PDT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>71 (93)</td>
<td>1 (50)</td>
</tr>
<tr>
<td></td>
<td>Conventional laser</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>SML</td>
<td>3 (4)</td>
<td>1 (50)</td>
</tr>
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**Notes:**<sup>a</sup> 56 (42%) eyes received half-dose PDT, 67 (50%) eyes received half-time PDT, and 11 eyes (8%) had unknown PDT settings; mean spot size: 1746±1109 µm.

<sup>b</sup> 28 (39%) eyes received half-dose PDT, 40 (57%) eyes received half-time PDT, and 3 (4%) eyes had full PDT settings; mean spot size: 2066±1256 µm.

**Abbreviations:** CSC, central serous chorioretinopathy; PDT, photodynamic therapy; SML, subthreshold micropulse diode laser

The average subjective reported interval between the onset of complaints and aCSC diagnosis was 4 weeks (range: 0-52 weeks; median: 1 week) in the early-treated patients, and 6 weeks (range: 0-52 weeks; median: 1 week) in the wait-and-see group; this difference was not significant (p=0.136). Moreover, these two groups did not differ significantly with respect to the location of the leakage “hot spot” (p=0.540), the presence of RPE alterations (p=0.821), or the extent of the RPE alterations (p=0.439).

Mean BCVA in the entire patient cohort was 79±9 ETDRS letters (Snellen equivalent: ~20/25) at the time of diagnosis and increased significantly to 86±6 ETDRS (Snellen equivalent: ~20/20) letters at the final follow-up visit (p<0.001). Initial BCVA in the early-treated group was significantly lower than in the wait-and-see group (78±9 ETDRS letters (Snellen equivalent: ~20/32) versus 80±9 ETDRS letters (Snellen equivalent: ~20/25),
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respectively; \( p=0.017 \), but did not differ significantly between groups at the final follow-up visit (86±5 ETDRS letters (Snellen equivalent: ~20/20) versus 86±7 ETDRS letters respectively; \( p=0.971 \)). In total, final BCVA was ≥80 ETDRS letters (Snellen equivalent: ~20/25) in 94% of eyes, and ≥85 ETDRS letters (Snellen equivalent: ~20/20) in 76%.

Self-reported complaints

Among patients with <12 months clinical follow-up (94 aCSC eyes), 3 patients (3 eyes, 3%) reported additional aCSC episodes through telephone survey. None of these patients had consulted an ophthalmologist since all reported episodes had resolved spontaneously. One patient reported 5 aCSC episodes during 2 years, each lasting less than 1 week. The second patient reported 2 episodes in 2 years, lasting for less than 2 weeks each. The third case reported 2 episodes during 3 years each lasting for less than 1 week (Figure 3).

Transition to recurrent and/or chronic CSC

Among the 201 eyes with ≥12 months of documented follow-up data, 75 (37%) had an average of 1.4 recurrences (range: 1-6 recurrences) with a mean follow-up of 53 months (range: 13-247 months). Among the 94 eyes with <12 months of follow-up data, 9 eyes (10%) had an average of 1.3 recurrences (range: 1-2 recurrences) documented by an ophthalmologist; 3 additional eyes had documented self-reported recurrences through the telephone survey. Thus, from the original cohort of 295 eyes with aCSC, a total of 87 eyes (29%) had evidence of recurrent CSC. The prevalence of SRF recurrence was significantly higher in the wait-and-see group compared to the early-treated group (24% versus 4%, respectively; \( p<0.001 \)). Moreover, Pearson’s correlation analysis revealed a significant correlation between treatment and reduced risk of recurrence (\( R=-0.333; p<0.001 \)). No other significant correlation was found between any demographic or clinical characteristics and the risk of recurrence, with the sole exception of the patient’s age at diagnosis (\( R=-0.161; p=0.005 \)), which was on average 4 years lower in the patients with a recurrence compared to the patients without a recurrence (41 years versus 45 years, respectively; \( p=0.005 \)). The distribution of eyes with recurrent disease and additional treatment are summarized in Figure 3.

With respect to the progression of RPE alterations in the 61 eyes (21%) with long-term follow-up FA examination, a clear increase in lesion size was observed in 22 of these eyes (36%). In 14 of these eyes (23%) both an increase in RPE alterations and recurrent SRF was observed. Furthermore, 23 unaffected contralateral eyes (37%) had minimal RPE alterations —but no active disease—at the final follow-up visit. A significant correlation was found between the progression of RPE alterations in the affected eyes and the presence of RPE alterations in the unaffected contralateral eyes at the final follow-up visit (\( R=0.346; p=0.008 \)). Among the 201 eyes with ≥12 months of follow-up data, 10 eyes (10/107, 9%) in the wait-and-see group and 4 eyes (4/94, 4%) in the early-treated group had both SRF recurrence and an increased area of RPE alterations (Figure 3). However, a Pearson’s correlation analysis showed no correlation between the progression of RPE alterations on
**Figure 3.** Flow chart depicting the distribution of the eyes in this study, with follow-up durations indicated. The development of CSC over time is based on recurrence of the disease, progression of RPE alterations, and the need for additional treatments.

Abbreviations: CSC, cute central serous chorioretinopathy; RPE, retinal pigment epithelium.
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one side, and the wait-and-see or treatment strategy on the other side (R=-0.103; \( p = 0.448 \)).

Finally, disease recurrence (presence of SRF) was not significantly correlated with the progression of RPE alterations (R=0.258; \( p = 0.162 \)).

DISCUSSION

Little is currently known regarding the risk of acute CSC transitioning to a chronic form of CSC. Previous reports indicated that 8-16% of patients with chronic CSC have a history of aCSC.\(^6\)\(^-\)\(^17\) In our retrospective study, 36% of eyes with long-term follow-up data began as typical aCSC and showed a clear progression of RPE alterations over time; therefore, these patients showed a tendency toward chronic disease. Wong et al. previously reported a higher percentage of progressive RPE alterations (61%) in a smaller cohort of 25 patients with aCSC who were followed for at least 5 years after initial resolution; however, they found no correlation between this progression and visual acuity.\(^18\)

In addition to changes in the RPE, persistent SRF is a characteristic feature of chronic CSC.\(^19\) In our study, none of the patients with long-term follow-up data had chronic persistent SRF. However, 23% of these patients had a combination of recurrent SRF and progressive RPE alterations, which could be considered chronic CSC in the strictest sense, as the presence of increased RPE changes alone may not necessarily be considered evidence of chronic disease. Nevertheless, an increase in RPE changes in the absence of active SRF leakage may still be a sign of chronic dysfunction of the underlying choroid. CSC is considered part of the pachychoroid disease spectrum, which is characterized by a congested and hyperpermeable choroid.\(^20\) In CSC, a thickened, leaking choroid may exert pressure on the overlying RPE, gradually causing structural changes that can lead to the focal breakdown of the outer blood-retina barrier formed by the RPE, with subsequent serous neuroretinal detachment.\(^21\) Bilateral RPE changes are often present in patients with pachychoroid pigment epitheliopathy.\(^21\)\(^-\)\(^23\) In our cohort, 61% of affected eyes and 42% of unaffected contralateral eyes had minimal (i.e., <1 DD) RPE changes at the time of diagnosis, consistent with pachychoroid pigment epitheliopathy. In this condition, chronic changes in the choroid are common and are often independent of active leakage. Therefore, an objective increase in RPE alterations may actually be a more robust indicator of chronic disease than the duration of persisting SRF, as is currently customary in clinical practice.\(^24\)

In our study, 29% of all cases had a recurrence of SRF. This percentage includes patients with limited documented follow-up data and patients who self-reported an episode by telephone survey. However, when considering only the patients with objective long-term follow-up data, the prevalence of recurrent SRF leakage was higher (37%). Therefore, our data suggest that the true rate of recurrence in typical aCSC lies somewhere between 29% and 37%, which is consistent with the sole study published regarding this topic.\(^25\) In our analysis, although the patients with recurrent disease were significantly younger
Transition from aCSC to cCSC

than the non-recurrent patients, no other demographic or clinical characteristics were associated with the recurrence of SRF. Disease recurrence was also not correlated with progressive changes in the RPE, which are often considered an important sign of a more chronic form of CSC. This might suggest that underlying choroidal changes—without active SRF leakage—are sufficient to cause changes in the RPE. Therefore, to a certain extent chronic CSC and recurrent CSC might represent two distinct disease entities. However, even in these cases we cannot exclude the possibility of intermittent mild SRF leakage as the cause of progressive RPE changes.

There is currently no universally accepted classification of clinical CSC subtypes, and the description and terminology of CSC and its subtypes is therefore a topic of debate. For example, some groups have proposed the following five categories for classifying the various phenotypes: acute CSC, non-resolving CSC, recurrent CSC, chronic CSC, and inactive CSC. Matet et al. recently reported a strong correlation between increased choroidal thickness and the risk of recurrence in CSC. A similar mechanism of action might have been present in our cohort. Although our data set lacked sufficient numbers of choroidal thickness measurements to assess this putative correlation, we frequently observed a thickened choroid (Figure 1). In our study cohort, SRF resolved faster in the treatment group compared to the wait-and-see group, and the prevalence of SRF recurrence was significantly lower in the group that received treatment (4% versus 24%, respectively), the majority of whom received PDT with reduced settings. Similarly, Ozkaya et al. reported a two-fold higher rate of recurrence in 41 untreated self-limiting aCSC cases compared to 36 aCSC patients who were treated with low-fluence PDT (51% vs 25%, respectively). Given that PDT treatment exerts its effects at the level of the choroid, it is conceivable that PDT not only accelerates the resorption of SRF by alteration of choroidal circulation, but it may also play a role in remodeling the choriocapillaris and Haller’s layer vessels, thereby reducing choroidal thickness and the risk of disease recurrence.

This study has some limitations that warrant discussion. First, due to the cross-sectional design, the patient data and imaging examinations were not available at similar follow-up intervals. We therefore only studied a subgroup of patients with relatively long-term follow-up FA data. Second, given that follow-up FA examinations are usually performed in cases of recurrent SRF and/or the suspicion of other retinal abnormalities, this subgroup may have been subject to selection bias. A third possible limitation is that the patients who had early complete recovery were often referred back to the referring ophthalmologist, and were therefore lost to follow-up. We attempted to address this issue by conducting telephone surveys of these patients; however, 36% of these patients could not be reached. Finally, some patients in the early-treatment group were treated relatively soon after diagnosis. This treatment may have been due to relatively worse visual acuity and/or a longer history of subjective complaints; however, subjective complaints duration did not differ significantly between the wait-and-see group and the early-treated group. Therefore,
we cannot exclude the possibility that at least some of the patients in the early-treatment group would have resolved spontaneously without treatment.

CONCLUSION

We report that approximately one-third of aCSC cases developed a recurrent episode of SRF leakage. An increase of atrophic RPE alterations was seen in 36% of the cases with long-term follow-up, and an increase of RPE alterations together with recurrent SRF in 23% of the cases; however, none of the patients in our study developed long-term chronic, persistent SRF leakage. Moreover, the presence of RPE alterations in the unaffected contralateral eye was associated with an increase in RPE alterations in the affected eye, possibly reflecting chronic disease. Treatment with low-setting PDT may be an effective means to significantly reduce the risk of recurrence, but prospective randomized controlled studies are needed to address this topic. Finally, our data suggest that there may be a certain degree of clinical overlap between aCSC and chronic CSC, as a subgroup of aCSC cases had both recurrent SRF and increased RPE alterations that may be viewed as signs of a transition to a more chronic form of the disease. In the future, long-term prospective studies will likely provide important insights into possible new biomarkers for predicting the transition to chronic CSC, and genetic studies may shed light on possible genetic risk factors.

Ethics approval

All procedures performed in this study, which involved human participants, were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local institutional review boards in all participating centers (‘Medisch Ethische Toetsingscommissie’ (METC) in Leiden University Medical Center, and the ‘Wetenschapscommissie’ in the Rotterdam Eye Hospital) did not require written consent from the participants for reviewing their medical records, as all data were anonymized upon collection.

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Disclosure
The authors report no conflicts of interest. An abstract version of these results was presented at the 2018 annual meeting of the Association for Research in Vision and Ophthalmology.

Conflict of interest
No conflicting relationship exists for any author.
REFERENCES


CHAPTER 2.2

Clinical characteristics and long-term visual outcome of severe phenotypes of chronic central serous chorioretinopathy

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ABSTRACT

Purpose: To investigate disease onset and disease progression in chronic central serous chorioretinopathy (cCSC) patients with severe disease.

Patients and methods: The medical records of 143 cCSC patients (199 eyes) were reviewed. All cases had visual complaints for more than 6 months and showed signs of a severe disease phenotype on optical coherence tomography and fluorescein angiography. Clinical presentation at onset was evaluated, together with disease progression on multimodal imaging, and final treatment outcome.

Results: Twenty-eight cases (14%) had a documented history of an acute episode of CSC, whereas 145 cases (73%) showed pre-existing features of chronicity already at first presentation. The first clinical presentation could not be evaluated in 13% of cases. Best-corrected visual acuity was 70 ± 18 ETDRS letters at onset, and 70 ± 22 ETDRS letters at final visit ($p = 0.770$). Among all studied cases, 173 eyes (87%) were treated, which resulted in complete resolution of subretinal fluid in 76% of eyes at final visit. In eyes with fluorescein angiographic follow-up, the area of diffuse atrophic retinal pigment epithelium abnormalities (DARA) had increased significantly in 43 eyes (68%) at final visit.

Conclusions: CSC encompasses a clinical spectrum which includes a range of severe phenotypes, in which retinal abnormalities tend to be progressive. Nevertheless, the long-term visual acuity may remain fairly stable with treatment. Few patients with severe chronic CSC have a history of acute CSC, which could indicate that there may be pathogenetic differences between these two CSC variants.
Clinical characteristics of severe cCSC

INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by a serous detachment of the neurosensory retina. Although the precise pathophysiology of CSC is unclear, a congested and hyperpermeable choriocapillaris (pachychoroid) may be the primary source of serous fluid leakage. Additionally, it is hypothesized that due to secondary retinal pigment epithelium (RPE) alterations, the outer blood-retinal barrier is dysfunctional which subsequently leads to fluid passage into the subretinal space. A prolonged presence of subretinal fluid (SRF) can lead to irreversible photoreceptor damage and dysfunction, resulting in visual complaints such as blurry vision, metamorphopsia, dyschromatopsia, micropsia, macropsia, and disturbed contrast vision. Men in the professional age range are affected most frequently. Thus far, the most important identified risk factors include the use of corticosteroids, endogenous hypercortisolism, mental stress, and pregnancy. Genetic risk factors have also been shown to be associated with CSC.

Although there is no generally accepted classification of CSC, 2 basic forms of CSC are often distinguished: acute and chronic CSC. The acute phenotype of CSC is typically defined as an acute episode of central vision loss due to SRF leakage, with a single ‘hot spot’ of leakage through the RPE seen on fluorescein angiography, without any atrophic RPE abnormalities. In this definition, acute CSC is supposedly self-limiting, with spontaneous resolution within 3-6 months after onset, and a favorable visual prognosis. In contrast, patients with chronic CSC (cCSC) do not tend to have a spontaneous resolution of SRF, have a more unfavorable visual prognosis, and a variable clinical manifestation. Some patients with cCSC may present with relatively limited atrophic RPE alterations, focal RPE detachments, and focal leakage.

There are other cases that show more severe forms of cCSC. They show widespread areas of RPE atrophy, larger and more numerous RPE detachments, diffuse areas of leakage through the RPE, posterior cystoid retinal degeneration, and in rare cases even inferior bullous retinal detachments are present. In the past, the term diffuse retinal pigment epitheliopathy has also been used to distinguish this severe disease course from more acute forms of CSC. Little is known about the clinical characteristics, the long-term outcome, and response to treatment in these severe cases of cCSC. Also, it is unclear whether severe cases of cCSC are generally preceded by one or more past episodes of typical acute CSC. As a consequence, there currently is an ongoing debate on whether acute CSC and (severe) cCSC are either part of a clinical and pathophysiological continuous spectrum, or if these phenotypes are more distinct with regard to their background, presentation, and treatment outcome.

In the current study, we describe a large group of cCSC cases that show phenotypic signs of severity. The aim of the study is to describe the range of clinical findings on multimodal imaging in these presumably severe cCSC cases, and to evaluate the long-term visual outcome and treatment response. Finally, we assess whether or not these severe cCSC cases were preceded by typical acute CSC.
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PATIENTS AND METHODS

Patient selection
Approval for this study was obtained at the local institutional review boards in all participating centers, and the study adhered to the tenets of the Declaration of Helsinki. In this retrospective multicenter study patients were included from 3 Dutch tertiary referral centers: the Department of Ophthalmology of Leiden University Medical Center (Leiden, the Netherlands), the Rotterdam Eye Hospital (Rotterdam, the Netherlands), and the Department of Ophthalmology of Radboud University Medical Center (Nijmegen, the Netherlands). Study patients were selected from a cohort of 1387 subjects who were diagnosed with acute and chronic CSC between 2005 and 2016. For the purpose of this study, we only included chronic CSC. Chronicity was defined as persistence of visual complaints for over 6 months, in the presence of anatomical abnormalities compatible with typical chronic CSC, such as multifocal diffuse RPE alterations and chronic SRF leakage based on multimodal imaging that included optical coherence tomography (OCT), fluorescein angiography (FA) and/or indocyanine green angiography (ICGA). In addition, a cCSC case was considered severe when at least one of the following abnormalities within the anatomical macular area inside the largest temporal vascular arcades (Figure 1) were present: 1. Cumulative areas (larger than 5 optic disc diameters (DD)) of diffuse atrophic RPE alterations (DARA) as visualized on mid-phase FA; 2. At least 2 ‘hot spots’ of leakage separated by at least 1 DD of non-hyperfluorescent healthy-appearing retina on mid-phase FA (multifocal ‘hot spots’); 3. An area of diffuse fluorescein leakage larger than 1 DD on mid-phase FA, without an evident leaking focus (diffuse leakage); 4. Presence of posterior cystoid retinal degeneration (PCRD) assessed on OCT. All included cases had to have at least one of these severe criteria, but could have up to all four criteria. Subjects were excluded when there was a suspicion of a (secondary) choroidal neovascularization and/or polypoidal choroidal vasculopathy, or in case of evidence of other underlying retinal diseases such as age-related macular degeneration (with presence of drusen in both eyes), multifocal choroiditis, retinal vascular occlusions, pseudoxanthoma elasticum, amblyopia, or high myopia (>6 diopters).

Clinical outcome measures
Retrospective data were collected on patient’s first presentation, based on available multimodal imaging (at least FA and OCT). This information was used to distinguish between an acute and a chronic first manifestation of CSC. RPE detachments outside the area of SRF leakage, evidence of RPE atrophy (visible as window defects on FA), and/or multifocal hot spots or diffuse fluorescein leakage were seen as signs of chronicity. In contrast, a presentation with well-defined pinpoint leakage on FA, lack of any RPE alterations, and a sudden neurosensory detachment followed by a spontaneous recovery in less than 6 months, were considered to represent a typical acute CSC episode. In case no images at first presentation were available, the clinical description by the treating ophthalmologist was used to distinguish between an acute and a chronic first
Clinical characteristics of severe cCSC presentation. Furthermore, information was collected on all treatment strategies and treatment response, the progression of atrophic retinal abnormalities, and visual acuity at presentation (baseline), and at last available follow-up visit (final follow-up). Information on the use of steroid-containing medication and endogenous hypercortisolism was collected. The extent of atrophic retinal abnormalities as DARA surface was quantified on FA images by using available caliper measurement tools on FA equipment, and expressed in number of DD. The location of DARA was identified and categorized as follows: 1. Including the fovea, 2. Within 1 DD of the fovea, but sparing the fovea, 3. More than 1 DD outside the fovea. The location of hot spots of leakage on FA was described as either inside or outside the largest temporal retinal vascular arcade. Central foveal thickness (CFT) was measured.

Figure 1. Illustration of the four criteria of severity on fluorescein angiography (FA), and optical coherence tomography (OCT). 1) Cumulative areas of diffuse atrophic retinal pigment epithelium alterations larger than 5 optic disc diameters visualized on mid-phase FA (A). 2) Multiple (at least 2) ‘hot spots’ of leakage separated by at least 1 optic disc diameter of non-hyperfluorescent healthy-appearing retina on mid-phase FA (B). 3) An area of diffuse fluorescein leakage larger than 1 optic disc diameter on mid-phase FA (C). 4) Presence of posterior cystoid retinal degeneration on OCT (D,E).
manually in patient in whom an spectral-domain OCT was available. CFT was defined as the distance from the inner border of the internal limiting membrane (ILM) to the inner border of the ellipsoid zone (EZ) to minimize measurement errors due to the presence of subretinal accumulation of debris and SRF in active cCSC. CFT was evaluated at the moment of diagnosis of severe cCSC and compared to final visit.

Clinical examinations

All patients underwent a range of ophthalmological and multimodal imaging examination at the moment of diagnosis and during follow-up. This included best-corrected visual acuity (BCVA) (measured with Snellen charts, which was converted to ETDRS letters for statistical comparisons),

16 slit lamp examination and/or color fundus photography (either Topcon Corp.; Tokyo, Japan, or Carl Zeiss Meditec; Dublin, CA, USA), either time-domain OCT (either Cirrus HD- OCT; Carl Zeiss Meditec, or OCT-HS100; Canon Inc, Tokyo, Japan) or spectral-domain OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany), FA (either Topcon Corp or Spectralis HRA+OCT, or Carl Zeiss Meditec), and ICGA (either Topcon Corp or Spectralis HRA+OCT, or Carl Zeiss Meditec).

Treatment

In this retrospective study, the decision for treatment, retreatment, and treatment modality was based on the preference of the treating ophthalmologist. Treatment was applied when there was persistent SRF affecting vision. Photodynamic therapy (PDT) was performed with different settings such as half-dose (3 mg/m2 verteporfin (Visudyne®)), half-time (treatment duration of 42 seconds), half-fluency (25 J/cm2), or the original settings (6 mg/m2 verteporfin, 83 seconds, and 50 J/cm2) as described for neovascular age-related macular degeneration. Other reviewed treatments included subthreshold micropulse diode laser (SML), and conventional thermal laser.

Statistical analysis

Statistical analysis was performed using IBM SPSS software for Windows, version 23 (IBM Corp, Armonk, NY, USA). Either a paired samples t-test, or a one-way ANOVA test was used for comparing means in continuous numerical data. Categorical data were analyzed using either a Chi-square test or a McNemar Chi-square test. Multivariate regression analyses were performed using a forward stepwise linear regression, where the final BCVA outcome was used as dependent variable, and multiple associated clinical findings (as will be described later on) as explanatory variables. The best linear model for grading of discrepancy decrease was calculated. A value of \( p < 0.05 \) was considered significant in all performed tests.
RESULTS

After a review of the medical charts and clinical characteristics on multimodal imaging, a total of 143 patients (199 eyes, 87% males, 83% Caucasians) with cCSC could be included who met our definition of severity in at least one eye. Mean age at diagnosis of CSC was 46 years, and mean follow-up duration was 7.5 years (Table 1). At final follow-up, 56 patients (39%) had a severe cCSC phenotype in both eyes. Severity manifested on average after 5.6 months (0-94 months) in the second eye in this subgroup. After reviewing data on the very first presentation of CSC, 28 eyes (14%) started with an acute episode with limited or no RPE damage, and spontaneous resolution of SRF. Most of the included subjects (145 eyes, 73%) however, already showed a chronic phenotype at first presentation, with one or more significant multifocal areas of atrophic RPE alterations, and/or multifocal areas of leakage. In 26 eyes (13%), insufficient information from the primary disease manifestation was available.

Table 1 Patient demographics

<table>
<thead>
<tr>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (eyes) 143 (199)</td>
</tr>
<tr>
<td>Male gender     121 (87%)</td>
</tr>
<tr>
<td>Caucasian ethnicity 119 (83%)</td>
</tr>
<tr>
<td>Mean age at diagnosis of CSC [range] 46 [26-78]</td>
</tr>
<tr>
<td>Mean available follow-up a in years [range] 7.5 [0.3-30.6]</td>
</tr>
<tr>
<td>Patients with recent b use of steroids 25 c (18%)</td>
</tr>
<tr>
<td>BCVA at first presentation (ETDRS letters) 70 ± 18</td>
</tr>
</tbody>
</table>

a) The mean time from CSC diagnosis to final visit  
b) Within 3 months prior to diagnosis  
c) One patient was diagnosed with Cushing syndrome  

BCVA: best-corrected visual acuity, CSC: central serous chorioretinopathy, ETDRS: Early Treatment of Diabetic Retinopathy Study

Characteristics on multimodal imaging

In 133 eyes (67%), more than one criterion of severity was present at some point during the follow-up. The distribution of these criteria of severity is summarized in Table 2. A gravitational tract was observed in 84 eyes (42%) on FA. Fifteen eyes (8%) had a secondary macular epiretinal membrane without evidence of other diseases than CSC explaining the membrane. Fundus photography, OCT, and FA revealed choroidal folds in 3 eyes (2%), without a hyperopic refractive error. Hard exudates were observed in 6 eyes (3%) without any sign of retinal (neo)vascular abnormalities or polypoidal choroidal vasculopathy on FA and ICGA. In one patient (1 eye, 0.5%) a bullous inferior retinal detachment secondary to cCSC was present (Figure 2). ICGA images were available in 134 of the studied eyes (67%). When comparing the cumulative area of hyperfluorescent RPE alterations and leakage
Clinical characteristics of severe cCSC

Figure 2. Clinical features on multimodal imaging of the right eye of a 44 year-old male patient with severe chronic central serous chorioretinopathy and a bullous inferior retinal detachment. Color fundus photograph showed extensive retinal abnormalities in the macula, with multifocal areas of whitish fibrinous subretinal material (A). The white arrow shows the scanning plane which is depicted on the spectral-domain optical coherence tomography (SD-OCT) scans (D,E). Fluorescein angiography (FA) imaging (B) revealed multiple foci of leakage, and widespread retinal pigment epithelium (RPE) alterations. The areas of hyperfluorescence on mid-phase indocyanine green angiography (ICGA) (C) depicted diffuse choroidal hyperpermeability which is larger as compared to the abnormalities on FA. An SD-OCT scan (D) at first presentation and prior to treatment revealed a subretinal serous fluid (SRF) accumulation, a subfoveal RPE detachment, and posterior cystoid retinal degeneration (PCRD) in the outer nuclear layer of the retina. At approximately 4 months after half-dose photodynamic therapy using a large spot size of 1200 µm centered on the hyperfluorescent zones on ICGA, both SRF and intraretinal fluid on OCT had resolved completely (E). The choroid before treatment was markedly thickened (D). This choroidal thickness reduced after PDT but showed large cavities in the deep with limited or no RPE damage, and spontaneous resolution of SRF layers (E).

on FA with the area(s) of hyperfluorescent choroidal hyperpermeability on ICGA in these 134 eyes, the cumulative area of abnormalities was larger on ICGA as compared to FA in 79 eyes (59%, 79/134), whereas in 50 eyes (37%, 50/134) these areas were equal in size. A smaller cumulative area of hyperfluorescent abnormalities on ICGA as compared to FA was present in only 5 eyes (4%, 5/134).

Table 2 Distribution of each criterion of severity among the severe cases of chronic central serous chorioretinopathy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Frequency and specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes with DARA</td>
<td>145 (73%)</td>
</tr>
<tr>
<td>Mean DARA surface (DD)</td>
<td>8.6 ± 4</td>
</tr>
<tr>
<td>Location of DARA</td>
<td>75 (52%) covering the fovea</td>
</tr>
<tr>
<td>47 (32%) within 1 DD of the fovea</td>
<td></td>
</tr>
<tr>
<td>23 (16%) outside 1 DD of the fovea</td>
<td></td>
</tr>
<tr>
<td>Eyes with PCRD</td>
<td>69 (35%)</td>
</tr>
<tr>
<td>Eyes with multiple hot spots</td>
<td>115 (58%)</td>
</tr>
<tr>
<td>Mean number of hot spots [range]</td>
<td>3 [2-7]</td>
</tr>
<tr>
<td>Location of hot spots</td>
<td>88 (75%) inside the temporal vascular arcade</td>
</tr>
<tr>
<td>3 (3%) outside the temporal vascular arcade</td>
<td></td>
</tr>
<tr>
<td>26 (22%) both inside and outside</td>
<td></td>
</tr>
<tr>
<td>Eyes with diffuse leakage</td>
<td>60 (30%)</td>
</tr>
</tbody>
</table>

a) DARA surface overlaps with the area as wide as 1 DD around the fovea, but do not cover the foveal depression
DARA: diffuse atrophic retinal pigment epithelium (RPE) alterations, DD: optic disc diameters, PCRD: posterior cystoid retinal degeneration
**Best-corrected visual acuity**

Mean BCVA in this cohort was 70 (± 18) ETDRS letters at first presentation (baseline BCVA). BCVA at the moment of diagnosis of severe CSC, on average 4 years after first presentation, was 68 (± 19) ETDRS letters. The final mean BCVA, on average 5.2 years (range: 0.1-25 years, median = 2.8 years) after first presentation, was 70 (± 22) ETDRS letters which was not statistically different in comparison with baseline (paired samples t-test, $p = 0.770$), and with the moment of diagnosis of severe CSC ($p = 0.061$) (Table 3). Among clinical characteristics (Table 4), final BCVA correlated most significantly with the location of DARA in the macula ($r = 0.4$, Pearson correlation, $p < 0.001$) (Table 4). Mean final BCVA in eyes showing DARA with foveal involvement was significantly worse (63 ± 22 ETDRS letters) compared to both eyes with DARA located within 1 DD of the fovea - but excluding the fovea - (74 ± 19 ETDRS letters, one-way ANOVA, $p = 0.003$), and eyes with DARA outside 1 DD of the fovea (78 ± 18 ETDRS letters, $p < 0.001$). Mean final BCVA did not significantly differ among eyes with DARA located within 1 DD of the fovea - but excluding the fovea - compared to eyes with DARA more than 1 DD away from the fovea ($p = 0.582$). In 9 eyes (5%), a BCVA drop more than 2 ETDRS lines was observed after PDT with reduced settings. All of these eyes showed central DARA with foveal involvement. BCVA in 3 out of these 9 eyes (2%, 3/199) never recovered after PDT until final follow-up. In the first patient BCVA

---

**Table 3 Characteristics at first presentation and disease progression in severe cases of chronic central serous chorioretinopathy**

<table>
<thead>
<tr>
<th></th>
<th>Severe manifestation of CSC</th>
<th>Final follow-up visit</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA (ETDRS letters)</td>
<td>68 ± 19</td>
<td>70 ± 22</td>
<td>0.061</td>
</tr>
<tr>
<td>Eyes with SRF</td>
<td>173 (87%)</td>
<td>47 (24%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Eyes with PCRD</td>
<td>69 (35%)</td>
<td>35 (18%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CFT a (µm)</td>
<td>105 ± 31</td>
<td>106 ± 30</td>
<td>0.930</td>
</tr>
<tr>
<td>DARA surface b (DD)</td>
<td>6.3 ± 3</td>
<td>9.0 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean number of treatments c [range]</td>
<td>n/a</td>
<td>2.5 [1-20]</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean number of recurrences d [range]</td>
<td>n/a</td>
<td>1.2 [0-9]</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Notes:**

a) CFT could be measured manually in 63 eyes (32%) with a spectral-domain optical coherence tomography

b) In 68 cases (34%) a follow-up FA (at least one year later) was available to be compared with baseline FA

c) Twenty-six cases (13%) were never treated, and were not included in this analysis

d) Twenty-one cases (11%) never showed a complete resolution of SRF, and were not included in this analysis

**Abbreviations:** BCVA: best-corrected visual acuity, CSC: central serous chorioretinopathy, CFT: central foveal thickness, DARA: diffuse atrophic retinal pigment epithelium (RPE) alterations, n/a: not applicable, DD: optic disc diameters, ETDRS: Early Treatment of Diabetic Retinopathy Study, FA: fluorescein angiography, PCRD: posterior cystoid retinal degeneration, SRF: subretinal fluid
had decreased from 83 to 70 ETDRS letters, in the second patient from 77 to 65 ETDRS letters, and in the third patient from 70 to 59 ETDRS letters. In 63 eyes (32%), evolution of DARA could be assessed on a second available FA, which was obtained on average 8 years (range: 1-27 years, median: 7 years) after the first FA images. In 43 of these eyes (68%, 43/63), the mean surface of DARA had increased on follow-up, from 6.5 DD to 10.3 DD ($p < 0.001$). In 20 eyes (32%, 20/63), DARA did not change as compared to the previous FA. A multiple linear regression model was computed to predict the final BCVA outcome based on the following parameters: baseline (before severity) BCVA, total area of DARA at first severe presentation, location of DARA, and presence of PCRD, which all correlated independently with final BCVA outcome. A significant regression equation was found ($F(4, 167) = 36.967, p < 0.001$) with an $R^2$ of 0.470, and an adjusted $R^2$ of 0.457. According to this model, baseline BCVA, total area of DARA, location of DARA, and presence of PCRD explain up to 47% of the observed variance in final BCVA outcome in the current study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Correlation with BCVA outcome</th>
<th>$r$</th>
<th>evaluated cases</th>
<th>Multivariate $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td></td>
<td>0.161</td>
<td>197</td>
<td>0.024</td>
</tr>
<tr>
<td>Age at disease onset</td>
<td></td>
<td>-0.086</td>
<td>197</td>
<td>0.225</td>
</tr>
<tr>
<td>Caucasian ethnicity</td>
<td></td>
<td>-0.045</td>
<td>197</td>
<td>0.526</td>
</tr>
<tr>
<td>Recent steroid use</td>
<td></td>
<td>0.042</td>
<td>197</td>
<td>0.551</td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
<td>-0.105</td>
<td>197</td>
<td>0.143</td>
</tr>
<tr>
<td>Baseline BCVA</td>
<td></td>
<td>0.543</td>
<td>197</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Presence of PCRD</td>
<td></td>
<td>-0.297</td>
<td>195</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Presence of multifocal hot spots</td>
<td></td>
<td>0.023</td>
<td>195</td>
<td>0.023</td>
</tr>
<tr>
<td>Mean number of hot spots</td>
<td></td>
<td>-0.036</td>
<td>152</td>
<td>0.656</td>
</tr>
<tr>
<td>Location of multifocal hot spots</td>
<td></td>
<td>-0.036</td>
<td>154</td>
<td>0.657</td>
</tr>
<tr>
<td>Presence of diffuse leakage</td>
<td></td>
<td>-0.163</td>
<td>195</td>
<td>0.023</td>
</tr>
<tr>
<td>Presence of DARA</td>
<td></td>
<td>-0.265</td>
<td>197</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Surface of DARA</td>
<td></td>
<td>-0.343</td>
<td>197</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Location of DARA</td>
<td></td>
<td>0.400</td>
<td>197</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>DARA involving the fovea</td>
<td></td>
<td>-0.386</td>
<td>197</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>DARA within 1 DD of the fovea, but sparing the fovea</td>
<td></td>
<td>0.128</td>
<td>197</td>
<td>0.072</td>
</tr>
<tr>
<td>DARA more than 1 DD outside the fovea</td>
<td></td>
<td>0.309</td>
<td>197</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Mean number of recurrences</td>
<td></td>
<td>-0.063</td>
<td>176</td>
<td>0.409</td>
</tr>
</tbody>
</table>

Chapter 2.2

**Treatment and disease recurrence**

In this cohort of severe cCSCs, 173 eyes (87%) were treated at least once (mean: 2.4 treatments, range: 1-20 treatments) from the diagnosis of CSC until final follow-up (Table 5). The majority of these eyes (83%, 143/173) were treated after the onset of severe disease. Eighty-one of these eyes (47%, 81/173) were treated only once until the final visit. Of these, 41 eyes (51%, 41/81) never experienced a recurrence after this single treatment. A complete resolution of SRF at final follow-up, on average 3.6 ± 4 years after disease onset, was seen in 72 eyes (89%, 72/81) in this subgroup. Treatment modality and the number of treatments varied widely among the severe cCSC cases (Table 5). Treatment efficacy, defined as a complete resolution of SRF and PCRD, was also highly variable among different treatment modalities (Table 5). In 173 of the 199 eyes (87%) there was SRF accumulation on OCT at the moment of first severe cCSC presentation. This presence of SRF was significantly less frequent at final visit (47 eyes (24%) McNemar test, $p < 0.001$). A comparable significant reduction from 35% (69 eyes) at severe presentation to 18% (35 eyes) at final visit was observed in the incidence of PCRD (Table 3). Throughout the follow-up period, 119 eyes (60%) had multiple SRF recurrences (mean: 1.2 recurrences, range: 1-9 recurrences), whereas in 59 eyes (30%) no recurrence occurred. In 21 eyes (10%) there was insufficient information on disease recurrence.

### Table 5 Frequency of all applied treatments in eyes with severe chronic central serous chorioretinopathy

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Frequency and specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of treatments per case [range]</td>
<td>2.4 [1-20]</td>
</tr>
<tr>
<td>Number of untreated cases</td>
<td>25 (14%)</td>
</tr>
<tr>
<td>Total number of PDTs</td>
<td>246 (60%)</td>
</tr>
<tr>
<td>Successful PDT</td>
<td>153 (62%)</td>
</tr>
<tr>
<td>PDT modality</td>
<td>6 (2%) full settings</td>
</tr>
<tr>
<td></td>
<td>160 (66%) half-dose</td>
</tr>
<tr>
<td></td>
<td>39 (16%) half-time</td>
</tr>
<tr>
<td></td>
<td>6 (2%) half-fluence</td>
</tr>
<tr>
<td></td>
<td>35 (14%) unknown</td>
</tr>
<tr>
<td>PDT spot size in µm [range]</td>
<td>4457 [1000-8800] b</td>
</tr>
<tr>
<td>Total number of SMLs</td>
<td>81 (20%)</td>
</tr>
<tr>
<td>Successful SMLs</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Total number of conventional thermal laser treatments</td>
<td>84 (20%)</td>
</tr>
<tr>
<td>Successful conventional thermal laser treatments</td>
<td>54 (64%)</td>
</tr>
</tbody>
</table>

---

a) Successful treatment was defined by a complete resolution of subretinal fluid and/or disappearance of posterior cystoid retinal degeneration

b) An average size is reported in case multiple PDT spots were used

PDT: photodynamic therapy, SML: subthreshold micropulse diode laser
DISCUSSION

In this retrospective multicenter study, we assessed the clinical characteristics in a large series of eyes with a severe variant of cCSC, after suggesting a definition for severity. The majority of the studied eyes (73%) manifested pre-existing signs of chronicity at first disease presentation, where only 14% started with a documented acute CSC episode. In contrast to a high percentage of SRF resolution, final visual outcome did not improve significantly after treatment in this cohort. The final visual outcome was strongly associated with baseline visual acuity, surface of diffuse atrophic RPE alteration (DARA), and the presence of DARA within one DD of the fovea.

CSC is considered the fourth most common macular disease associated with SRF and/or intraretinal fluid leakage, after age-related macular degeneration, diabetic macular edema, and retinal vascular occlusions. A prolonged disease course in CSC is known to cause progressive visual decline, and can lead to secondary choroidal neovascularization and/or polypoidal choroidal vasculopathy. Although there is no consensus on the exact definition of chronicity, the most prevalent retinal and choroidal abnormalities characterizing a chronic course are generally agreed upon. These general clinical characteristics of chronicity include one or more significant multifocal areas of atrophic RPE alterations, and/or multifocal areas of leakage. Nevertheless, a large variety of clinical presentations within cCSC exists, ranging from mild to severe manifestations with clinical characteristics as described here. Therefore, the diagnosis and treatment decision making may form a challenging task in daily clinical practice when confronted with the clinical spectrum of CSC.

In the current study, only 14% of the severe cCSC patients had a history of documented acute CSC. Otsuka et al reported a larger incidence of previous acute episodes (36% in 25 severe cCSC cases) as compared to the current study, whereas Yannuzzi et al reported that merely 8% of 25 cCSC patients in their study had previously experienced an acute CSC episode. Therefore, these observations at least indicate that a well observed, clinical episode of acute CSC is not required to evolve to chronicity in CSC and to develop extensive, severe cCSC. Since 73% of the studied eyes showed signs of chronicity at first presentation, it is conceivable that chronic choroidal leakage and congestion may cause gradual, subclinical damage to the overlying RPE. This may explain why most severe cCSC cases in our cohort showed pre-existing signs of long-standing disease at first presentation. We also observed that the area of choroidal hyperpermeability on ICGA was larger than the area of leakage on FA in most cases. This can also be an indication of a more widespread underlying choroidal disease process that is slumbering and gradually damaging the RPE. This process may have already started subclinically long before an actual RPE outer blood-retinal barrier breakdown with SRF accumulation and vision loss may occur. The multifocal and/or diffuse leakage on FA in some severe cCSC cases can be considered as the ‘tip of the iceberg’ of a larger underlying area of dysfunctional leaking choroid. Eventually, focal and/or diffuse damage to the RPE and the outer blood-retinal barrier can result in more...
pronounced damage to the overlying neuroretina, for instance through the development of RPE atrophy, SRF accumulation, and PCRD.

In the present study, final visual outcome was most strongly correlated with baseline BCVA (before severe presentation), location of DARA within 1 DD from the fovea, and DARA surface size. Despite a high percentage of post-treatment SRF resolution in most cases (76%), final visual outcome did not improve significantly in our cohort. This BCVA at final visit was on average 70 ETDRS letters. In another smaller study, including patients with presumably severe disease, a final BCVA of more than 0.5 Snellen (70 ETDRS letters) was reported in 80% of the eyes (37/46). Wang et al. have postulated that SRF leakage lasting over 4 months may cause retinal atrophy and irreversible visual loss, but little is known about the exact time that has to ensue before chronic SRF accumulation causes photoreceptor degeneration, neuroretinal atrophy, and consequent vision loss. In the current study, most cases had a disease duration that was far longer than 4 months, and experienced multiple recurrences of SRF accumulation. It is therefore plausible to assume that irreversible macular photoreceptor dysfunction due to prolonged disease has contributed to irreversible BCVA loss.

In this study, DARA was the most prevalent finding among severely affected patients, and DARA surface also tended to expand over time. The development of diffuse RPE atrophy has been related to corticosteroid use. In the current cohort, 18% of the patients reported corticosteroid use. However, we did not observe a significant negative correlation between corticosteroid use and a poor post-treatment BCVA, confirming our earlier findings in patients with steroid-associated cCSC who were treated with PDT.

Among our studied cases, the majority (87%) was treated during follow-up. Nevertheless, SRF persisted in 24% of cases, and PCRD remained in 18% until final visit. Silva et al previously reported a 93% SRF resolution, and a 100% post-treatment PCRD resolution in a cohort of 46 general cCSC cases. It has been previously suggested that outer retinal ischemia due to chronic retinal detachment may contribute to PCRD development. Despite increasing evidence on the superiority of PDT as first-choice treatment for CSC, a large variability in CSC treatment exists in clinical practice. In our study, PDT with reduced settings was the most common used treatment modality, with the highest success rate (62%) in resolution of SRF and PCRD. This success rate is lower when compared to literature on outcome of PDT in a general cCSC population, which may be related to the disease severity as well as our strict definition of success: a complete resolution of SRF and PCRD.

In the present study, we proposed a definition for severity in cCSC. The choice of the suggested criteria such as a large cumulative surface of DARA in the macula of more than 5 DD was somewhat arbitrary, based on clinical experience of the involved retina specialists. Future research must establish the validity of these criteria of severity. In order to report a history of acute CSC in this retrospective study, we were dependent on symptomatic
disease episodes. Therefore, the abovementioned percentage of patients with a history of acute CSC may be an underestimation, since a small proportion of acute CSC episodes may occur asymptptomatically. Here, we could demonstrate that patient characteristics including baseline BCVA, total area of DARA, location of DARA, and presence of PCRD can predict up to 47% of the variance in final BCVA outcome in severe cCSCs. Future prospective studies may provide additional information on the retinal and choroidal vasculature conditions, and reveal other prognostic factors associated with progression and visual outcome in cCSC.

In conclusion, based on the suggested definition in this study, CSC appears to encompass a clinical spectrum that includes a group of severe cases of cCSC which often respond to treatment, but with a more guarded visual prognosis as compared to cCSC cases without characteristics of severity. Most of these severe cCSC cases already have a chronic phenotype at presentation, whereas only a minority of them have a documented history of acute CSC. This may indicate that acute CSC and (severe) cCSC may be relatively distinct phenotypes both clinically and pathophysiologically. Future studies can be directed towards a further distinction of different phenotypes within the CSC spectrum, to gain further insight in possible differences in genetic background, pathophysiology, optimal treatments, and treatment outcome.

**Ethics approval**

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local institutional review boards in all participating centers did not require written consent from the participants for reviewing their medical records, as all data were anonymized upon collection.

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**Disclosure**

The authors report no conflicts of interest in this work.
REFERENCES


CHAPTER 2.3

Clinical characteristics and outcome of posterior cystoid macular degeneration in chronic central serous chorioretinopathy

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Chapter 2.3

ABSTRACT

Purpose: To assess clinical characteristics and visual outcome in chronic central serous chorioretinopathy (cCSC) patients with posterior cystoid retinal degeneration (PCRD).

Methods: Patients’ medical records were reviewed retrospectively in 62 cases (83 eyes, mean age = 59 years, 88% male). Data were collected at CSC diagnosis, at PCRD manifestation, and at final visit. All treatment modalities were reviewed. Main Outcome measures were treatment efficacy in achieving PCRD resolution, and final best corrected visual acuity (BCVA).

Results: In 63 eyes (76%) subretinal fluid (SRF) was present at first PCRD manifestation, while fluorescein angiography showed active focal or diffuse leakage in 65 eyes (78%). Seventy-six eyes (81%) received treatment, and PCRD had resolved completely in 31 eyes (37%) at the final visit. Photodynamic therapy (PDT) was most successful in achieving a complete PCRD resolution. BCVA did not improve, even after complete PCRD resolution (mean baseline BCVA = 69 ±19, and mean final BCVA = 67 ±20 ETDRS letters (20/40 and 20/50 in Snellen equivalent respectively), P = 0.354).

Conclusions: PCRD is a relatively common finding in cCSC, which is often accompanied by active SRF leakage. Treatment may be beneficial to stop the SRF leakage component, but is less likely to result in a complete PCRD resolution and/or a BCVA improvement.
INTRODUCTION

Chronic central serous chorioretinopathy (cCSC) is characterized by a persistent or intermittent subretinal serous leakage, presence of a serous neuroretinal detachment, and diffuse irregularities and atrophy of the retinal pigment epithelium (RPE). Patients with cCSC may have a decreased vision-related quality of life and the disease is associated with progressive vision loss. Variability exists in the anatomical abnormalities among patients with cCSC, which may reflect the progression or stage of the disease. Besides chronic subretinal fluid (SRF) leakage, most cCSC patients show more extensive and/or multifocal RPE detachments and atrophic RPE changes in comparison to acute, self-limiting CSC. In contrast, acute central serous chorioretinopathy (aCSC) is characterized by an acute onset of a neurosensory detachment that often shows spontaneous resolution with a full recovery of vision, with little atrophic RPE changes.

A considerable number of cCSC patients show an extensive and presumably severe disease phenotype with diffuse atrophic RPE alterations (DARA), numerous ‘hot spots’ of leakage on fluorescein angiography (FA), subretinal fibrin deposits, and/or occasionally posterior cystoid retinal degeneration (PCRD) at first presentation. These severe cCSC cases seem to form a distinct entity within the spectrum of CSC with the worst visual prognosis. PCRD, first described by Piccolino et al. in 2008, in particular was shown to be present in up to 35% of severe cCSC cases.

In contrast to cystoid macular edema (CME), which is generally associated with vascular hyperpermeability and active leakage, presence of PCRD as seen in cCSC may have a more degenerative origin related to the primary choroidopathy and RPE dysfunction. For example, in contrast to retinal vascular diseases with secondary CME, there seems to be no vascular endothelial growth factor (VEGF) driven mechanism involved in PCRD, as anti-VEGF medication was shown to be ineffective in PCRD. The recently described entity of “peripapillary pachychoroid syndrome”, which is characterized by peripapillary intraretinal cystoid changes, belongs to the pachychoroid disease spectrum just like CSC, with involvement of hyperpermeable choroidal vessels, that do not respond to intravitreal anti-VEGF either.

Little is known about the etiology of PCRD. The development of PCRD may be explained at least partially by the hyperpermeability of choroidal vessels and the dysfunctional outer blood-retina barrier of the RPE, which is a characteristic of cCSC and other pachychoroid associated disease, even though PCRD can occur in absence of active SRF leakage. As PCRD has been associated with a severely reduced visual acuity, resolution of PCRD is desirable. However, at present only a few relatively small studies are available on the clinical characteristics and treatment of PCRD in cCSC.
Chapter 2.3

The purpose of the present study is to describe the clinical characteristics on multimodal imaging in cCSC patients with PCRD, to review the outcome of treatments, especially for PDT, and to assess the final visual outcome.

MATERIALS AND METHODS

Patients were included for this study from three Dutch tertiary referral centers: the Department of Ophthalmology at Leiden University Medical Center (Leiden, the Netherlands), the Rotterdam Eye Hospital (Rotterdam, the Netherlands), and Radboud University Medical Center (Nijmegen, the Netherlands). This study was approved by the respective institutional review boards at the participating centers and was performed in accordance with the tenets of the Declaration of Helsinki.

Patients were included when visual complaints existed for over 6 months. Chronic CSC was defined according to a previous definition: evidence of persistent SRF for at least 3 months, RPE window defects and at least one “hot spot” of focal leakage on FA, and corresponding hyperfluorescent zones on indocyanine green angiography (ICGA) when available. All cases had cCSC-associated PCRD at some point during follow-up. PCRD was recognized on OCT according to a previous definition by Piccolino et al, as intraretinal spaces separated by reflective tissue from the RPE which were detected within the temporal vascular arcades. Patients were excluded when intraretinal cystoid abnormalities were caused by other retinal or choroidal vascular abnormalities, such as (secondary) choroidal neovascularization (CNV). We also excluded patients with cystoid degeneration caused by trauma, evident epiretinal membrane, retinoschisis, and degeneration due to previous thermal laser treatment.

The medical charts were evaluated and information was collected concerning general medical background and steroid use, as well as diagnosis-related data including: date of CSC diagnosis, date of PCRD determination, fellow eye diagnosis, follow-up duration, treatment modalities and treatment effect, and best corrected visual acuity (BCVA) at diagnosis and at final visit. BCVA which was originally assessed with a Snellen chart was converted to early treatment of diabetic retinopathy study (ETDRS) letters for further analysis. The location of PCRD was assessed and reported as: adjacent to the temporal side of the optic disc (peripapillary region), between the optic disc and the foveal region without peripapillary or foveal involvement (papillomacular region), covering the fovea, and elsewhere in the posterior pole. Treatment was considered effective only when there was a complete resolution of SRF and PCRD.
Clinical examinations

Subjects were included when ophthalmological and multimodal imaging examinations were available at diagnosis and during follow-up. Minimum available multimodal imaging examination included either time-domain OCT (Cirrus HD-OCT, Carl Zeiss Meditec or OCT-HS100, Canon Inc., Tokyo, Japan) or spectral-domain OCT (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) at the moment of PCRD manifestation and at final visit; and a FA (Topcon Corp., Spectralis HRA+OCT, or Carl Zeiss Meditec) after PCRD manifestation. ICGA (Topcon Corp., Heidelberg Spectralis HRA+OCT, or Carl Zeiss Meditec) was performed when a CNV had to be ruled out. The following characteristics were determined on FA imaging: presence of active leakage, type of leakage (focal vs. diffuse), and the area of DARA associated with PCRD. The extent of DARA area was quantified by using available caliper measurement tools on FA equipment and expressed in number of optic disc diameters (DD).

Statistical analysis

Statistical analyses were performed using IBM SPSS software for Windows, version 23 (IBM Corp., Armonk, NY, USA). Continuous numerical data were compared using a paired or unpaired Student’s t-test. Categorical data were analyzed using a chi-square test. A COX proportional hazard model was computed to predict the effect size of multiple clinical and patient characteristics on complete resolution of PCRD. Hazard ratios (HR) and 95% confidence intervals (CI) are reported for each risk factor according to an univariate and a multivariate analysis. For all tests, a P-value of <0.05 was considered significant.

RESULTS

In total, 62 patients (83 eyes, 73 (88%) male) were included for analysis (Table 1). The mean age at first documented PCRD manifestation was 59 years (range: 36-80 years). The mean time between cCSC diagnosis and PCRD manifestation was 61 months (range: 0-347 months). Twenty-one cases had bilateral PCRD. General medical background in the study cases was as follows: cardiovascular (coronary artery obstruction, hypertension, transient ischemic attack, etc.) in 26 cases (31%), diabetes mellitus without diabetic retinopathy in 8 cases (10%), and autoimmune disorders in 6 cases (7%). The baseline demographic characteristics are summarized in Table 2.
Table 1 Patient Selection

<table>
<thead>
<tr>
<th>Exclusion due to</th>
<th>Patients (Eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cCSC eyes evaluated for the study</td>
<td>83 (106)*</td>
</tr>
<tr>
<td>PCV</td>
<td>1 (1)</td>
</tr>
<tr>
<td>AMD</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diabetic macular edema</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Paraneoplastic syndrome</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Choroidal naevus</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Central retinal vein occlusion</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Retinoschisis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Occult CNV</td>
<td>8 (10)</td>
</tr>
<tr>
<td>PCRD induced by thermal laser</td>
<td>6 (6)</td>
</tr>
<tr>
<td>cCSC eyes included in the study</td>
<td>62 (83)†</td>
</tr>
</tbody>
</table>

*In a cohort including 1811 CSC patients, 83 patients were identified with a chronic disease and PCRD on OCT imaging.
†Twenty-one cases had bilateral and 41 cases had unilateral PCRD. 18 fellow eyes in unilateral cases showed active CSC, 7 fellow eyes had signs of CSC without active leakage on FA, 10 fellow eyes had mild RPE changes compatible with pachychoroid pigment epitheliopathy without active CSC, and 3 fellow eyes were completely normal. Three fellow eyes had other diseases (1 CNV, 1 retinal venous obstruction, 1 uveitis).
AMD, age-related macular degeneration; CNV, choroidal neovascularization; PCV, polypoidal choroidal vasculopathy.

Table 2 Patient demographics and clinical features

<table>
<thead>
<tr>
<th>Features</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes (Patients)</td>
<td>83 (62)</td>
</tr>
<tr>
<td>Male gender, No. (%)</td>
<td>73 (88)</td>
</tr>
<tr>
<td>Age at CSC diagnosis in years, mean ± SD</td>
<td>54 ± 12</td>
</tr>
<tr>
<td>Age at PCRD presentation in years, mean ± SD</td>
<td>59 ± 10</td>
</tr>
<tr>
<td>Caucasian, No. (%)</td>
<td>68 (82)</td>
</tr>
<tr>
<td>Recent steroid use, No. (%)</td>
<td>20 (24)</td>
</tr>
<tr>
<td>BCVA at diagnosis, in ETDRS letters, mean ± SD</td>
<td>68 ± 19* (20/40 in Snellen equivalent)</td>
</tr>
<tr>
<td>Time from CSC diagnosis until PCRD presentation in months (range)</td>
<td>61 (0-347)</td>
</tr>
<tr>
<td>Mean follow-up duration form CSC diagnosis in months (range)</td>
<td>95 (4-373)</td>
</tr>
</tbody>
</table>

*Two patients (2 eyes) could only recognize hand movements
ETDRS, Early Treatment Diabetic Retinopathy Study
Clinical characteristics of PCRD in cCSC

**Characteristics on OCT imaging**

In 63 eyes (76%), active SRF leakage was present on OCT at first PCRD manifestation (Table 3). In 45 eyes (54%), PCRD was overlying a dome-shaped (15 eyes, 18%) or a flat irregular RPE detachment (30 eyes, 36%) (Table 3). In most cases PCRD was present in the peripapillary region (32 eyes, 39%) or in the papillomacular region (35 eyes, 30%), while the fovea was involved in 15 eyes (18%). Eleven eyes (13%) showed PCRD outside these regions and without foveal involvement (Figure 1). PCRD could be localized in the inner nuclear layer (INL) of the retina, the outer nuclear layer (ONL), the ganglion cell layer, but was most frequently observed to be present in multiple layers as summarize in Table 3. In 24 eyes (29%) large cystoid changes were observed which penetrated multiple retinal layers (Figure 2, F and H).

At final available visit, on average 35 ±29 months after the first PCRD manifestation, PCRD had completely resolved in 31 eyes (37%). PCRD was reduced in 17 eyes (21%), remained unchanged in 30 eyes (36%), and showed an increase in 5 eyes (6%) as compared to baseline. SRF in this cohort had resolved completely in 68 eyes (82%) at final visit.

**Characteristics on FA imaging**

The first FA imaging after PCRD manifestation showed active (multi)focal fluorescein leakage in 29 eyes (35%) (on average: 2.4 focal ‘hot spots’ of leakage, range: 1-7 ‘hot spots’), while 36 eyes (43%) showed more diffuse leakage, attributed to SRF. In 18 eyes (22%), there was no fluorescein leakage (Table 3). In 50 eyes (60%), the area of leakage was associated with the location of PCRD. The mean cumulative area of DARA on FA was 7.1 DD (range: 0-20 DD), and in 69 eyes (83%) DARA included the location of PCRD (Table 3).

**Treatment outcome and PCRD resolution**

Among all eyes included in this study, 27 eyes (32%) had previous treatment for cCSC prior to PCRD manifestation, while 56 eyes (68%) were treatment-naive (Table 4). Sixty-seven study eyes (81%) were treated after PCRD manifestation, of which 21 eyes (21/67, 31%) had previously received treatment prior to PCRD manifestation. Out of a total of 67 treated eyes, 36 eyes (54%) had a complete resolution of PCRD. Complete resolution occurred after a single treatment in 27 eyes (33%) (of which PDT in 25 eyes, 30%), and after multiple treatments in 7 eyes (9%). In 2 eyes (2%), PCRD resolved independent of treatment (Figure 2, Table 4, and Table 5). Among cases with foveal involvement of PCRD which were treated (14/67, 21%), 8 eyes (8/14, 57%) had a complete PCRD resolution. Forty-nine study eyes (49/67, 73%) had received PDT as first treatment option, among which 23 eyes (23/49, 47%) showed a complete resolution of PCRD after this first PDT. Recurrence of PCRD was observed in 4 eyes (4/23, 17%) with an initial PCRD resolution after first successful PDT treatment.
## Table 3 Findings on multimodal imaging in patients with cCSC and secondary PCRD manifestation

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Features</th>
<th>No. of eyes (%/SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT at first PCRD manifestation</td>
<td>SRF</td>
<td>52 (63)</td>
</tr>
<tr>
<td></td>
<td>Subfoveal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral</td>
<td>11 (13)</td>
</tr>
<tr>
<td></td>
<td>No SRF</td>
<td>20 (24)</td>
</tr>
<tr>
<td>PCRD association with PD</td>
<td>Dome-shaped</td>
<td>15 (18)</td>
</tr>
<tr>
<td></td>
<td>Irregular flat</td>
<td>30 (36)</td>
</tr>
<tr>
<td></td>
<td>No PD association</td>
<td>38 (46)</td>
</tr>
<tr>
<td>PCRD location in posterior pole</td>
<td>Peripapillary region</td>
<td>32 (39)</td>
</tr>
<tr>
<td></td>
<td>Papillomacular region</td>
<td>35 (30)</td>
</tr>
<tr>
<td></td>
<td>Foveal</td>
<td>15 (18)</td>
</tr>
<tr>
<td></td>
<td>Other †</td>
<td>11 (13)</td>
</tr>
<tr>
<td>PCRD location in retinal layers †</td>
<td>ONL</td>
<td>16 (19)</td>
</tr>
<tr>
<td></td>
<td>INL, ONL</td>
<td>61 (74)</td>
</tr>
<tr>
<td></td>
<td>INL, OPL, ONL</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>GCL, INL, ONL</td>
<td>1 (1)</td>
</tr>
<tr>
<td>OCT at final visit</td>
<td>SRF</td>
<td>9 (11)</td>
</tr>
<tr>
<td></td>
<td>Subfoveal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral</td>
<td>6 (7)</td>
</tr>
<tr>
<td></td>
<td>Complete resolution</td>
<td>68 (82)</td>
</tr>
<tr>
<td>Presence of PCRD</td>
<td>Complete resolution</td>
<td>31 (37)</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>17 (21)</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>Unchanged</td>
<td>30 (36)</td>
</tr>
<tr>
<td>FA after PCRD manifestation</td>
<td>Fluorescein leakage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Focal</td>
<td>29 (35)</td>
</tr>
<tr>
<td></td>
<td>Diffuse</td>
<td>36 (43)</td>
</tr>
<tr>
<td></td>
<td>No leakage</td>
<td>18 (22)</td>
</tr>
<tr>
<td></td>
<td>Leakage associated with PCRD</td>
<td>50 (60)</td>
</tr>
<tr>
<td></td>
<td>Area of RPE atrophy in DD</td>
<td>7.1 (SD = 4)</td>
</tr>
<tr>
<td></td>
<td>RPE atrophy associated with PCRD</td>
<td>69 (83)</td>
</tr>
</tbody>
</table>

* Other PCRD locations without foveal involvement included: 5 eyes (6%) temporal and nasal to fovea, 3 eyes (4%) temporal to fovea, 2 eyes (2%) inferior to fovea, 1 eye (1%) in papillomacular region and temporal to fovea.

† The cystoid changes were larger and more prominent in the ONL in 70 eyes (84%), in 9 eyes (11%) in the INL, and in 4 eyes (5%) cystoid changes were equally prominent in the INL and ONL.

DD, optic disc diameter; ETDRS, Early Treatment Diabetic Retinopathy Study; GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; PD, RPE detachment.
### Table 4: Treatment strategies and treatment efficacy in eyes with cCSC and secondary PCRD

<table>
<thead>
<tr>
<th>Treatment before PCRD manifestation</th>
<th>Eyes (%/range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously treated eyes</td>
<td>27 (32)</td>
</tr>
<tr>
<td>Mean number of treatments</td>
<td>2 (range = 1-8)</td>
</tr>
<tr>
<td>Previously untreated eyes</td>
<td>56 (68)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment after PCRD manifestation</th>
<th>Eyes (%/range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated eyes</td>
<td>67 (81%)</td>
</tr>
<tr>
<td>Mean number of treatments</td>
<td>2 (range = 1-10)</td>
</tr>
<tr>
<td>Untreated eyes</td>
<td>16 (19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment effect after PCRD manifestation</th>
<th>Eyes (%/range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution after mono treatment</td>
<td>27 (33)</td>
</tr>
<tr>
<td>Resolution after multiple treatments</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Resolution independent of treatment</td>
<td>2 (2)</td>
</tr>
<tr>
<td>No resolution despite treatment</td>
<td>31 (37)</td>
</tr>
<tr>
<td>Not treated and no resolution</td>
<td>16 (19)</td>
</tr>
</tbody>
</table>

### Table 5: Frequency of all applied treatments in eyes with cCSC with secondary PCRD manifestation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Specifications</th>
<th>Eyes (%/range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT</td>
<td>Total number</td>
<td>82 (59)</td>
</tr>
<tr>
<td>- Half-dose PDT</td>
<td>56 (68)</td>
<td></td>
</tr>
<tr>
<td>- Half-time PDT</td>
<td>10 (12)</td>
<td></td>
</tr>
<tr>
<td>- Half-fluency PDT</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>- Full-dose PDT</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>- Unknown settings</td>
<td>9 (11)</td>
<td></td>
</tr>
<tr>
<td>- Successful treatment*</td>
<td>32 (39)</td>
<td></td>
</tr>
<tr>
<td>SML</td>
<td>Total number</td>
<td>25 (18)</td>
</tr>
<tr>
<td>- Successful treatment*</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Conventional thermal laser</td>
<td>Total number</td>
<td>18 (13)</td>
</tr>
<tr>
<td>- Successful treatment*</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>Anti-VEGF injections</td>
<td>Total number</td>
<td>14 (10)</td>
</tr>
<tr>
<td>- Bevacizumab</td>
<td>10 (72)</td>
<td></td>
</tr>
<tr>
<td>- Aflibercept</td>
<td>3 (21)</td>
<td></td>
</tr>
<tr>
<td>- Combination</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>- Mean number of injections</td>
<td>2.9 (range = 2-6)</td>
<td></td>
</tr>
<tr>
<td>- Successful treatment*</td>
<td>2 (14)</td>
<td></td>
</tr>
</tbody>
</table>

*Successful treatment = complete resolution of PCRD

VEGF, vascular endothelial growth factor; SML, subthreshold micropulse diode laser.
Figure 1. Fluorescein angiography (FA) (A, C, E, G) and optical coherence tomography (B, D, F, H) imaging in four cases of chronic central serous chorioretinopathy (cCSC) with secondary posterior cystoid retinal degeneration (PCRD). Figure depicts four locations of PCRD lesions in posterior pole, including the peripapillary region (A, B), the papillomacular region without peripapillary or foveal involvement (C, D), the foveal region (E, F), and outside papillomacular intersection, in this case temporal to the fovea (G, H). The red square in each FA imaging illustrates the distribution area of cystoid lesions. The cystoid lesions were most prominently located in the outer nuclear layer (ONL) (B, F) of the retina, and to a lesser degree also in the inner nuclear layer (INL) (D, H).
Clinical characteristics of PCRD in cCSC

Figure 2. Optical coherence tomography imaging showing variable treatment response in four cases of chronic central serous chorioretinopathy (cCSC) with secondary posterior cystoid retinal degeneration (PCRD) (A-H). Four patterns of PCRD progression are illustrated during follow-up and until the final available visit. Complete resolution of PCRD and subretinal fluid (SRF) occurred in the left eye of a 62-year-old male patient, after one treatment with half-dose photodynamic therapy (PDT) (A and B). PCRD at final visit had decreased but not resolved in the right eye of a 67-year-old male patient, who was treated with three half-dose PDT sessions and two intravitreal injections of bevacizumab (C and D). In a 62-year-old male patient (E and F), PCRD showed an increase in volume in the right eye, despite multiple treatments (3 PDT treatments, 1 focal thermal laser, 1 subthreshold micropulse diode laser). The macula of a 42-year-old male, who was treated with focal thermal laser and 3 PDT treatments showed fluctuations of PCRD without a clear response to treatment (G and H).
Chapter 2.3

**BCVA Outcome**

The mean baseline BCVA in the entire group was 69 ±19 ETDRS letters (20/40 in Snellen equivalent), reducing slightly to 67 ±20 ETDRS letter (20/50 in Snellen equivalent) at final visit ($P = 0.354$). Final BCVA outcome did not differ significantly among eyes with and without PCRD resolution (64 ±23 and 67 ±20 ETDRS letters respectively (20/50 and 20/40 in Snellen equivalent respectively), $P = 0.499$). The follow-up duration after PCRD manifestation was comparable in eyes with and without complete PCRD resolution (36 ±32 and 32 ±23 months respectively, $P = 0.515$). BCVA improvement after a complete PCRD resolution was variable depending on the location of PCRD (Table 6).

**Table 6** Visual outcome in patient with cCSC and secondary PCRD during follow-up.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Baseline BCVA ±SD in ETDRS letters (Snellen equivalent)</th>
<th>Final BCVA ±SD in ETDRS letters (Snellen equivalent)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire group</td>
<td>83</td>
<td>69 ±19 (20/40)</td>
<td>67 ±20 (20/50)</td>
<td>0.354</td>
</tr>
<tr>
<td>Eyes with resolved PCRD</td>
<td>30</td>
<td>64 ±22 (20/50)</td>
<td>64 ±23 (20/50)</td>
<td>0.083</td>
</tr>
<tr>
<td>Foveal location</td>
<td>6</td>
<td>46 ±24 (20/125)</td>
<td>47 ±25 (20/125)</td>
<td>0.691</td>
</tr>
<tr>
<td>Peripapillary location</td>
<td>6</td>
<td>77 ±10 (20/32)</td>
<td>81 ±5 (20/25)</td>
<td>0.524</td>
</tr>
<tr>
<td>Papillomacular location</td>
<td>13</td>
<td>62 ±23 (20/63)</td>
<td>68 ±21 (20/40)</td>
<td>0.039</td>
</tr>
<tr>
<td>Other locations</td>
<td>3</td>
<td>78 ±8 (20/25)</td>
<td>74 ±9 (20/25)</td>
<td>0.520</td>
</tr>
<tr>
<td>Eyes with no PCRD resolution</td>
<td>49</td>
<td>72 ±16 (20/40)</td>
<td>67 ±20 (20/50)</td>
<td>0.087</td>
</tr>
</tbody>
</table>

ETDRS, Early Treatment Diabetic Retinopathy Study.

**Factors influencing PCRD resolution**

Univariate COX regression analysis indicated that presence of SRF as a sign of active leakage at first PCRD manifestation (HR = 4.09, CI = 1.23-13.54, $P = 0.021$), and older age at initial cCSC diagnosis (HR = 1.05, CI = 1.02-1.09, $P = 0.004$), increased the probability (hazard) of PCRD resolution. On the other hand, a larger surface of DARA (HR = 0.86, CI = 0.77-0.96, $P = 0.005$) decreased the probability (hazard) of PCRD resolution (Table 7). After performing a multivariate analysis of hazard ratios, SRF leakage at first PCRD manifestation (HR = 2.47, CI = 0.65-9.45, $P = 0.186$), and the size of DARA surface (HR = 0.90, CI = 0.81-1.01, $P = 0.065$), although still indicative, lost statistical significance as predictive factors for PCRD resolution. Older age at initial cCSC diagnosis (HR = 1.05, CI = 1.01-1.09, $P = 0.025$) remained a statistically significant predictor (Table 7).
**Clinical characteristics of PCRD in cCSC**

**Table 7** Hazard ratios of factors predicting complete resolution of PCRD in cCSC patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.02(0.36-2.86)</td>
<td>0.967</td>
<td>1.16(0.36-3.71)</td>
<td>0.807</td>
</tr>
<tr>
<td>Caucasian ethnicity</td>
<td>1.60(0.70-3.65)</td>
<td>0.262</td>
<td>0.39(0.14-1.07)</td>
<td>0.068</td>
</tr>
<tr>
<td>Steroid use</td>
<td>1.08(0.47-2.52)</td>
<td>0.852</td>
<td>0.64(0.22-1.88)</td>
<td>0.420</td>
</tr>
<tr>
<td>SRF leakage at PCRD manifestation</td>
<td>4.09(1.23-13.54)</td>
<td><strong>0.021</strong></td>
<td>2.47(0.65-9.45)</td>
<td>0.186</td>
</tr>
<tr>
<td>SRF leakage under PCRD</td>
<td>0.46(0.62-2.83)</td>
<td>0.464</td>
<td>1.35(0.52-3.56)</td>
<td>0.540</td>
</tr>
<tr>
<td>Foveal location of PCRD</td>
<td>2.24(0.98-5.12)</td>
<td>0.055</td>
<td>1.78(0.73-4.32)</td>
<td>0.205</td>
</tr>
<tr>
<td>DARA surface</td>
<td>0.86(0.77-0.96)</td>
<td><strong>0.005</strong></td>
<td>0.90(0.81-1.01)</td>
<td>0.065</td>
</tr>
<tr>
<td>Age at cCSC diagnosis</td>
<td>1.05(1.02-1.09)</td>
<td><strong>0.004</strong></td>
<td>1.05(1.01-1.09)</td>
<td><strong>0.025</strong></td>
</tr>
</tbody>
</table>

* The overall model was statistically significant with a Chi-square P of 0.003

DARA, diffuse atrophic RPE alteration.

**DISCUSSION**

PCRD is a common feature in patients with advanced cCSC and can be viewed upon as a sign of more severe disease. In the present study, most PCRD cases also showed active leakage on FA, serous neurosensory detachment, and associated RPE atrophy. While treatment led to a complete resolution of SRF in 82% of the cases, less than half of the cases showed resolution of PCRD. Interestingly, the probability (hazard) of PCRD resolution was most strongly associated with coexistence of active SRF leakage. BCVA outcome was relatively poor as compared to uncomplicated cCSC and did not change during follow-up, even in cases with PCRD resolution.

The pathogenesis of PCRD is unclear. A complex hemostatic equilibrium maintains a dehydrated state, and thereby the transparency and functionality of the retina. An imbalance in fluid entry and/or drainage can therefore lead to retinal edema. While the inner blood-retinal barrier prevents serum passage by the act of the intercellular junctions of the endothelial cells and transendothelial transport, the outer-retinal barrier regulates fluid drainage through the intercellular tight junction complex of the RPE cells and the external limiting membrane (ELM). Dysfunctionality of these natural barriers contributes to an increased fluid entry in the retina or subretinal space. Leukostasis, which may arise as a result of local ischemia or an inflammatory process, was suggested as a possible cause of reduced capillary flow in the deep retinal plexus in the sites of retinal edema. This may in turn prevent a normal fluid drainage by the deep capillary plexus. Furthermore, an impairment in the natural pumping function of the RPE cells and the Müller cells is suggested to contribute to insufficient fluid drainage, and subsequent subretinal and intraretinal fluid accumulation. This loss of pumping function may occur through structural cell damage, cell disorganization, and cell death by atrophy. All these factors contribute to the
appearance of cystoid macular edema. Cystoid maculopathy is most frequently associated with retinal vasculopathies. However, cystoid maculopathies may also occur in diseases originating in the choroid, such as chronic CSC. The mechanism of PCRD in cCSC may be predominantly related to outer blood-retinal barrier breakdown and decreased active fluid drainage, which are both the result of a dysfunctional RPE layer. Our observations in this study support this theory, as presence of DARA directly underneath PCRD was observed in 83% of our cases. Previous studies on cCSC-associated PCRD also reported that the largest cystoid spaces were often close to the atrophic RPE lesions.

Spontaneous resolution of PCRD in our cohort was rare, and treatment was therefore often used. Currently no standard treatment exists for cCSC-associated PCRD, and small case series have reported inconsistent results. PCRD in our cohort was accompanied by active SRF leakage in most cases, and 81% of these eyes received treatment. A large variety in treatment strategies and treatment frequency was used in the present study. Therefore, evaluating treatment efficacy in PCRD cases was challenging. Nevertheless, 54% of the cases showed a complete resolution of PCRD, often after a single PDT treatment with reduced settings for the presence of SRF. Overall, PDT was the most frequently used treatment with the relatively highest rate of complete PCRD resolution after treatment (39%) compared to the other used treatments. This rate of complete PCRD resolution after PDT is relatively high in comparison to previous smaller studies on PCRD. Still, the success rate for PDT on resolution of PCRD fluid, which is located intraretinally, is considerably lower than the reported success rates of 67-100% in resolving SRF in cCSC. PCRD thus appears to be more therapy-resistant than SRF in cCSC. Also, BCVA in our PCRD cases showed no overall changes during follow-up even after PCRD resolution, presumably due to irreversible retinal cell loss. Treatment of cCSC before the occurrence of PCRD may therefore be advisable.

We showed that cases with active SRF leakage in conjunction with PCRD manifestation had a higher probability of PCRD resolution after treatment (often PDT). This indicates that PCRD is at least partly dependent on the underlying active choroidal/RPE leakage process, and therefore may resolve well when this process becomes more quiescent after treatment. The group of PCRD without SRF leakage was less likely to show resolution after treatment, indicating that this subgroup is less dependent on underlying choroidal/RPE leakage and more degenerative in nature. These observations suggest that the mechanism in PCRD manifestation consists of a variable contribution of two components: 1) a homeostatic fluid imbalance component, leading to intraretinal fluid (PCRD) and SRF. This component appears more likely to respond to (PDT) treatment. 2) a degenerative component, leading to tissue loss and intraretinal cystoid cavity formation. This component is less likely to respond to treatment. A degenerative loss of tissue, especially loss of Müller cells, have been previously suggested in the occurrence of macular edema. Müller cells may die presumably due to intracytoplasmic edema, and leave a cystoid space behind. A similar process may explain the degenerative component of PCRD in our study.
In the current study PCRD was located peripapillary in more than a third of patients. This pattern of extra-foveal localization, which was also observed in previous studies, may distinguish PCRD from macular edema in the context of other retinal vasculature abnormalities. The recently described clinical picture of peripapillary pachychoroid syndrome (PPS), which like PCRD is also characterized by peripapillary intraretinal cystoid changes in association with hyperpermeable choroidal vessels, shares many features that we also observed within the spectrum of cCSC with PCRD. SRF leakage for instance, was frequently observed in both PPS cases (74%) and in our cohort (76%). Atrophic RPE associated with cystoid changes were observed in 100% of PPS cases, while PCRD associated DARA was present in 83% of our cases. Due to the similarities, PPS may be regarded as a peripapillary form of cCSC with PCRD. However, unlike PPS cases, BCVA outcome in our PCRD cases was poor, and showed no overall changes during follow-up even after PCRD resolution. This lack of reversible visual acuity is another characteristic of PCRD in comparison with other forms of retinal edema or PPS, where BCVA may improve more significantly once edema is resolved.

In this study, some of our observations may have been subject to bias due to the retrospective study design and limitations in availability of certain data. For instance, the follow-up duration and treatment regimens were variable. Also, no suitable control group was available in order to compare treatment outcome (especially after PDT treatment) in cCSC cases with and without PCRD manifestation. Nevertheless, important conclusions can still be drawn. Our study suggests that PCRD in cCSC is a sign of retinal cell loss, as treatment was less successful in resolving PCRD compared to SRF resolution, and since final BCVA outcome remained poor. Further studies are needed to assess if earlier treatment of cCSC may prevent the development of PCRD and the associated irreversible vision loss, and to assess the best treatment options for PCRD.

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**Conflict of interest**

The authors report no conflicts of interest in this work.
REFERENCES


Clinical characteristics of PCRD in cCSC


CHAPTER 3
Genetic characteristics of CSC phenotypes
CHAPTER 3.1
Genetic risk factors in acute central serous chorioretinopathy

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ABSTRACT

Purpose: To investigate genetic associations in white patients with acute central serous chorioretinopathy (aCSC), and to assess genetic differences between aCSC and chronic CSC (cCSC).

Methods: A total of 135 aCSC patients, 272 cCSC patients, and 1385 control individuals were included. Eight single nucleotide polymorphisms (SNPs) were genotyped for ARMS2 (rs10490924), CFH (rs800292, rs1061170, rs1065489, rs1329428, rs2284664, rs3753394), and NR3C2 (rs2070951). Also, C4B gene copy numbers were analyzed.

Results: Three SNPs in the CFH gene were significantly associated with aCSC: rs800292 ($P = 0.003, OR = 1.53 \ [95\% \ CI = 1.15-2.03]$), rs1061170 ($P = 0.002, OR = 0.64 \ [95\% \ CI = 0.48-0.86]$), and rs1329428 ($P = 5.87 \times 10^{-6}, OR = 1.83 \ [95\% \ CI = 1.40-2.38]$). A significant difference was found in the distribution of C4B gene copy numbers in aCSC patients compared to controls ($P = 0.0042$). No differences could be found among the selected variants between aCSC and cCSC patients.

Conclusions: Three variants in the CFH gene and copy number variations in C4B were found to be significantly associated with the risk of aCSC development. Despite the differences in clinical presentation, acute and chronic CSC may share a similar genetic predisposition based on our present analysis. Other genetic and/or non-genetic risk factors may be more influential in the differentiation toward an acute or a chronic phenotype of CSC.
INTRODUCTION

Acute central serous chorioretinopathy (aCSC) is a sudden-onset and relatively common macular disease.\(^1\) It is characterized by a neuroretinal detachment with serous subretinal fluid (SRF) accumulation as seen on optical coherence tomography (OCT).\(^2\) Patients with aCSC characteristically show a single focal “hot spot” of leakage on fluorescein angiography (FA).\(^3\) This leakage occurs because of a small defect in a focally detached retinal pigment epithelium (RPE), which normally constitutes the outer blood-retina barrier.\(^3,4\) Acute CSC has been described to be a self-limiting condition and visual acuity recovers completely in most cases.\(^5\)

In contrast to aCSC, the phenotype of chronic CSC (cCSC) is characterized by prolonged and usually persistent SRF accumulation, larger and/or multiple RPE detachments, often more diffuse RPE leakage, and more extensive multifocal atrophic RPE changes.\(^1\) A timely diagnosis and treatment is required in order to accelerate SRF resolution, and to prevent irreversible photoreceptor damage, vision loss and decreased vision-related quality of life.\(^6\) It is hypothesized that a congested and hyperpermeable choroid lies at the pathophysiological basis of CSC, as part of the pachychoroid spectrum.\(^1,7\) Dysfunction of the RPE, secondary to these choroidal abnormalities, would then result in SRF leakage and neuroretinal detachment, but the exact etiology of the disease is still unknown.\(^2,8\) There is ongoing debate about whether aCSC and cCSC form two distinct entities, or whether they belong to a continuum of the same disease.\(^9,10\)

Recently, single nucleotide polymorphisms (SNPs) in the \textit{ARMS2} gene and the \textit{CFH} gene (involved in the complement system) were found to be significantly associated with cCSC.\(^11-13\) An association of these SNPs was previously identified in age-related macular degeneration (AMD), pointing to a genetic and pathophysiologic overlap between CSC and AMD. An important role for the choroid has been postulated in both diseases, which both manifest at the choriocapillaris-Bruch’s membrane-RPE-neuroretina interface. Interestingly, some risk-conferring alleles in \textit{ARMS2} and \textit{CFH} in AMD were found to be protective in cCSC and vice versa.\(^11\) We also identified an association of a SNP in the \textit{NR3C2} gene that encodes the mineralocorticoid receptor in cCSC.\(^14\) Furthermore, genomic copy number variations in the \textit{complement component 4} (\textit{C4B}) gene were shown to be associated with cCSC.\(^15\) To the best of our knowledge, no genetic studies have been performed to date in patients with an acute phenotype of CSC characterized by only a single focal leak on FA and without any other signs of chronicity. Additionally, clinically distinct aCSC and cCSC phenotypes have not been compared genetically thus far.

In the present study, we therefore assessed whether SNPs in \textit{ARMS2} (rs10490924), \textit{CFH} (rs800292, rs1061170, rs1065489, rs1329428, rs2284664, rs3753394), and \textit{NR3C2} (rs2070951), and the copy numbers of \textit{C4B} gene are associated with aCSC in a white patient cohort. Furthermore, these genetic variants were compared between white aCSC and cCSC patients, to assess whether there are significant differences in these genetic risk factors that could indicate that these disease subtypes are (patho)genetically distinct.
Chapter 3.1

METHODS

A total of 135 white subjects with aCSC was included in the study. Subjects were selected from a large cohort of CSC patients from three referral centers: 47 patients from the Department of Ophthalmology at Leiden University Medical Center (Leiden, the Netherlands), 72 patients from the Rotterdam Eye Hospital (Rotterdam, the Netherlands), and 16 patients from University Hospital of Cologne (Cologne, Germany).

Phenotyping of aCSC patients was performed by two experienced retina specialists (SY, CJFB), who had to agree on the aCSC phenotype being typical, which was based on findings on fundoscopy, OCT, FA, and indocyanine green angiography (ICGA) when available. For purposes of comparison to chronic CSC strict criteria for the diagnosis of aCSC were used. Also, only patients who met the definition of aCSC were included when there was at least one follow-up visit and complete resolution of SRF during the first CSC episode (Figure 1). For this study, aCSC was identified on multimodal imaging as a combination of: 1. Documented serous SRF accumulation on OCT; 2. A single focal leakage point (“hot spot”) on FA; 3. Atrophic RPE alterations (including RPE detachments) limited to less than one optic disc diameter in size in the affected eye. Also, the contralateral eyes were not allowed to show any signs of chronicity, such as presence of atrophic RPE changes or chronic SRF leakage. Patients with other possible causes of SRF accumulation such as choroidal neovascularization, or polypoidal choroidal vasculopathy were excluded. In this study, previous steroid use was not an exclusion criterion.

The control group consisted of white individuals enrolled in the European Genetic Database (EUGENDA; www.eugenda.org), in whom no signs of maculopathy were found when evaluated by multimodal imaging, and 176 subjects from the blood bank of the Radboud University Medical Center (Nijmegen, the Netherlands). The control group for the analysis of ARMS2 and CFH included 826 controls, whereas the analysis of NR3C2 and C4B included 1385 and 250 controls, respectively. Additionally, to assess the genetic difference between aCSC and cCSC we included a cohort of 272 white patients with typical cCSC (Figure 1), as described in a previous genetic analysis on cCSC by our group. Both controls and a subgroup of the cCSC patients were genotyped in previous studies. Approval for this study was obtained at the local institutional review boards in all participating centers and the study was in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to blood collection for genetic analysis.

SNP and copy number genotyping

DNA was isolated from peripheral blood by using standard procedures. The choice of the most relevant genetic variants to be analyzed was based on findings in earlier studies. Genotyping of the selected SNPs was performed using KASP assays (LGC Genomics; Berlin, Germany) as described previously according to the manufacturer’s instructions. Data were read out with the 7900HT Fast Real-Time PCR system (Applied Biosystems by Life
C4B copy numbers were measured as previously described using a TaqMan genotyping assay (Hs07226350_cn, Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA) with RNaseP as a reference assay.15

![Figure 1](image-url)

**Figure 1.** Clinical features visible on multimodal imaging of the left eye of a 41-year-old male patient (A-F) with acute central serous chorioretinopathy (aCSC) and the right eye of a 40 year-old male patient (G-L) with chronic CSC (cCSC). (B) Fluorescein angiography (FA) revealed a single “hot spot” of leakage and no atrophic retinal pigment epithelium (RPE) changes in the aCSC patient. (C) On mid-phase indocyanine green angiography (ICGA) a small hyperfluorescent lesion was observed at the location of the “hot spot” on FA. (D) Fundus autofluorescence (FAF) imaging showed granular hyper-autofluorescent changes at the site of the serous neuroretinal detachment. (E and F) Optical coherence tomography (OCT) scan at first presentation revealed a subretinal serous fluid (SRF) accumulation (E), which resolved after four weeks (F). (H) FA imaging in the cCSC patient revealed a large area of atrophic RPE changes and multiple leakage spots. (I) ICGA imaging in this patient revealed diffuse choroidal hyperpermeability which was slightly larger than the area of leakage visible on FA, and FAF imaging showed a mixture of intense areas of hyper-autofluorescence together with granular hypo-autofluorescent changes. At diagnosis, foveal SRF and a small RPE detachment were observed on the OCT scan of the cCSC patient (K), which both resolved within three weeks after treatment with half-dose photodynamic therapy (L).
**Statistical analysis**

The allele frequency of the SNPs was compared between aCSC and unaffected controls or cCSC patients using a 2-sided Pearson’s chi-square test (IBM SPSS Statistics, version 22, SPSS Inc., Chicago, IL, USA). The C4B copy numbers distribution was compared with a 2-sided Fisher’s exact test and a logistic model correcting for gender was performed setting two copies of C4B as a reference, as previously described. Bonferroni correction for multiple testing was performed for nine variants and P-values <0.0056 were considered statistically significant. The combined effect of the selected six variants in CFH was assessed using a haplotype analysis correcting for gender. Haplotype analysis was performed using R (v3.0.2) using the haplo.stats package (v1.6.8). The two most frequent haplotypes were separately used as a reference in the haplo.glm command to determine odds ratios (ORs) for the haplotypes with a frequency >5% and the aggregate of the haplotypes with a frequency <5%.

**RESULTS**

Of the 135 aCSC patients included, 92 patients (68%) were men, with a mean age of 47 ± 10 years (Table 1). Fifty-six aCSC patients (41%) underwent ICGA imaging and in none of them signs of a CNV were detected. Recent steroid use (< 3 months prior to diagnosis) was reported in 29 aCSC patients (21%). The demographic characteristics of aCSC patients, cCSC patients and controls are summarized in Table 1.

**Table 1** Demographic characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>aCSC patients</th>
<th>cCSC patients</th>
<th>Controls ARMS2 &amp; CFH</th>
<th>Controls C4B</th>
<th>Controls NR3C2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>135</td>
<td>272</td>
<td>826</td>
<td>250</td>
<td>1385</td>
</tr>
<tr>
<td>No. of males</td>
<td>92 (68%)</td>
<td>216 (79%)</td>
<td>424 (51%)</td>
<td>198 (79%)</td>
<td>635 (46%)</td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
<td>47 ± 10</td>
<td>51 ± 10</td>
<td>64 ± 12</td>
<td>51 ± 10</td>
<td>51 ± 10</td>
</tr>
</tbody>
</table>

**Association of SNPs in ARMS2, NR3C2, and CFH genes with aCSC**

No association could be found with the rs10490924 variant in ARMS2 in aSCs (Table 2). An initial significant association in the rs2070951 variant in NR3C2 was lost after correction for multiple testing (Table 2). Among the six tested variants in CFH gene, five variants showed an association with aCSC. Among these, two variants, rs1065489 (P = 0.019, odds ratio (OR) = 0.63 [95% confidence interval (CI) = 0.43-0.93]) and rs2284664 (P = 0.013, OR = 1.44 [95% CI = 1.08-1.93]) showed an association, which was lost after correction for multiple testing (Table 2). Three variants were significantly associated with aCSC after correction for multiple testing: rs800292 (P = 0.003, OR = 1.53 [95% CI = 1.15-2.03]), rs1061170 (P = 0.002, OR = 0.64 [95% CI = 0.48-0.86]), and rs1329428 (P = 5.87 × 10^{-6}, OR = 1.83 [95% CI = 1.40-2.38]).
Table 2 Analysis of eight single nucleotide polymorphisms in acute central serous chorioretinopathy

<table>
<thead>
<tr>
<th>SNP (gene)</th>
<th>Alleles in controls (Major/Minor)</th>
<th>aCSC</th>
<th>MAF aCSC</th>
<th>Controls (n)</th>
<th>MAF controls</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10490924 (ARMS2)</td>
<td>G/T</td>
<td>132</td>
<td>0.174</td>
<td>812</td>
<td>0.217</td>
<td>0.111</td>
<td>0.76 (0.54-1.07)</td>
</tr>
<tr>
<td>rs2070951 (NR3C2)</td>
<td>C/G</td>
<td>132</td>
<td>0.538</td>
<td>1385</td>
<td>0.468</td>
<td>0.0287</td>
<td>1.33 (1.03-1.71)</td>
</tr>
<tr>
<td>rs800292 (CFH)</td>
<td>G/A</td>
<td>133</td>
<td>0.320</td>
<td>798</td>
<td>0.235</td>
<td>3.06 × 10⁻³</td>
<td>1.53 (1.15-2.03)</td>
</tr>
<tr>
<td>rs1061170 (CFH)</td>
<td>T/C</td>
<td>133</td>
<td>0.259</td>
<td>803</td>
<td>0.353</td>
<td>2.82 × 10⁻³</td>
<td>0.64 (0.48-0.86)</td>
</tr>
<tr>
<td>rs1065489 (CFH)</td>
<td>G/T</td>
<td>134</td>
<td>0.119</td>
<td>794</td>
<td>0.177</td>
<td>0.0199</td>
<td>0.63 (0.43-0.93)</td>
</tr>
<tr>
<td>rs1329428 (CFH)</td>
<td>C/T</td>
<td>133</td>
<td>0.579</td>
<td>787</td>
<td>0.429</td>
<td>5.87 × 10⁻⁶</td>
<td>1.83 (1.40-2.38)</td>
</tr>
<tr>
<td>rs2284664 (CFH)</td>
<td>C/T</td>
<td>134</td>
<td>0.287</td>
<td>805</td>
<td>0.219</td>
<td>0.0132</td>
<td>1.44 (1.08-1.93)</td>
</tr>
<tr>
<td>rs3753394 (CFH)</td>
<td>C/T</td>
<td>131</td>
<td>0.263</td>
<td>800</td>
<td>0.293</td>
<td>0.324</td>
<td>0.86 (0.64-1.16)</td>
</tr>
</tbody>
</table>

P < 0.0055 was considered significant.
MAF = minor allele frequency.
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Association of CFH haplotypes with aCSC

Haplotype analysis corrected for gender identified five haplotypes in the CFH gene with a frequency above 5% and an aggregate of the haplotypes with a frequency lower than 5%. When using the most common haplotype (H1) as a reference, an association with aCSC was found for the risk-conferring H2 ($P = 0.003$, OR = 1.75 [95% CI = 1.21-2.53]), H4 ($P = 0.0180$, OR = 1.69 [95% CI = 1.09-2.6]) and H5 ($P = 0.001$, OR = 2.3 [95% CI = 1.39-3.83]), of which H2 and H5 were significant after correction for multiple testing (Table 3). Using the H2 haplotype as a reference, a protective effect for the H1 ($P = 0.003$ OR = 0.57 [95% CI = 0.39-0.83]) and H3 ($P = 0.010$, OR = 0.54 [95% CI 0.33-0.86]) haplotypes was identified, but only the association with H1 remained after correction for multiple testing.

C4B copy number determination in aCSC

Carriers of two copies of the C4B gene were more frequent in the aCSC group (68%) compared to the control group (57%), whereas carrying three C4B gene copies was observed less frequently in the aCSC group (5.3% versus 18% in controls) (see Figure 2, which demonstrates the C4B gene copy distribution). The distribution of C4B in aCSC patients compared to controls was significantly different after correction for multiple testing ($P = 0.0042$). The effect size of different C4B copy numbers on aCSC was assessed by a logistic regression model corrected for gender. The overall model was not significant ($P = 0.051$) (Table 4), but carriers of three C4B copies appeared to have a reduced risk of aCSC ($P = 0.002$, OR = 0.27 [95% CI = 0.12-0.63]) (Table 4).

Differences between aCSC and cCSC

The minor allele frequencies of the tested ARMS2, NR3C2, and CFH variants were not significantly different between aCSC and cCSC patients (See Table 5, which demonstrates minor allele frequencies in aCSC versus cCSC). Haplotype H4 in CFH showed a higher frequency in aCSC compared to cCSC (0.164 in aSCs versus 0.111 in cSCs, $P = 0.0250$, OR = 1.78 [95% CI = 1.08-2.95]), but this was not significant after correction for multiple testing (See Table 6, which demonstrates CFH haplotypes in aCSC versus cCSC). The distribution of C4B copy numbers was not significantly different between aCSC and cCSC patients ($P = 0.345$), and the logistic regression model was also not significant ($P = 0.472$) (See Table 7, which demonstrates logistic regression model for C4B load in aCSC versus cCSC).
### Table 3 Complement factor H (CFH) gene haplotypes in aCSC

<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>Variants</th>
<th>HF aCSC</th>
<th>HF controls</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>C G C C C G</td>
<td>0.249</td>
<td>0.329</td>
<td>Base</td>
<td>Base</td>
<td><strong>0.003</strong></td>
<td>0.57 (0.39-0.83)</td>
</tr>
<tr>
<td>H2</td>
<td>C A T T T G</td>
<td>0.272</td>
<td>0.209</td>
<td><strong>0.003</strong></td>
<td>1.75 (1.21-2.53)</td>
<td>Base</td>
<td>Base</td>
</tr>
<tr>
<td>H3</td>
<td>T G T C C T</td>
<td>0.102</td>
<td>0.158</td>
<td>0.799</td>
<td>0.94 (0.58-1.52)</td>
<td>0.010</td>
<td>0.54 (0.33-0.86)</td>
</tr>
<tr>
<td>H4</td>
<td>C G T C T G</td>
<td>0.164</td>
<td>0.133</td>
<td>0.018</td>
<td>1.69 (1.09-2.6)</td>
<td>0.859</td>
<td>0.96 (0.64-1.46)</td>
</tr>
<tr>
<td>H5</td>
<td>T G T C T G</td>
<td>0.114</td>
<td>0.072</td>
<td><strong>0.001</strong></td>
<td>2.3 (1.39-3.83)</td>
<td>0.280</td>
<td>1.32 (0.8-2.17)</td>
</tr>
<tr>
<td>Rare</td>
<td>* * * * * *</td>
<td>0.100</td>
<td>0.098</td>
<td>0.107</td>
<td>1.52 (0.91-2.52)</td>
<td>0.578</td>
<td>0.87 (0.53-1.43)</td>
</tr>
</tbody>
</table>

*P < 0.0083 was considered significant.

HF = haplotype frequency; MAF = minor allele frequency.
Figure 2. Distribution of \( C4B \) copy numbers among acute central serous chorioretinopathy (CSC), chronic CSC, and controls.
### Table 4 Logistic regression model for C4B load

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 250)</th>
<th>aCSC patients (n = 133)</th>
<th>P</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall significance model P = 0.051</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>198 (79%)</td>
<td>91 (68%)</td>
<td>0.066</td>
<td>1.58 (0.97-2.57)</td>
</tr>
<tr>
<td>C4B copy number</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (2.4%)</td>
<td>4 (3.0%)</td>
<td>0.788</td>
<td>1.20 (0.33-4.39)</td>
</tr>
<tr>
<td>1</td>
<td>55 (22%)</td>
<td>32 (24%)</td>
<td>0.704</td>
<td>0.91 (0.54-1.51)</td>
</tr>
<tr>
<td>2</td>
<td>142 (57%)</td>
<td>90 (68%)</td>
<td>Base</td>
<td>Base</td>
</tr>
<tr>
<td>3</td>
<td>44 (18%)</td>
<td>7 (5.3%)</td>
<td>0.002</td>
<td>0.27 (0.12-0.63)</td>
</tr>
<tr>
<td>4</td>
<td>3 (1.2%)</td>
<td>0</td>
<td>0.999</td>
<td>NA</td>
</tr>
</tbody>
</table>

P <0.0055 was considered significant.

NA = not annotated.

### Table 5 Comparison of allele frequencies in aCSC versus cCSC

<table>
<thead>
<tr>
<th>SNP (gene)</th>
<th>aCSC (n)</th>
<th>MAF aCSC</th>
<th>cCSC (n)</th>
<th>MAF cCSC</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10490924 (ARMS2)</td>
<td>132</td>
<td>0.174</td>
<td>243</td>
<td>0.193</td>
<td>0.520</td>
<td>0.88 (0.60-1.30)</td>
</tr>
<tr>
<td>rs2070951 (NR3C2)</td>
<td>132</td>
<td>0.538</td>
<td>269</td>
<td>0.520</td>
<td>0.642</td>
<td>1.07 (0.80-1.44)</td>
</tr>
<tr>
<td>rs800292 (CFH)</td>
<td>133</td>
<td>0.320</td>
<td>245</td>
<td>0.296</td>
<td>0.500</td>
<td>1.12 (0.81-1.54)</td>
</tr>
<tr>
<td>rs1061170 (CFH)</td>
<td>133</td>
<td>0.259</td>
<td>245</td>
<td>0.320</td>
<td>0.0801</td>
<td>0.74 (0.53-1.04)</td>
</tr>
<tr>
<td>rs1065489 (CFH)</td>
<td>134</td>
<td>0.119</td>
<td>244</td>
<td>0.133</td>
<td>0.587</td>
<td>0.88 (0.56-1.39)</td>
</tr>
<tr>
<td>rs1329428 (CFH)</td>
<td>133</td>
<td>0.579</td>
<td>244</td>
<td>0.510</td>
<td>0.0707</td>
<td>1.32 (0.98-1.78)</td>
</tr>
<tr>
<td>rs2284664 (CFH)</td>
<td>134</td>
<td>0.287</td>
<td>244</td>
<td>0.275</td>
<td>0.709</td>
<td>1.07 (0.76-1.48)</td>
</tr>
<tr>
<td>rs3753394 (CFH)</td>
<td>131</td>
<td>0.263</td>
<td>242</td>
<td>0.273</td>
<td>0.783</td>
<td>0.95 (0.68-1.34)</td>
</tr>
</tbody>
</table>

P < 0.0055 was considered significant.

MAF = minor allele frequency.
Table 6 *Complement factor H* (*CFH*) gene haplotypes in aCSC versus cCSC

<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>Variants</th>
<th>rs3753394</th>
<th>rs800292</th>
<th>rs1061170</th>
<th>rs2284664</th>
<th>rs1329428</th>
<th>rs1065489</th>
<th>HF aCSC</th>
<th>HF cCSC</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>C</td>
<td>G</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>G</td>
<td></td>
<td>0.249</td>
<td>0.301</td>
<td>Base</td>
<td>Base</td>
<td>0.219</td>
<td>0.77 (0.51-1.16)</td>
</tr>
<tr>
<td>H2</td>
<td>C</td>
<td>A</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>G</td>
<td></td>
<td>0.272</td>
<td>0.262</td>
<td>0.219</td>
<td>1.29 (0.86-1.94)</td>
<td>Base</td>
<td>Base</td>
</tr>
<tr>
<td>H3</td>
<td>T</td>
<td>G</td>
<td>T</td>
<td>C</td>
<td>C</td>
<td>T</td>
<td></td>
<td>0.102</td>
<td>0.104</td>
<td>0.408</td>
<td>1.28 (0.71-2.30)</td>
<td>0.976</td>
<td>0.99 (0.57-1.73)</td>
</tr>
<tr>
<td>H4</td>
<td>C</td>
<td>G</td>
<td>T</td>
<td>C</td>
<td>T</td>
<td>G</td>
<td></td>
<td>0.164</td>
<td>0.111</td>
<td>0.025</td>
<td>1.78 (1.08-2.95)</td>
<td>0.201</td>
<td>1.38 (0.84-2.26)</td>
</tr>
<tr>
<td>H5</td>
<td>T</td>
<td>G</td>
<td>T</td>
<td>C</td>
<td>T</td>
<td>G</td>
<td></td>
<td>0.114</td>
<td>0.115</td>
<td>0.373</td>
<td>1.28 (0.75-2.18)</td>
<td>0.963</td>
<td>0.99 (0.59-1.66)</td>
</tr>
<tr>
<td>Rare</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td>0.100</td>
<td>0.108</td>
<td>0.515</td>
<td>1.21 (0.68-2.16)</td>
<td>0.822</td>
<td>0.94 (0.54-1.64)</td>
</tr>
</tbody>
</table>

P < 0.0083 was considered significant.
MAF = minor allele frequency.
Table 7 Logistic regression model for C4B load aCSC versus cCSC

<table>
<thead>
<tr>
<th>Overall significance model P = 0.472</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>cCSC patients (n = 220)</td>
</tr>
<tr>
<td>aCSC patients (n = 133)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>216 (79%) 91 (68%)</td>
</tr>
<tr>
<td>0.026</td>
</tr>
<tr>
<td>1.75 (1.07-2.88)</td>
</tr>
<tr>
<td>C4B copy number</td>
</tr>
<tr>
<td>0 12 (5.4%) 4 (3.0%)</td>
</tr>
<tr>
<td>0.247</td>
</tr>
<tr>
<td>0.50 (0.16-1.61)</td>
</tr>
<tr>
<td>1 66 (30%) 32 (24%)</td>
</tr>
<tr>
<td>0.142</td>
</tr>
<tr>
<td>0.69 (0.41-1.14)</td>
</tr>
<tr>
<td>2 126 (57%) 90 (68%)</td>
</tr>
<tr>
<td>Base</td>
</tr>
<tr>
<td>3 15 (6.8%) 7 (5.2%)</td>
</tr>
<tr>
<td>0.361</td>
</tr>
<tr>
<td>0.64 (0.25-1.66)</td>
</tr>
<tr>
<td>4 1 (0.4%) 0 (0%)</td>
</tr>
<tr>
<td>Base</td>
</tr>
</tbody>
</table>

P < 0.0055 was considered significant.
NA = not annotated.

DISCUSSION

To the best of our knowledge, this is the first study to analyze potential genetic associations specifically in aCSC patients, and to compare them with known genetic associations that were previously identified in cCSC. We have found a significant association between three variants in the CFH gene and copy numbers of the C4B gene in patients with aCSC compared to healthy individuals. Among these CFH variants, two SNPs were risk-conferring and one was protective. Additionally, the H1 haplotype in the CFH gene was protective, whereas H2 and H5 were risk-conferring for aCSC. Three copy numbers of C4B conferred a protective effect for aCSC. No association was found between polymorphisms in ARMS2 or NR3C2 and the risk of aCSC. Finally, no significant differences were identified in these variants between aCSC and cCSC patients.

Genetic variation in different components of the complement system, which is an essential part of innate immunity, such as factor H (FH) and complement component 4B (C4B) proteins, have previously been associated with cCSC. Of the six tested variants in the CFH gene, five variants were associated with aCSC of which three were significant after correction for multiple testing. When comparing our findings in aCSC patients with available literature in cCSC patients, our data confirmed the protective effect of rs1061170, and the risk-conferring effects of rs1329428 and rs800292. However, for these variants the observed effect size in aCSC was larger than previously described in white cCSC patients, respectively, rs1061170 (OR = 0.64 versus 0.83), rs1329428 (OR = 1.83 versus 1.47) and rs800292 (OR = 1.53 versus 1.50).

Additionally, as observed in cCSC patients, the H1 haplotype in CFH was found to be protective for aCSC. Similar to the single variants, the protective effect of the H1
haplotype was stronger for aCSC compared to cCSC (OR = 0.57 versus 0.83). The H2 and H5 haplotypes which were previously reported to increase the risk of cCSC, showed the same association in aCSC patients and their effect size was again larger in aCSC patients compared to cCSC (OR = 1.75 versus 1.33 and OR = 2.30 versus 1.37, respectively). It has been suggested that factor H, which is encoded by the \textit{CFH} gene, can influence the choroidal hemodynamic properties. Also, it has been suggested that an altered activity of factor H protein could cause RPE damage and dysfunction, but the exact mechanism of factor H in the etiology of CSC is still unknown. Both an absence and low copy numbers of \textit{C4B} are known to increase the risk of cCSC, whereas carrying three copies is protective against cCSC. In our study, this protective effect was confirmed in aCSC patients, with an even larger effect size (OR = 0.27) compared to previous reports of cCSC.

Exogenous administration of glucocorticoids, or an endogenous excess (Cushing syndrome) was previously found as an important risk factor in development of CSC. The glucocorticoid receptor and mineralocorticoid receptor are the most important targets for glucocorticoids, and therefore their involvement in the pathogenesis of CSC is conceivable. We have previously found a significant association of a genetic variant in the \textit{NR3C2} gene, encoding the mineralocorticoid receptor, with an increased risk of cCSC. In the present study, we did not find a significant association between the rs2070951 SNP in \textit{NR3C2} with aCSC patients after correction for multiple testing, which could have occurred due to a lack of statistical power. Future larger studies can shed a light on whether this finding is indeed due to a lack of power or if it reflects a true difference in \textit{NR3C2} rs2070951 risk SNP load between aCSC and healthy individuals.

In a previous study, we have found an association between genetic variations in the \textit{ARMS2} gene and cCSC. A possible mechanistic explanation for this association was speculated to be the potential interaction of the ARMS2 protein with the extracellular matrix at the level of the choroid and RPE, which are also primarily affected in CSC. Although the mechanism of action is not fully understood, presence of the rs10490924 variant in the \textit{ARMS2} gene was shown to be protective against cCSC development. This association with the rs10490924 SNP in \textit{ARMS2} was not found in the current aCSC cohort. Again, this may be due to a lack of power, but could also indicate a difference in genetic predisposition between aCSC and healthy controls.

Acute CSC and cCSC generally show contrasting clinical presentations in terms of extent of retinal abnormalities and final visual outcome. There is currently no consensus on the classification of CSC, the definition of chronicity, and the exact period of time after which CSC should be considered chronic differs between studies, ranging from two to six months. Besides a time based definition, cCSC is usually distinguished from aCSC by its more extensive retinal abnormalities on multimodal imaging, which includes multiple focal or diffuse leakage spots and widespread bilateral RPE alterations. A typical aCSC, on the other hand, presents with a single leakage spot, with only very few RPE changes.
Although some patients with cCSC have a history of aCSC, many patients present with a chronic phenotype at the first presentation.\(^9,24\) Therefore, it is still unclear whether these two are part of a continuum with the same pathophysiological background, or if they are essentially different entities. A combination of genetic and non-genetic risk factors such as steroid use, hypertension, and pregnancy,\(^{25-27}\) may play a role in the aspect and severity of CSC, and the risk of progression of aCSC towards a chronic disease course.

Our data suggest a genetic overlap between aCSC and cCSC. No genetic difference could be found when comparing the selected variants in the cCSC and aCSC cohort. However, the effect size of the genetic variants associated with both aCSC and cCSC appears to be systematically larger in aCSC compared to cCSC. The lack of a significant difference between aCSC and cCSC with regard to the associated genetic variants may be partially caused by the small sample size of the current aCSC cohort, and thus a limited power. The larger effect size observed for aCSC suggests that genetic risk factors may play a larger role in the development of aCSC. It has been previously suggested that in multifactorial retinal diseases with genetic involvement such as age-related macular degeneration, patients who develop the disease at a younger age have a stronger genetic predisposition.\(^{28,29}\) A similar mechanism could explain the larger genetic predisposition among aCSC patients, who are generally younger than cCSC patients.\(^9\) Other limitations in the present study are the different sample sizes in the control groups, and the possible ethnical differences between German and Dutch patients, whom we considered equal as one white population.

In conclusion, variants rs800292 and rs1329428 in \textit{CFH} gene were found to be significantly associated with a higher risk of aCSC, whereas variant rs1061170 in this gene was protective against aCSC. Three copy numbers of the \textit{C4B} gene was protective against aCSC, and copy number of the gene differed between aCSC patients and controls. These specific \textit{CFH} SNPs and the \textit{C4B} copy numbers showed an even stronger association with aCSC than previously reported for cCSC. Our findings indicate that despite the differences in clinical presentation, acute and chronic CSC might share genetic risk and protective factors, at least among the currently known variants. Presumably, other non-genetic risk factors, or other currently unknown genetic variants are more influential in the differentiation toward an acute or a chronic disease course in CSC. Future genotype-phenotype correlation analyses in larger cohorts may provide important clues about interaction between these different risk factors.

\textbf{Acknowledgments}

Dr. Magda Meester, PhD, from the Department of Ophthalmology of the Erasmus medical center, and coordinator of the CORRBI biobank in Rotterdam Eye Hospital, is thanked for her assistance in the storage and preparation of DNA materials. Also prof. dr. Hein Verspaget, PhD, from the Department of Gastroenterology and Hepatology, and chairman of the biobank facilities of the Leiden University Medical Center, is thanked for his assistance and support.
Chapter 3.1

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Conflict of interest
The authors report no conflicts of interest.
REFERENCES

Chapter 3.1

CHAPTER 3.2

Genetic risk factors in severe, non-severe, and acute phenotypes of central serous chorioretinopathy

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Chapter 3.2

ABSTRACT

Purpose: To study genetic predispositions and differences between severe chronic central serous chorioretinopathy (cCSC), non-severe cCSC, and acute CSC (aCSC).

Methods: 173 severe cCSC patients, 272 non-severe cCSC patients, 135 aCSC patients, and 1385 control individuals were included. Eight single nucleotide polymorphisms (SNPs) were genotyped in the ARMS2 (rs10490924), CFH (rs800292, rs1061170, rs1065489, rs1329428, rs2284664, rs3753394), and NR3C2 (rs2070951). Additionally, C4B gene copy numbers were analyzed.

Results: A significant association in 5 SNPs in the CFH gene could be reproduced among severe cCSC patients including rs800292 ($P = 0.0014$, OR = 1.93 [95%CI = 1.51-2.47]), rs1065489 ($P = 2.22 \times 10^{-4}$, OR = 0.49 [95%CI = 0.34-0.72]), rs1329428 ($P = 0.001$, OR = 1.89 [95%CI = 1.49-2.40]), rs2284664 ($P = 1.21 \times 10^{-4}$, OR = 1.65 [95%CI = 1.28-2.13]), and rs3753394 ($P = 6.10 \times 10^{-4}$, OR = 0.61 [95%CI = 0.46-0.81]). Carrying three C4B copies was protective for severe cCSC ($P = 0.001$, OR = 0.29 [95%CI = 0.14-0.61]). No significant differences in allele frequencies could be found among the CSC phenotypes.

Conclusions: Acute CSC, non-severe cCSC, and severe cCSC all showed a similar association with the CFH and C4B genes, and the three phenotypes could not be distinguished based on the genetics. This shows that, despite the differences in clinical presentation and severity, there is an overlap in the genetic predisposition of different CSC phenotypes. Non-genetic factors may play a more important role in determining the clinical course of CSC.
INTRODUCTION

Central serous chorioretinopathy (CSC) is a chorioretinal disease, characterized by serous fluid accumulation in the subretinal space, often affecting the macula with subsequent visual impairment. The underlying pathophysiology of CSC is not fully understood. However, a congested, hyperpermeable, and leaking choroid, together with a damaged and dysfunctional retinal pigment epithelium (RPE) are thought to underlie the subretinal fluid (SRF) accumulation in CSC.

At least two different CSC phenotypes can be distinguished: acute and chronic CSC. Acute CSC (aCSC) is generally considered self-limiting with a near-complete visual recovery, thus not requiring treatment in most cases. In contrast, chronic CSC (cCSC) often has persistent SRF with more extensive atrophic RPE changes, in which treatment can be beneficial. There is no consensus on the duration threshold that distinguishes acute and chronic CSC, but an arbitrary period of four to six months duration of active disease (SRF leakage) is often considered for the definition of chronicity. Apart from chronic SRF leakage, patients with cCSC may present with a wide spectrum of retinal abnormalities. In mild cCSC cases there are limited areas of RPE atrophy, few RPE detachments, and a circumscribed area of leakage. More severe cCSC cases show widespread or multifocal (or both) areas of RPE atrophy, more numerous RPE detachments, diffuse areas of leakage, and intraretinal cystoid degeneration. Moreover, this spectrum of severe cCSC was previously shown to have the worst visual prognosis among all cCSC cases, even after treatment and complete resolution of SRF. Therefore, severe cCSC may be considered a distinct clinical subgroup within the spectrum of CSC.

Recently, specific single nucleotide polymorphisms (SNPs) in the age-related maculopathy susceptibility 2 (ARMS2), the complement factor H (CFH), and the nuclear receptor subfamily 3 group C member 2 (NR3C2) genes were found to be associated with the risk of cCSC. Genomic copy number variations in the complement component 4 (C4B) gene were also shown to be associated with cCSC. As aCSC, ‘non-severe’ cCSC, and ‘severe’ cCSC appear substantially distinct CSC subgroups with regard to clinical manifestation and prognosis (Figure 1), these different CSC forms may also have different genetic risk profiles.

In the present study, we analyzed the association of SNPs in the ARMS2, CFH, NR3C2 genes, and copy numbers of C4B gene, in a cohort of cCSC patients who showed a severe disease presentation based on previously published disease characteristics. In addition, we analyzed and compared the association of the aforementioned risk SNPs between three Caucasian CSC subgroups, including aCSC, cCSC without characteristics of severity, and cCSC patients with severity characteristics.
Chapter 3.2
Comparing genetic risk factors in different CSC phenotypes

**Figure 1.** Clinical features on multimodal imaging in different central serous chorioretinopathy (CSC) phenotypes. The right eye of a 34-year-old male with acute CSC (aCSC) is shown in A-D. In E-H the left eye of a 43-year-old male patient with non-severe chronic CSC (cCSC) is shown. In I-L the right eye of a 61-year-old male patient with severe cCSC is shown. Fluorescein angiography (FA) imaging revealed a single “hot spot” of leakage and no atrophic retinal pigment epithelium (RPE) changes in the aCSC patient (A). FA in the non-severe cCSC showed a leakage spot and multifocal small areas of RPE changes (E), while in the severe cCSC case large and widespread RPE atrophy and diffuse leaking areas were seen (I). On mid-phase indocyanine green angiography (ICGA) in the aCSC case, a small hyperfluorescent lesion was observed at the site of the “hot spot” on FA (C). In contrast, ICGA in the severe and non-severe cCSC patients showed more extensive multifocal hyperfluorescent changes (G, K). Fundus autofluorescence (FAF) imaging showed a mix of granular hyper-autofluorescent and hypo-autofluorescent changes which were most prominent in the severe cCSC patient (B, F, J). Optical coherence tomography (OCT) scan at first presentation revealed a subretinal serous fluid (SRF) accumulation and subretinal debris in all patients (D, H, L). Furthermore, a typical irregular shallow RPE detachment was present in the severe cCSC case (L), which is often observed in combination with chronic SRF leakage.

**MATERIALS AND METHODS**

In total, 173 Caucasian subjects with a severe cCSC phenotype were included, originating from four tertiary referral centers: 65 patients from the Department of Ophthalmology of Leiden University Medical Center (Leiden, the Netherlands), 67 patients from Radboud University Medical Center (Nijmegen, the Netherlands), 24 patients from the Rotterdam Eye Hospital (Rotterdam, the Netherlands), and 17 patients from University Eye Hospital of Cologne (Cologne, Germany).

Patients were phenotyped by two experienced retina specialists (SY, CJFB). For phenotyping, a complete ophthalmological examination was used including fundoscopy, optical coherence tomography (OCT), fluorescein angiography (FA), and when available indocyanine green angiography (ICGA). Caucasian patients were included in the severe group of cCSC when they had a history of active disease for over 6 months, in combination with at least one of the following abnormalities: 1. Cumulative areas of larger than five optic disc diameters (DD) of diffuse atrophic RPE alterations visible on mid-phase FA; 2. At least 2 “hot spots” of leakage on mid-phase FA; 3. An area of diffuse fluorescein leakage larger than one DD on mid-phase FA, without an evident leaking focus; 4. Presence of posterior cystoid retinal degeneration assessed on OCT. Subjects were excluded when there was a suspicion of a (secondary) choroidal neovascularization, aneurysmal choroidal vasculopathy, age-related macular degeneration, multifocal choroiditis, retinal vascular occlusions, or high myopia. The presumably steroid-induced CSC cases (steroid use within 3 months prior to CSC diagnosis) were not excluded from analysis.

The cohort of severe cCSC was genetically compared to a cohort of 272 Caucasian patients with non-severe cCSC, who had a history of persistent disease but did not have any of the 4 previously mentioned characteristics of severity. Additionally, severe cCSC was compared to 135 Caucasian patients with aCSC, defined as a combination of: 1. Documented serous...
SRF accumulation on OCT; 2. A single focal leakage point on FA; 3. Atrophic RPE alterations limited to less than one DD in size. The control group included Caucasian individuals enrolled in the European Genetic Database (EUGENDA; www.eugenda.org), in whom no signs of macular disease were found on multimodal imaging, and 176 subjects included in the blood bank of the Radboud University Medical Center. Approval for this study was obtained at the local institutional review boards in all participating centers, and the study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to blood collection for genetic analysis.

**Single nucleotide polymorphism genotyping**

DNA was isolated from peripheral blood by using standard procedures. The most relevant genetic variants to be analyzed were chosen based on findings in earlier genetic studies in CSC, and included the following variants: \textit{ARMS2} (rs10490924), \textit{CFH} (rs800292, rs1061170, rs1065489, rs1329428, rs2284664, rs3753394), and \textit{NR3C2} (rs2070951), and copy number variations in the \textit{C4B} gene. KASP assays (LGC Genomics; Berlin, Germany) were used for SNP genotyping, as described previously and according to manufacturer’s instructions. A 7900HT Fast Real-Time PCR system (Applied Biosystems by Life Technologies, Austin, TX, USA) was used to read out the genotyping data. Data analysis was performed with SDS (version 2.4, Applied Biosystems). A TaqMan genotyping assay (Hs07226350_cn, Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA) with RNaseP as a reference assay was used to measure C4B gene copy numbers, as described previously.

**Statistical analysis**

The allele frequency of the SNPs in severe cCSC patients was compared to either unaffected controls, non-severe cCSC, or aCSC using a 2-sided Pearson’s Chi-square test (IBM SPSS Statistics, version 22, SPSS Inc., Chicago, IL, USA). The C4B copy numbers distribution was compared with a 2-sided Fisher’s exact test. Additionally, a logistic model correcting for gender was designed and two copies of \textit{C4B} were set as a reference. \textit{P}-values $<0.0056$ were considered statistically significant after a Bonferroni correction for multiple testing for 9 variants. Haplotype analysis correcting for gender was performed to assess the combined effect of the selected six variants in \textit{CFH} using R (R Core Team, v3.0.2) with the haplo.stats package (v1.7.7). As a reference, the two most frequent haplotypes were used in the haplo.glm command to determine odds ratios (ORs) for the haplotypes with a frequency $>5\%$, and the aggregate of the haplotypes with a frequency $<5\%$.

**RESULTS**

In the present study, we included 173 patients with severe cCSC (mean age: 54 $\pm$ 10 years, 151 (87\%) males), 272 patients with non-severe cCSC (mean age: 51 $\pm$ 10 years, 216 (79\%) males), and 135 patients with aCSC (mean age: 47 $\pm$ 10 years, 92 (68\%) males). The demographic characteristics are summarized in Table 1.
Comparing genetic risk factors in different CSC phenotypes

### Table 1 Demographic characteristics of the study population and controls per tested gene

<table>
<thead>
<tr>
<th></th>
<th>Severe cCSC</th>
<th>Non-severe cCSC</th>
<th>aCSC</th>
<th>Controls ARMS2 &amp; CFH</th>
<th>Controls C4B</th>
<th>Controls NR3C2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>173</td>
<td>272</td>
<td>135</td>
<td>826</td>
<td>250</td>
<td>1385</td>
</tr>
<tr>
<td>Number of males</td>
<td>151 (87%)</td>
<td>216 (79%)</td>
<td>92 (68%)</td>
<td>424 (51%)</td>
<td>198 (79%)</td>
<td>635 (46%)</td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
<td>54 ± 10</td>
<td>51 ± 10</td>
<td>47 ± 10</td>
<td>64 ± 12</td>
<td>51 ± 10</td>
<td>51 ± 10</td>
</tr>
</tbody>
</table>

*ARMS2 = age-related maculopathy susceptibility 2; CFH = complement factor H; C4B = complement component 4; NR3C2 = nuclear receptor subfamily 3 group C member 2.*

### Association with SNPs in the ARMS2, NR3C2, and CFH genes

No significant association was found with the rs10490924 variant in ARMS2 gene, nor with the rs2070951 variant in the NR3C2 gene in the severe cCSC group after correction for multiple testing (Table 2). Also, no difference was observed in allele frequencies of these tested variants when comparing severe cCSC with non-severe cCSC or aCSC (Table 3). An association could be found in six tested variants in the CFH gene in the severe cCSC group (Table 2). Associations of five CFH variants remained significant after correction for multiple testing: rs800292 \( (P = 0.0014, \text{OR} = 1.93 [95\% \text{CI} = 1.51-2.47]) \), rs1065489 \( (P = 2.22 \times 10^{-4}, \text{OR} = 0.49 [95\% \text{CI} = 0.34-0.72]) \), rs1329428 \( (P = 0.001, \text{OR} = 1.89 [95\% \text{CI} = 1.49-2.40]) \), rs2284664 \( (P = 1.21 \times 10^{-4}, \text{OR} = 1.65 [95\% \text{CI} = 1.28-2.13]) \), rs3753394 \( (P = 6.10 \times 10^{-4}, \text{OR} = 0.61 [95\% \text{CI} = 0.46-0.81]) \). No difference was observed when comparing allele frequencies of the six tested variants in the CFH gene between severe cCSC and either non-severe cCSC or aCSC (Table 3).

### Association with CFH haplotypes

Five haplotypes in the CFH gene with a frequency above 5% and an aggregate of the haplotypes with a frequency lower than 5% were identified. When using the most common haplotype (H1) as a reference and correcting for gender, severe cCSC showed an association with H2, H3, H4, H5, and the low frequency aggregated haplotypes (Table 4). However, only H2 remained significant after correction for multiple testing, which was risk carrying for severe cCSC \( (P = 0.001, \text{OR} = 1.73 [95\% \text{CI} = 1.24-2.41]) \), Table 4). Using the H2 haplotype as a reference, H1 and H3 were both associated with severe cCSC after correction for multiple testing, carrying a protective effect \( (P = 0.0013, \text{OR} = 0.58 [95\% \text{CI} = 0.41-0.81]) \) and \( P = 4.14 \times 10^{-6}, \text{OR} = 0.30 [95\% \text{CI} = 0.18-0.50] \), respectively) (Table 4). When comparing the haplotype frequencies of severe cCSC to this frequencies in non-severe cCSC and aCSC, no significant differences were found after correction for multiple testing (Table 5 and Table 6).
<table>
<thead>
<tr>
<th>Single nucleotide polymorphism (locus)</th>
<th>Alleles in controls (major/ minor)</th>
<th>Severe cCSC (n)</th>
<th>MAF in severe cCSC</th>
<th>Controls (n)</th>
<th>MAF among controls</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10490924 (ARMS2)</td>
<td>G/T</td>
<td>171</td>
<td>0.187</td>
<td>812</td>
<td>0.217</td>
<td>0.214</td>
<td>0.83 (0.62-1.11)</td>
</tr>
<tr>
<td>rs2070951 (NR3C2)</td>
<td>C/G</td>
<td>172</td>
<td>0.494</td>
<td>1385</td>
<td>0.468</td>
<td>0.350</td>
<td>1.11 (0.89-1.39)</td>
</tr>
<tr>
<td>rs800292 (CFH)</td>
<td>G/A</td>
<td>172</td>
<td>0.372</td>
<td>798</td>
<td>0.235</td>
<td>0.0014*</td>
<td>1.93 (1.51-2.47)</td>
</tr>
<tr>
<td>rs1061170 (CFH)</td>
<td>T/C</td>
<td>172</td>
<td>0.282</td>
<td>803</td>
<td>0.353</td>
<td>0.012</td>
<td>0.72 (0.56-0.93)</td>
</tr>
<tr>
<td>rs1065489 (CFH)</td>
<td>G/T</td>
<td>172</td>
<td>0.096</td>
<td>794</td>
<td>0.177</td>
<td>2.22 × 10^-4*</td>
<td>0.49 (0.34-0.72)</td>
</tr>
<tr>
<td>rs1329428 (CFH)</td>
<td>C/T</td>
<td>171</td>
<td>0.588</td>
<td>787</td>
<td>0.429</td>
<td>0.0010*</td>
<td>1.89 (1.49-2.40)</td>
</tr>
<tr>
<td>rs2284664 (CFH)</td>
<td>C/T</td>
<td>171</td>
<td>0.316</td>
<td>805</td>
<td>0.219</td>
<td>1.21 × 10^-4*</td>
<td>1.65 (1.28-2.13)</td>
</tr>
<tr>
<td>rs3753394 (CFH)</td>
<td>C/T</td>
<td>171</td>
<td>0.202</td>
<td>800</td>
<td>0.293</td>
<td>6.10 × 10^-4*</td>
<td>0.61 (0.46-0.81)</td>
</tr>
</tbody>
</table>

* 2-sided $P < 0.00556$ was considered significant after correction for multiple testing.

ARMS2 = *age-related maculopathy susceptibility 2*; CFH = *complement factor H*; MAF = minor allele frequency; NR3C2 = *nuclear receptor subfamily 3 group C member 2*.
Table 3 Comparison of allele frequencies in severe cCSC versus non-severe cCSC, and aCSC

<table>
<thead>
<tr>
<th>SNPs (locus)</th>
<th>Group 1*</th>
<th>Group 2†</th>
<th>Group 3‡</th>
<th>Group 2 vs 1</th>
<th>Group 3 vs 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe cCSC MAF (n)</td>
<td>Non-severe cCSC (n)</td>
<td>MAF</td>
<td>aCSC (n)</td>
<td>MAF</td>
</tr>
<tr>
<td>rs10490924 (ARMS2)</td>
<td>171</td>
<td>0.187</td>
<td>243</td>
<td>0.193</td>
<td>132</td>
</tr>
<tr>
<td>rs2070951 (NR3C2)</td>
<td>172</td>
<td>0.494</td>
<td>269</td>
<td>0.520</td>
<td>132</td>
</tr>
<tr>
<td>rs800292 (CFH)</td>
<td>172</td>
<td>0.372</td>
<td>245</td>
<td>0.296</td>
<td>133</td>
</tr>
<tr>
<td>rs1061170 (CFH)</td>
<td>172</td>
<td>0.282</td>
<td>245</td>
<td>0.320</td>
<td>133</td>
</tr>
<tr>
<td>rs1065489 (CFH)</td>
<td>172</td>
<td>0.096</td>
<td>244</td>
<td>0.133</td>
<td>134</td>
</tr>
<tr>
<td>rs1329428 (CFH)</td>
<td>171</td>
<td>0.588</td>
<td>244</td>
<td>0.510</td>
<td>133</td>
</tr>
<tr>
<td>rs2284664 (CFH)</td>
<td>171</td>
<td>0.316</td>
<td>244</td>
<td>0.275</td>
<td>134</td>
</tr>
<tr>
<td>rs3753394 (CFH)</td>
<td>171</td>
<td>0.202</td>
<td>242</td>
<td>0.273</td>
<td>131</td>
</tr>
</tbody>
</table>

* Group 1: severe chronic central serous chorioretinopathy; † Group 2: non-severe chronic central serous chorioretinopathy; ‡ Group 3: acute central serous chorioretinopathy.

2-sided P <0.00556 was considered significant after correction for multiple testing.

ARMS2 = age-related maculopathy susceptibility 2; CFH = complement factor H; MAF = minor allele frequency; NR3C2 = nuclear receptor subfamily 3 group C member 2.
**Table 4** Complement factor H haplotypes in severe cCSC

<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>Variants</th>
<th>HF among controls</th>
<th>HF among severe cCSC</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>C G C C C G</td>
<td>0.329</td>
<td>0.255</td>
<td>Base</td>
<td>Base</td>
<td>1.25 x 10^{-3}*</td>
<td>0.58 (0.41-0.81)</td>
</tr>
<tr>
<td>H2</td>
<td>C A T T T G</td>
<td>0.209</td>
<td>0.300</td>
<td>0.0013*</td>
<td>1.73 (1.24-2.41)</td>
<td>Base</td>
<td>Base</td>
</tr>
<tr>
<td>H3</td>
<td>T G T C C T</td>
<td>0.158</td>
<td>0.065</td>
<td>0.012</td>
<td>0.52 (0.31-0.87)</td>
<td>4.14 x 10^{-6}*</td>
<td>0.30 (0.18-0.50)</td>
</tr>
<tr>
<td>H4</td>
<td>C G T C T G</td>
<td>0.133</td>
<td>0.164</td>
<td>0.030</td>
<td>1.57 (1.05-2.35)</td>
<td>0.615</td>
<td>0.90 (0.61-1.34)</td>
</tr>
<tr>
<td>H5</td>
<td>T G T C T G</td>
<td>0.072</td>
<td>0.094</td>
<td>0.011</td>
<td>1.91 (1.16-3.15)</td>
<td>0.697</td>
<td>1.10 (0.67-1.82)</td>
</tr>
<tr>
<td>Rare</td>
<td>* * * * * *</td>
<td>0.098</td>
<td>0.122</td>
<td>0.028</td>
<td>1.65 (1.06-2.57)</td>
<td>0.829</td>
<td>0.95 (0.61-1.49)</td>
</tr>
</tbody>
</table>

* * P < 0.0083 was considered significant after correction for multiple testing.  
HF = haplotype frequency; MAF = minor allele frequency.
Table 5 *Complement factor H* haplotypes in non-severe cCSC versus severe cCSC

<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>Variants</th>
<th>HF among non-severe cCSC</th>
<th>HF among severe cCSC</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>C G C C C G</td>
<td>0.301</td>
<td>0.255</td>
<td>Base</td>
<td>Unadjusted</td>
<td>0.170</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>allelic P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2</td>
<td>C A T T T G</td>
<td>0.262</td>
<td>0.300</td>
<td>0.170</td>
<td>1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Base</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H3</td>
<td>T G T C C T</td>
<td>0.104</td>
<td>0.065</td>
<td>0.216</td>
<td>0.69</td>
<td>0.034</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.38-1.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H4</td>
<td>C G T C T G</td>
<td>0.111</td>
<td>0.164</td>
<td>0.038</td>
<td>1.66</td>
<td>0.302</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.03-2.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H5</td>
<td>T G T C T G</td>
<td>0.115</td>
<td>0.094</td>
<td>0.897</td>
<td>0.97</td>
<td>0.034</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.59-1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>* * * * * *</td>
<td>0.108</td>
<td>0.122</td>
<td>0.281</td>
<td>1.32</td>
<td>0.946</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.8-2.17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P* < 0.0083 was considered significant after correction for multiple testing. HF = haplotype frequency; MAF = minor allele frequency.
<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>Variants</th>
<th>HF among aCSC</th>
<th>HF among severe cCSC</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
<th>Unadjusted allelic P</th>
<th>Allelic odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>C G C C C C G</td>
<td>0.249</td>
<td>0.255</td>
<td>0.690</td>
<td>1.10</td>
<td>Base</td>
<td>Base</td>
</tr>
<tr>
<td>H2</td>
<td>C A T T T G</td>
<td>0.272</td>
<td>0.300</td>
<td>Base</td>
<td>Base</td>
<td>0.690</td>
<td>0.91</td>
</tr>
<tr>
<td>H3</td>
<td>T G T C C T</td>
<td>0.102</td>
<td>0.065</td>
<td>0.110</td>
<td>0.60</td>
<td>0.608</td>
<td>0.55</td>
</tr>
<tr>
<td>H4</td>
<td>C G T C T G</td>
<td>0.164</td>
<td>0.164</td>
<td>0.940</td>
<td>0.98</td>
<td>0.683</td>
<td>0.89</td>
</tr>
<tr>
<td>H5</td>
<td>T G T C T G</td>
<td>0.114</td>
<td>0.094</td>
<td>0.628</td>
<td>1.91</td>
<td>0.435</td>
<td>0.79</td>
</tr>
<tr>
<td>Rare</td>
<td>* * * * * *</td>
<td>0.100</td>
<td>0.122</td>
<td>0.677</td>
<td>1.14</td>
<td>0.903</td>
<td>1.04</td>
</tr>
</tbody>
</table>

P < 0.0083 was considered significant after correction for multiple testing.

HF = haplotype frequency; MAF = minor allele frequency.
Comparing genetic risk factors in different CSC phenotypes

**C4B copy number determination**

The distribution of \( C4B \) copy numbers was significantly different in severe cCSC compared to controls after correction for multiple testing \( (P = 0.0020) \) (Figure 2). A logistic regression model showed that carrying three \( C4B \) copies was protective for severe cCSC \( (P = 0.001, \text{OR} = 0.29 \ [95\%\text{CI} = 0.14-0.61]) \) (Table 7). The distribution of \( C4B \) copy numbers was not significantly different between severe cCSC, non-severe cCSC, and aCSC groups (Figure 2). In addition, the overall logistic regression model for effect size was not significant when comparing severe cCSC with non-severe cCSC \( (P = 0.665) \), or when comparing severe cCSC with aCSC \( (P = 0.551) \) (Table 8 and Table 9).

### Table 7 Logistic regression model for \( C4B \) load in severe cCSC patients

<table>
<thead>
<tr>
<th>Overall significance model ( P = 0.007 )</th>
<th>Controls ( (n = 250) )</th>
<th>Severe cCSC ( (n = 164) )</th>
<th>( P )</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>198 (79%)</td>
<td>143 (87%)</td>
<td>0.010</td>
<td>0.48 (0.27-0.84)</td>
</tr>
</tbody>
</table>

**C4B copy number**

| 0 | 6 (2.4%) | 4 (2%) | 0.781 | 0.83 (0.23-3.04) |
| 1 | 55 (22%) | 51 (31%) | 0.225 | 1.33 (0.84-2.12) |
| 2 | 142 (57%) | 99 (60%) | Base | Base |
| 3 | 44 (18%) | 10 (6%) | \( \textbf{0.001}^* \) | 0.29 (0.14-0.61) |
| 4 | 3 (1.2%) | 0 | 0.999 | NA |

* \( P <0.0055 \) was considered significant after correction for multiple testing.

\( \text{cCSC} = \text{chronic central serous chorioretinopathy; CI = confidence interval; } C4B = \text{complement component 4; } NA = \text{not annotated.} \)

### Table 8 Logistic regression model for \( C4B \) load in severe versus non-severe cCSC

<table>
<thead>
<tr>
<th>Overall significance model ( P = 0.665 )</th>
<th>Non-severe cCSC ( (n = 220) )</th>
<th>Severe cCSC ( (n = 164) )</th>
<th>( P )</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>216 (79%)</td>
<td>143 (87%)</td>
<td>( \textbf{0.043} )</td>
<td>0.56 (0.32-0.98)</td>
</tr>
</tbody>
</table>

**C4B copy number**

| 0 | 12 (5.4%) | 4 (2%) | 0.131 | 0.41 (0.13-1.31) |
| 1 | 66 (30%) | 51 (31%) | 0.878 | 0.97 (0.61-1.52) |
| 2 | 126 (57%) | 99 (60%) | Base | Base |
| 3 | 15 (6.8%) | 10 (6%) | 0.678 | 0.83 (0.36-1.95) |
| 4 | 1 (0.4%) | 0 | 1 | NA |

\( P <0.0055 \) was considered significant after correction for multiple testing.

\( C4B = \text{complement component 4; } NA = \text{not annotated.} \)
Figure 2. Distribution of C4B copy numbers among severe chronic central serous chorioretinopathy (cCSC), non-severe cCSC, acute CSC (aCSC), and controls.
Table 9 Logistic regression model for C4B load in severe cCSC versus aCSC

<table>
<thead>
<tr>
<th></th>
<th>aCSC (n = 133)</th>
<th>Severe cCSC (n = 164)</th>
<th>P</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>91 (68%)</td>
<td>143 (87%)</td>
<td>1.26 x 10^{-4}</td>
<td>0.32 (0.17-0.57)</td>
</tr>
<tr>
<td>C4B copy number</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (3.0%)</td>
<td>4 (2%)</td>
<td>0.622</td>
<td>0.70 (0.17-2.90)</td>
</tr>
<tr>
<td>1</td>
<td>32 (24%)</td>
<td>51 (31%)</td>
<td>0.194</td>
<td>1.43 (0.83-2.46)</td>
</tr>
<tr>
<td>2</td>
<td>90 (68%)</td>
<td>99 (60%)</td>
<td>Base</td>
<td>Base</td>
</tr>
<tr>
<td>3</td>
<td>7 (5.2%)</td>
<td>10 (6%)</td>
<td>0.794</td>
<td>1.15 (0.41-3.20)</td>
</tr>
</tbody>
</table>

P < 0.0055 was considered significant after correction for multiple testing.

C4B = complement component 4; NA = not annotated.

DISCUSSION

There is a wide variety in clinical presentation of CSC, ranging from aCSC to severe chronic CSC, and it is unclear whether these subgroups are different with regard to pathogenesis and genetic background. In the present study, we analyzed specific genetic risk factors in severe cCSC patients and compared them to non-severe cCSC and aCSC patients. Our data showed that in patients with severe cCSC, three variants (rs800292, rs1329428, and rs2284664) in the CFH gene were significantly associated with an increased risk of the disease, while two variants (rs1065489 and rs3753394) were protective. Also, having three copies of the C4B gene was protective against severe cCSC. However, no differences were identified between severe, non-severe and acute CSC phenotypes.

A comparison of the genetic associations in the three phenotypic subgroups indicated similar risk and protective profiles in the CFH gene variants, CFH haplotypes, and C4B gene copy numbers. Interestingly, although the groups were not significantly different, the genetic effect size, in terms of protective or risk-conferring odds ratios, was systematically larger in the severe cCSC subgroup compared to non-severe cCSC and aCSC. This was also true when comparing the genetic effect size of CFH variants rs800292, rs1329428, and rs1065489 in severe cCSC with cCSC patients in literature. Severe cCSC may therefore have a stronger genetic predisposition than milder CSC subtypes. Our findings indicate that there is a significant overlap in the known genetic risk factors and therefore likely also pathophysiological overlap between CSC subtypes, despite clinical differences.

A role for the complement system, and the CFH gene in particular, in the pathogenesis of CSC was suggested previously based on genetic association studies. Our present study confirms this association in all three CSC phenotypic subtypes. As the choroid and choriocapillaris play a central role in the pathogenesis of CSC, while complement activity
Chapter 3.2 is abundant in choroidal tissue, complement system dysregulation may be a key factor in CSC disease mechanism. A range of variants in genes involved in the complement system have also been identified in age-related macular degeneration. In contrast to age-related macular degeneration, no systemic complement abnormalities were found in a relatively small group of cCSC patients. Local complement system effects may be more important in CSC, rather than systemic complement system abnormalities. However, larger studies on systemic complement differences in cCSC patients are necessary.

CSC patients share certain clinical characteristics with age-related macular degeneration, such as macular fluid leakage and RPE abnormalities, as well as possible complication of choroidal neovascularization, but there are also clear differences such as an earlier age at onset, an absence of drusen, the presence of pachychoroid, and association with steroid use. The \( \text{CFH} \) variants reported in this study appear to have opposite effects in CSC compared to age-related macular degeneration, which may point to a different role of the complement system in the pathophysiology of these diseases as suggested before. In our current cohorts, we could not replicate the associations with the \( \text{ARMS2} \) gene and \( \text{NR3C2} \) gene variants as demonstrated previously. This lack of a significant association may be explained by the smaller sample size of the subgroups.

In the present study, a possible role of other, currently unknown, genetic variants cannot be excluded. Other factors may have a more prominent role than genetic factors in determining the course and severity of the disease. Daruich et al. suggested that older age (>40 years), presence of high (>50 µm) RPE detachments, and a thickened (>500 µm) choroid are significantly correlated with a prolonged episode of aCSC. Long-term steroid use has been suggested not only to increase the risk of CSC but also to cause a more severe bilateral chronic disease with multiple RPE leaking sites, more extended areas of RPE atrophy, and even bullous retinal detachments. Piccolino et al. have shown that presence of posterior cystoid retinal degeneration, which was considered a sign of severity in our study, is specifically associated with steroid use, longer duration of symptoms and subretinal fibrin accumulation. Furthermore, severe cCSC presentations were previously described in pregnant women, and among certain ethnic groups. Our findings suggest that the profile of known genetic risk SNPs between phenotypically different CSC patients is similar, and therefore it is likely that other factors such as described above determine disease course and outcome.

In conclusion, associations between \( \text{CFH} \) genetic variants and \( \text{C4B} \) copy numbers and severe CSC were demonstrated, but no marked genetic differences were found between acute, non-severe, and severe chronic phenotypes of CSC in the tested variants. This study indicates that different phenotypes of CSC may not develop due to genetic predisposition, at least among the currently known CSC-associated \( \text{CFH} \) variants. Presumably, other non-genetic risk factors such as environmental factors, or currently unknown genetic variants may play a role in the clinical course of CSC. Future genetic and clinical studies in larger cohorts.
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may provide important clues about the different risk factors associated with CSC disease severity.

**Acknowledgments**

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**Conflict of interest**

The authors report no financial/conflicting interests in this work.
REFERENCES

Comparing genetic risk factors in different CSC phenotypes


CHAPTER 4
Efficacy of photodynamic therapy in CSC
CHAPTER 4.1

Efficacy of photodynamic therapy in steroid-associated chronic central serous chorioretinopathy: a case–control study

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Chapter 4.1

ABSTRACT

Purpose: To investigate whether patients who developed chronic central serous chorioretinopathy (cCSC) in association with corticosteroid treatment respond differently to photodynamic therapy (PDT) as compared to patients who have not used corticosteroids.

Methods: Clinical evaluation included visual acuity (VA), fundoscopy, optical coherence tomography (OCT), fluorescein and indocyanine green angiography. The main outcome measure was a complete resolution of subretinal fluid (SRF) on OCT after PDT.

Results: One hundred and twenty-three eyes (117 patients), including 35 steroid associated cases (29%), who received PDT treatment with reduced settings for active cCSC were included. Complete resolution of SRF on OCT was seen in 69% of the steroid-associated cases and in 50% of the controls after PDT treatment ($p = 0.062$). At the final follow-up moment, 74% of the cases had a complete resolution of SRF compared to 60% in the control group ($p = 0.142$). The VA at the first visit after therapy showed an increase in both groups (mean VA before treatment; cases: $69\pm14$ Early Treatment Diabetic Retinopathy Study (ETDRS) letters, controls: $74\pm13$ ETDRS letters, mean VA first visit after treatment; cases: $76\pm13$ ETDRS letters, controls: $75\pm13$ ETDRS letters). No significant differences were seen in response to PDT between the patients who continued corticosteroid treatment and those who ceased the use of corticosteroids.

Conclusions: Photodynamic therapy appears to be equally effective in patients suffering from steroid-associated cCSC as compared to patients with cCSC who do not use corticosteroids. Continuation of corticosteroids at the time of PDT treatment does not seem to adversely affect PDT response.
INTRODUCTION

Central serous chorioretinopathy (CSC) is a relatively common early onset eye disease, characterized by an accumulation of leaked serous fluid under the retina, causing a detachment of the neuroretina. This subretinal fluid (SRF) leakage results from dysfunction of the retinal pigment epithelium (RPE), presumably caused by choroidal congestion and thickening and hyperpermeability of the choroid.1-4

Two main subtypes can be distinguished: acute CSC and chronic CSC (cCSC).1-8 In acute CSC, patients manifest with sudden and marked vision loss, and acute CSC is characterized by a focal leakage spot seen on fluorescein angiography (FA) that indicates leakage at the level of the retinal pigment epithelium (RPE).1-10 In most patients with acute CSC, this SRF resolves spontaneously within 3 months with near-complete visual recovery.2,4

Compared to patients with acute CSC, patients with cCSC present at an older age, with a disease onset that is generally experienced as less sudden.7,8 Furthermore, cCSC generally shows a more diffuse and sometimes multifocal leakage pattern on FA and especially on indocyanine green angiography (ICGA), often with more widespread and irregular RPE changes associated with various degrees of low-grade leakage as compared to acute CSC.1-11 In contrast to acute CSC, the SRF accumulation in cCSC tends to persist for more than 3 months, although it can wax and wane multiple times.4-6 Additionally, ICGA characteristically demonstrates widespread hyperfluorescent areas of choroidal congestion and hyperpermeability, which are more extensive in cCSC than in acute CSC.1,9,12-14 These abnormalities mostly overlap with those seen on FA, but can also be present without any evidence of leakage on FA in cCSC.9

A persistent serous neuroretinal detachment in cCSC can cause progressive and irreversible photoreceptor damage.1-15,16 Therefore, it is common practice to treat these patients, although prospective multicenter randomized controlled trials on the optimal treatment are largely lacking. Currently, photodynamic laser therapy (PDT) is one of the most frequently used treatment modalities in cCSC, with reported anatomical success rates in retrospective studies ranging from 70–100%.17-20 This is a relatively broad range. Therefore, it is of clinical relevance to identify possible factors that could influence treatment success.

Although the exact mechanism by which CSC develops is largely unclear, several associations and risk factors have been described in the literature, such as male gender, stress, type A personality, pregnancy and the use of corticosteroids.21-23 In addition, genetic risk factors have recently been identified in CSC.24-26 In particular, the use of corticosteroids is one of the most prominent risk factors known in CSC, although the reported effect sizes vary (odds ratio: 2.4 and 10.3).23,27 Some patients report a clear association between the initiation of corticosteroids and the start of CSC-associated visual complaints. This could indicate possible differences in the disease mechanisms between steroid users and non-
steroid users. The previous or ongoing use of corticosteroids is likewise thought to be a risk factor for ongoing disease activity in cCSC and could potentially limit the efficacy of treatment.

In studies on PDT as treatment for cCSC, the use of corticosteroids is often an exclusion criterion; therefore, it is unclear whether the outcome of PDT in cCSC is different compared to patients who have no history of current or previous corticosteroid use.

The aim of this study was to investigate whether the response to PDT is different in treatment-naive patients presenting with steroid-associated cCSC versus cCSC patients without a history of steroid use.

**PATIENTS AND METHODS**

**Patients**

The patients enrolled for this retrospective case–control study were seen at the outpatient clinics of the Departments of Ophthalmology of the Radboud University Medical Center (Nijmegen, the Netherlands) and the Leiden University Medical Center (Leiden, the Netherlands) between January 2004 and February 2015. We retrospectively reviewed the medical records of all patients who had been diagnosed with cCSC and who consequently had been treated with PDT as first-line therapy. The diagnosis of cCSC was based on characteristic features as seen on multimodal imaging consisting of optical coherence tomography (OCT), FA and ICGA. These features included presence of SRF in the macula on OCT, and irregular diffuse and/or multifocal hyperfluorescent areas in the posterior pole, corresponding to irregular RPE window defects with or without obvious hot spots of leakage on FA, with one or more corresponding hyperfluorescent areas on ICGA (Fig. 1). Approval for this study was obtained at the local institutional review boards, and the study adhered to the tenets of the Declaration of Helsinki.
Figure 1. Examples of the typical abnormalities as observed on multimodal imaging techniques [left to right; fundus autofluorescence (FAF), early fluorescein angiography (FA), mid-phase indocyanine green angiography (ICGA) and optical coherence tomography (OCT)] in three patients with chronic central serous chorioretinopathy (cCSC). The images in the upper two rows belong to two patients with steroid-associated cCSC. (A–D) The right eye of a 45-year-old male bodybuilder with frequent steroid injections, illustrating juxtafoveal hyperautofluorescent irregularities of the retinal pigment epithelium (RPE) layer on FAF(A), multifocal leakage on FA and ICGA (B-C), and subfoveal subretinal fluid (SRF) on OCT(D). (E–H) The left eye of a 48-year-old male who used topical steroid cream for skin problems. The FAF shows hyperautofluorescence inferotemporal of the optic disc (E), and hot spots indicating leakage are seen on FA and ICGA accompanied by SRF on OCT (F–H). (I–L) The right eye of 56-year-old male who did not report the use of corticosteroids. FAF shows central hyperautofluorescence corresponding to hyperfluorescent leakage on FA and ICGA (I–K), and a flat SRF accumulation on OCT(L).

At the visit prior to the PDT, at the first evaluation visit after therapy and at the last available follow-up visit, the following parameters were collected: visual acuity (VA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, start date of visual symptoms, the use of corticosteroids (including reason for use and route of administration), presence of SRF on OCT and central retinal thickness (CRT) as measured automatically by the integrated software of the Spectralis TM RA+OCT (Heidelberg Engineering, Heidelberg, Germany). Due to a satisfying response to treatment, only the first evaluation visit was available in a part of the cases and controls. If the first evaluation visit after treatment was also the last available follow-up visit, the collected information was only used in the analysis for the first evaluation visit. An exception was made for the absence of SRF at final follow-up.
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**Steroid use**
Patients were divided into two groups based on their reported use of corticosteroids: patients who used corticosteroids within 12 months prior to the development of the cCSC (cases) and patients who did not have a history of current or prior use of any type of corticosteroids controls). For the first group, only patients in whom a relation between steroid use and the onset of CSC symptoms was highly suspected were included. This probability of a causal relationship was assessed by the treating physician at the moment of diagnosis.

For subanalysis in the cases, a further distinction was made between patients who continued steroid use in the period when PDT had been performed and those who ceased corticosteroid use before treatment.

**Photodynamic therapy**
For this study, PDT treatment was performed with reduced settings, either with half-dose or half-time as compared to the original settings described for neovascular age-related macular degeneration, depending on the preference of the treating physician (Liu et al. 2014; Tsai & Hsieh 2014). Before treatment, the pupils were dilated (with 1.0% tropicamide and 2.5% phenylephrine). Verteporfin [Visudyne®; 3 mg/m2 (for the half-dose PDT) and 6 mg/m2 (for the half-time PDT)] was intravenously administered, with an infusion time of 10 min. At 15 min after the start of the infusion, an anesthetic eye drop was applied (oxybuprocaine 0.4% or equivalent), a contact lens (Volk® PDT lens) was positioned on the affected eye, and a laser beam was focused on the area to treat of which the spot size was based on hyperfluorescence as seen on mid-phase (approximately 10 min) ICGA. The PDT was performed with standard 50 J/cm² fluency, a PDT laser wavelength of 689 nm and a treatment duration of 83 seconds in patients treated with half-dose PDT and 42 seconds in the half-time PDT.

**Definition of the outcomes**
Effectiveness of the PDT was based on the anatomical recovery as seen on OCT, defined as a complete absence of SRF. Furthermore, we compared the VA and the CRT before and after treatment in each patient and between the (sub)groups. Additionally, we analyzed the period of time needed to achieve a complete resolution of SRF between the cases and controls. To evaluate the effectiveness of PDT over time, we analyzed the number of recurrences and also the number of additional treatments that each patient received until the end of the study.

**Statistical analysis**
Statistical analyses were performed using IBM SPSS software for Windows version 20. For comparisons of continuous numerical data in demographic characteristics and study outcome measures, we performed a dependent t-test, an independent t-test or a Mann–Whitney U-test as appropriate. Categorical data were analyzed using a chi-square test.
Furthermore, two survival analyses were performed and Kaplan–Meier survival plots were generated comparing the cases with the controls. The following events were used: ‘complete resolution of SRF after one PDT treatment’ and ‘complete resolution of SRF at final follow-up’. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Demographics
Thirty-five eyes of 33 patients (mean age at time of PDT treatment: 55 ± 11.7 years) with corticosteroid-associated cCSC and 88 eyes of 84 patients (mean age at time of PDT treatment: 52 ± 11.1 years) who did not report any use of corticosteroids were included in this study (Table 1). General characteristics including age, gender, reported duration of complaints, elapsed time between treatment and first control visit, baseline VA and mean CRT as measured on OCT at baseline did not differ significantly between the steroid users and the non-steroid users (Table 1).

Table 1 Patient demographics in cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes (patients)</td>
<td>35 (33)</td>
<td>88 (84)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>24/11</td>
<td>72/16</td>
<td>0.109</td>
</tr>
<tr>
<td>Age [range] in years</td>
<td>54.6 [31-80]</td>
<td>52.0 [29-81]</td>
<td>0.285</td>
</tr>
<tr>
<td>VA pre-therapy in ETDRS letters (SD)</td>
<td>69 (14)</td>
<td>74 (13)</td>
<td>0.065</td>
</tr>
<tr>
<td>CRT before therapy (SD)</td>
<td>381.3μm (111)</td>
<td>374.9μm (116)</td>
<td>0.782</td>
</tr>
<tr>
<td>Duration of complaints in weeks [range]</td>
<td>38.8 [3.1-706.9]</td>
<td>30.3 [3.7-566.0]</td>
<td>0.445</td>
</tr>
<tr>
<td>Half-dose PDT / Half-time PDT</td>
<td>30 / 5</td>
<td>82 / 6</td>
<td>0.190</td>
</tr>
</tbody>
</table>

a Age at the time of photodynamic therapy treatment
b Median number of weeks between the start of the complaints and therapeutic intervention

ETDRS; Early Treatment Diabetic Retinopathy Study, PDT; Photodynamic Therapy, SD; Standard Deviation, VA; Visual Acuity

Among the 33 patients with reported (previous) use of corticosteroids, nine patients (27%) used corticosteroid cream, nine patients (27%) reported nasal spray containing corticosteroids, seven patients (21%) used oral corticosteroids, four patients (12%) used corticosteroids by an inhaler, one patient (3%) received illegal corticosteroid injections for professional bodybuilding, and the remaining three patients (9%) reported (previous) use of corticosteroids via more than one way of administration.
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The corticosteroid use was continued before, during and after PDT treatment in 16 of 35 eyes (46%).

Optical coherence tomography
At the first control visit after PDT (on average 7.4 ± 2.8 weeks after treatment in the cases, and 7.9 ± 2.9 weeks after treatment in the controls), 22 eyes (63%) of the patients with steroid associated cCSC and 40 eyes (45%) of the controls showed a complete absence of SRF on OCT. Moreover, a clear reduction in SRF was seen in 26% (n = 9) of the steroid-associated patients and in 28% (n = 25) of the non-steroid associated controls. During follow-up, this reduction led to a complete absence of SRF in two of these cases (22%) and in four eyes (16%) of these controls. In three of 35 steroid-associated eyes (9%) with cCSC, and 17 of the 88 eyes (19%) of controls with cCSC, no changes in SRF were observed on OCT at the first control visit. One eye with steroid associated cCSC (3%) and six eyes (7%) in the control group showed an increase in SRF.

When comparing the resolution of SRF using a survival analysis, there was a trend for subjects in the corticosteroid associated cCSC group to have a faster complete resolution of SRF as compared to the controls (Fig. 2). A reduction in CRT was seen in both groups at the first and final follow-up after treatment (Table 2). There was no significant difference in the mean reduction in CRT between both groups at final follow-up [steroid users (n = 21); 114.1 ± 143.9 µm, non-steroid users (n = 46); 109.4 ± 109.7 µm, p = 0.883, independent t-test].

Table 2 Comparison of variables of interest at visit pre- and post-photodynamic therapy in cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT pre-therapy in µm (SD)</td>
<td>381.1 (111) (n=35)</td>
<td>374.9 (116) (n=88)</td>
<td>0.782</td>
</tr>
<tr>
<td>CRT at first follow-up a in µm (SD)</td>
<td>290.9 (121) (n=35)</td>
<td>282.4 (81) (n=88)</td>
<td>0.655</td>
</tr>
<tr>
<td>CRT at final follow-up b in µm (SD)</td>
<td>289.4 (114) (n=21)</td>
<td>261.7 (54) (n=46)</td>
<td>0.298</td>
</tr>
<tr>
<td>VA pre-therapy in ETDRS letters (SD)</td>
<td>69 (14) (n=35)</td>
<td>74 (13) (n=88)</td>
<td>0.665</td>
</tr>
<tr>
<td>VA at first follow-up in ETDRS letters a (SD)</td>
<td>76 (13) (n=35)</td>
<td>75 (13) (n=88)</td>
<td>0.499</td>
</tr>
<tr>
<td>VA at final follow-up in ETDRS letters b (SD)</td>
<td>72 (18) (n=21)</td>
<td>71 (14) (n=45)</td>
<td>0.943</td>
</tr>
</tbody>
</table>

a Average number of weeks between therapeutic intervention and first follow-up in the steroid group: 7.4 weeks, in the non-steroid group: 7.9 weeks (p = 0.445)

b Average number of weeks between therapeutic intervention and final follow-up in the steroid group: 48.4 weeks, in the non-steroid group: 49.6 weeks (p = 0.886)

CRT; Central Retinal Thickness, ETDRS; Early Treatment of Diabetic Retinopathy Study, SD; Standard Deviation, VA; Visual Acuity
Figure 2. Kaplan–Meier curves showing the cumulative fraction in treated patients with chronic central serous chorioretinopathy. A. End-point: 'Full resolution of subretinal fluid (SRF) after 1 photodynamic therapy'; median duration before SRF fully resolved in cases: 8.9 weeks [95% CI: 6.4–11.3] and controls: 10.0 weeks [95% CI: 5.2–14.8] (p = 0.064). B. End-point: 'Complete resolution of SRF at final follow-up'; median duration before SRF fully resolved in cases: 31.7 weeks [95% CI: 18.6–44.8] and controls: 36.8 weeks [95% CI: 25.5–48.2] (p = 0.344). PDT= photodynamic therapy.
During follow-up, a recurrence of SRF on OCT was seen in six of the 24 patients (25%) with steroid-associated cCSC and in nine of the 44 patients (20%) with non-steroid-associated cCSC who initially showed a good response (absence of SRF on OCT) after PDT.

At the final visit (on average 48.4 ± 31.4 weeks post-therapy in cases, and 49.6 ± 49.7 weeks post-therapy in controls), SRF had completely resolved in 26 of 35 eyes (74%) with steroid-associated cCSC, of which five eyes (19%) had received additional treatments that consisted of either a second PDT, conventional laser therapy of the hot spot, high-density subthreshold micropulse laser treatment, intravitreal bevacizumab or a combination of the aforementioned treatments [mean number of additional treatments; 1.8 (range 1–3)]. In the control group, 53 eyes (60%) had complete absence of SRF at final follow-up. Of these eyes, 18 eyes (34%) received additional treatment consisting of either a second PDT treatment, high-density subthreshold micropulse laser treatment, intravitreal bevacizumab, intravitreal aflibercept or a combination of the aforementioned treatments [mean number of additional treatments; 1.7 (range 1–4)].

Of the eyes with SRF on OCT at the last available visit [nine eyes (26%) in the steroid-associated cases and 35 eyes (40%) in the controls], 18 eyes received additional treatment [two eyes (22%) in the cases and 16 eyes (46%) in the controls].

**Patients with suspected neovascularization**

In both groups, a subretinal choroidal neovascularization (CNV) was suspected during follow-up in three eyes (9%) in the steroid-associated cCSC group, and four eyes (5%) in the controls, for which intravitreal antivascular growth factor treatment (anti-VEGF) was initiated. One of these patients initially responded well to the first PDT treatment with absence of SRF on OCT, followed by recurrence of the SRF. After anti-VEGF therapy, two eyes (29%) had complete resolution of SRF, and five eyes (71%) had persistent SRF. Re-evaluation of the baseline imaging showed small lesions on OCT, FA or ICGA that retrospectively could indicate a subtle pre-existent occult CNV or a small polypoidal choroidal vasculopathy (PCV) at baseline in four eyes (57%). The mean age of the seven patients suspected to have a CNV or PCV during follow-up was 64 years, which was significantly older as compared to the general group (mean age; 52 years, \( p = 0.006 \), independent t-test). None of these patients had evidence of drusen on ophthalmoscopy, OCT and FA.

**Visual acuity**

The mean VA increased significantly after PDT treatment in the steroid associated cCSC group when comparing the VA pre-PDT (69 ± 14 ETDRS letters) to the VA at the first control visit after treatment (76 ± 13 ETDRS letters, \( p < 0.001 \), independent t-test). This was also the case in the nonsteroid-associated patient group (VA before treatment; 74 ± 13 ETDRS letters, VA after treatment; 75 ± 13 ETDRS letters, \( p = 0.014 \), independent t-test).
At the last available visit, the mean VA was comparable between cases [72 ± 18 ETDRS letters (n = 21)] and controls [71 ± 14 ETDRS letters (n = 45)] (Table 2). Of those patients in the case group who showed a complete resolution of SRF (n = 24), the VA had improved significantly after the PDT (VA pre-PDT: 70 ± 15 ETDRS letters; VA post-PDT: 78 ± 13 ETDRS letters, \( p = 0.001 \)). This was also the case in control eyes with a complete SRF resolution (n = 44) after the PDT (VA pre-PDT: 72 ± 15 ETDRS letters; VA post-PDT: 78 ± 13 ETDRS letters, \( p = 0.001 \)).

No significant differences were found in treatment response on OCT and visual outcome when dividing the group of steroid users into a group of patients who continued the use of corticosteroids (oral, cutaneous creme, nasal spray, inhaler or a combination) during the study period (46% of 35 cases) and a group of patients who stopped the use of corticosteroids during therapy (54%) (Table 3). In particular, of the six eyes of five patients who continued the use of oral corticosteroids during the PDT treatment, four eyes (67%) showed a complete resolution of SRF on OCT after PDT treatment at last available visit.

Table 3 Comparison of central retinal thickness and visual acuity between patients who continued corticosteroid use during photodynamic therapy (PDT) and those who ceased corticosteroid treatment before PDT.

<table>
<thead>
<tr>
<th></th>
<th>Steroids were continued</th>
<th>Steroids were ceased</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT pre-therapy in µm (SD)</td>
<td>405.0 (98) (n=16)</td>
<td>361.0 (119) (n=19)</td>
<td>0.249</td>
</tr>
<tr>
<td>CRT at first follow-up (^a) (SD)</td>
<td>286.3 (103) (n=16)</td>
<td>294.7 (137) (n=19)</td>
<td>0.841</td>
</tr>
<tr>
<td>CRT at final follow-up (^b) (SD)</td>
<td>227.9 (107) (n=11)</td>
<td>203.1 (125) (n=10)</td>
<td>0.638</td>
</tr>
<tr>
<td>VA pre-therapy in ETDRS letters (SD)</td>
<td>66 (14) (n=16)</td>
<td>71 (14) (n=19)</td>
<td>0.285</td>
</tr>
<tr>
<td>VA at first follow-up in ETDRS letters (^a) (SD)</td>
<td>74 (14) (n=16)</td>
<td>78 (11) (n=19)</td>
<td>0.272</td>
</tr>
<tr>
<td>VA at final follow-up in ETDRS letters (^b) (SD)</td>
<td>69 (23) (n=11)</td>
<td>75 (12) (n=10)</td>
<td>0.434</td>
</tr>
</tbody>
</table>

\(^a\) Average number of weeks between therapeutic intervention and first follow-up in patients who continued corticosteroid treatment: 8.0 weeks, in patients who stopped corticosteroids: 6.9 weeks (\( p=0.265 \))

\(^b\) Average number of weeks between therapeutic intervention and final follow-up in patients who continued corticosteroid treatment: 23.6 weeks, in patients who stopped corticosteroids: 21.7 weeks (\( p=0.801 \))

CRT; Central Retinal Thickness, ETDRS; Early Treatment of Diabetic Retinopathy Study, SD; Standard Deviation, VA; Visual Acuity
DISCUSSION

This study suggests that the current or recent use of corticosteroids in cCSC does not adversely affect the response to PDT. No significant differences were seen between the corticosteroid-associated cCSC cases and the controls regarding the treatment response on OCT and on visual outcome.

Current literature reports an improvement of retinal anatomy and VA in 70–100% of cCSC after PDT treatment. The success rate of PDT treatment, defined as a complete absence of SRF on OCT, found in the present study is lower than reported in previous studies. A possible explanation could be that our study evaluated a phenotypically different patient group. Previous studies have differentiated acute and chronic CSC either based on the duration of presence of SRF or based on phenotypic characteristics. However, thus far no consensus exists on how to define chronicity in CSC. Where some authors consider duration of presence of SRF up to 2–3 months as typical for acute CSC, which implicates that if the SRF accumulation would exist longer than 3 months one can speak of a cCSC, others argue that CSC becomes chronic after a duration of more than 6 months. Also, division based on the extensity of abnormalities as seen on multimodal imaging has been described, and Wang et al. demonstrated that in case of a subretinal detachment of more than 4 months, irreversible atrophy in the macula may already ensue. Therefore, in the current study, patients with cCSC were included not only based on a disease duration of more than 3 months, but also on the presence of features indicative of chronicity on multimodal imaging: presence of SRF in the macula on OCT, and irregular diffuse and/or multifocal hyperfluorescent areas in the posterior pole, corresponding to irregular RPE window defects with or without obvious hot spots of leakage on FA, with one or more corresponding hyperfluorescent areas on ICGA. In contrast to acute CSC, patients with cCSC have (and often present with) more widespread abnormalities on multimodal imaging. Although the current study included cases who seemed to have a follow-up less than 3 months before receiving an intervention, all patients presented phenotypic features that confirmed chronicity. It is likely that the short follow-up time was caused by lack of information about the exact moment of onset of symptoms.

In our study, no differences were found in efficacy of PDT in patients with cCSC who ceased the corticosteroids in comparison with the patients who continued corticosteroids. Lee et al. previously found a treatment response with absence of SRF in 100% of the cases, using either full dose or half-time PDT, in a retrospective study of nine patients with steroid associated CSC. In this study, five of the nine patients discontinued the steroid use, which could be of influence on the response. The findings in our study are encouraging as they suggest that the continuation of corticosteroid treatment, if inevitable for other medical indications, does not preclude a favorable response to PDT. It is unclear through which pathophysiological mechanisms corticosteroid use is associated with cCSC. For instance, it is still unknown whether corticosteroids are required to develop cCSC in...
PDT treatment in steroid-associated cCSC

the first place or whether the use of corticosteroids is merely an additional trigger for a subclinical disease state that is already present. The use of corticosteroids is postulated to induce platelet aggregation and vasoconstriction and to suppress vasodilators (e.g. nitric oxide and prostaglandins). Consequently, this may lead to microthrombus formation, which may alter choroidal perfusion and vascular permeability. On the other hand, corticosteroids do not have the same effect in every patient; Han et al., for example, demonstrated that the choroidal thickening seen in steroid-induced CSC seems to be more an exceptional rather than a dose-dependent response that may be selectively present in vulnerable individuals. Choroidal congestion and hyperpermeability appear to be present in patients with cCSC using corticosteroids as well as in those who do not. Photodynamic therapy (PDT) may be an effective treatment in both patient subgroups as it is presumed to induce a remodeling of the choroidal vasculature, supposedly through selective vascular occlusion due to damage to choroidal endothelial cells and subsequent thrombotic events of the choriocapillaris that cause a decrease in choroidal thickness, a reduction in choroidal vascular hyperpermeability and leakage through the RPE, and a restoration in the fluid balance in the subretinal space. Photodynamic therapy (PDT) using standard settings (verteporfin dose of 6 mg/m2, fluency of 50 J/cm2, treatment time of 830 seconds) has been associated with adverse effects such as choroidal ischemia, RPE atrophy and CNV formation, although a 4-year follow-up study in cCSC has not found any adverse effects using this treatment in 46 eyes with cCSC. Photodynamic therapy (PDT) using reduced settings has commonly been adopted as this strategy appears to be equally effective and potentially safer compared to standard settings. However, retrospective evaluation of the baseline imaging in our study showed that of seven patients who were suspected to have a CNV or PCV during follow-up, four patients had small lesions that were suspect for CNV or PCV. These lesions, however, were very subtle and easily overlooked even by experienced ophthalmologists. In the remaining three patients, who had no suspect lesions at baseline, it remains unclear whether the PDT with reduced settings may have triggered further growth of a possible concealed small CNV. This would indicate that the CNV or the PCV could have been primarily associated with CSC-like changes before PDT was performed, as reported previously. Therefore, patients with cCSC should be monitored closely for possible occult CNV and/or PCV, especially elderly patient with a cCSC phenotype, and in case of non-response to PDT, the initial diagnosis should be reevaluated.

In conclusion, this study shows that PDT is an effective treatment in patients suffering from steroid-associated cCSC, and suggests that the efficacy is comparable to PDT in patients with cCSC who do not use corticosteroids. Although the pathophysiological mechanism may not be identical in both patient groups, it is not reflected in the overall treatment outcome of PDT. Therefore, PDT can also be offered as a treatment strategy in patients who are (or previously have been) on corticosteroid treatment.
Chapter 4.1

Acknowledgments

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Chapter 4.1


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Clinical spectrum of severe chronic central serous chorioretinopathy and outcome of photodynamic therapy

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ABSTRACT

Purpose: To describe a spectrum of severe chronic central serous chorioretinopathy (cCSC) cases and their response to photodynamic therapy (PDT).

Patients and methods: A total of 66 patients (81 eyes) with active severe cCSC were studied, and their response to PDT was compared to a control group consisting of 35 active cCSCs (37 eyes) that did not display characteristics of severity. Best-corrected visual acuity (BCVA) and complete resolution of subretinal fluid (SRF) were considered as main outcome measures.

Results: In severe cCSC cases we found cumulative areas of diffuse atrophic retinal pigment epithelium alterations in 48 eyes (59%), multiple “hot spots” of leakage in 36 eyes (44%), posterior cystoid retinal degeneration in 25 eyes (31%), and 13 eyes (16%) had a diffuse leakage on fluorescein angiography. After PDT treatment, BCVA increased in both groups, from 66 to 72 ETDRS letters in the case group (p < 0.001), and from 78 to 82 ETDRS letters in the control group (p < 0.001). SRF had resolved completely in 87% of severe cCSC cases and in 95% of controls at final follow-up visit.

Conclusions: A spectrum of severe cCSC exists, and PDT seems an effective treatment in both severe cCSC and non-severe cCSC in terms of resolution of SRF. Final BCVA shows a significant improvement in both groups after PDT treatment.
INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by an accumulation of serous fluid under the retina, often affecting the macula. The presence of subretinal fluid (SRF) is presumed to result from a dysfunctional choroid that is swollen and hyperpermeable, in association with a disturbance of the retinal pigment epithelium (RPE) that compromises the outer blood-retinal barrier. SRF accumulation causes a neuroretinal detachment with resulting photoreceptor dysfunction and vision loss. Other common abnormalities in CSC include RPE detachments, a variable degree in RPE atrophy, focal leakage (“hot spots”) or diffuse areas of fluorescein leakage through an RPE defect visualized with fluorescein angiography (FA). Indocyanine green angiography (ICGA) often shows more widespread choroidal abnormalities compared to those on FA, with leakage from a hyperpermeable, thickened and congested choroid. The use of corticosteroids, endogenous hypercortisolism, mental stress, and pregnancy have been suggested to be risk factors for the development of CSC. In addition, genetic protective and risk factors have been shown to be associated with CSC.

Two main subtypes of CSC are often distinguished. Patients with acute CSC (aCSC) typically present with sudden vision loss due to a focal leak in the RPE, without significant atrophic RPE changes, and show spontaneous resolution within weeks. In comparison with this aCSC phenotype, patients with chronic CSC (cCSC) tend to have prolonged subfoveal SRF accumulation, more atrophic RPE changes, and more diffuse and/or multifocal leakage on FA and ICGA. In contrast to the relatively favorable prognosis of aCSC, cCSC is typically not self-limiting and is associated with progressive visual loss and a decreased vision-related quality of life. Therefore, treatment is generally advocated in cCSC. Previously, multiple treatments have been suggested, including conventional thermal laser, subthreshold micropulse diode laser, photodynamic treatment (PDT), anti-vascular endothelial growth factor injection, and oral mineralocorticoid receptor antagonist agents. The PLACE trial, the first large prospective randomized controlled trial for cCSC, has shown that PDT with reduced settings seems to be the superior treatment option in terms of efficacy and safety. The extent of retinal abnormalities may vary strongly between cCSC cases. A significant subgroup of cCSC patients seems more severely affected and displays relatively large areas of RPE atrophy, multifocal areas of leakage on FA, posterior cystoid retinal degeneration (PCRD), and/or subretinal fibrin accumulation. Despite the clinical observation that cCSC includes a spectrum of severe disease characteristics, little is known about this clinical spectrum, its long-term visual prognosis, and treatment outcome in this subgroup. In this study, we hypothesized that those cCSC cases with the most severe phenotype may have a different disease course and a less favorable treatment outcome.

Here, we describe the clinical spectrum and outcome of PDT in a large group of cCSC patients with a severe clinical phenotype, and compare them with a cohort of cCSC cases that do not manifest those characteristics of presumed severity.
Chapter 4.2

METHODS

Patients
Approval for this study was obtained at the local institutional review boards in all participating centers, and the study adhered to the tenets of the Declaration of Helsinki. The cCSC patients included in this study were diagnosed and treated at the Department of Ophthalmology of Leiden University Medical Center (Leiden, the Netherlands), and the Rotterdam Eye Hospital (Rotterdam, the Netherlands). The diagnosis of cCSC was defined as presence of cCSC-related visual symptoms for more than 6 months, as well as the presence of chronic SRF on optical coherence tomography (OCT) for more than 3 months, RPE window defects on FA with at least 1 “hot spot” and/or diffuse leakage, and corresponding hyperfluorescent areas on ICGA when available. Chronic CSC patients were subsequently categorized as having a severe phenotype (cases) or a non-severe phenotype (controls).

Criteria of severity of cCSC
A cCSC phenotype was considered severe when at least one of the following clinical findings was observed at some point during the disease course: 1. Cumulative areas (larger than 5 optic disc diameters) of diffuse atrophic RPE alterations (DARA) as visualized on mid-phase FA (previously described as: diffuse retinal pigment epitheliopathy);20, 23 2. At least 2 “hot spots” of leakage separated by at least one disc diameter of non-hyperfluorescent healthy-appearing retina on mid-phase FA (multifocal “hot spots”); 3. An area of diffuse fluorescein leakage larger than one optic disc diameter on mid-phase FA, without an evident leaking focus (diffuse leakage); 4. Presence of posterior cystoid retinal degeneration (PCRD) assessed on OCT, as described previously.18, 19 The described abnormalities were considered relevant only when manifesting within the largest outer temporal vascular arcades. Patients were categorized as having a non-severe cCSC (controls) when none of the previously mentioned criteria of severity where present. We excluded patients with evidence of other retinal diagnoses, such as a history of exudative age-related macular degeneration, suspicion of secondary choroidal neovascularization, polypoidal choroidal vasculopathy, multifocal choroiditis, retinal vascular occlusions, pseudoxanthoma elasticum, amblyopia, and severe myopia (more than-6 diopters).

Clinical examinations
All patients underwent an extensive ophthalmological evaluation and multimodal imaging at diagnosis and during follow-up: Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) measurement (a previously published method was used to convert Snellen BCVA to ETDRS BCVA, when this was not available),24 slit lamp examination and/or color fundus photography (Topcon Corp; Tokyo, Japan, or Carl Zeiss Meditec; Dublin, CA, USA), either time-domain OCT (Cirrus HD-OCT; Carl Zeiss Meditec, or OCT-HS100; Canon Inc, Tokyo, Japan) or spectral-domain OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany), FA (Topcon Corp or Spectralis HRA+OCT, or Carl Zeiss Meditec), and ICGA (Topcon Corp or Spectralis HRA+OCT, or Carl Zeiss Meditec).
**Photodynamic therapy**

In this study, PDT treatment was performed with different reduced settings, based on the preference of the treating ophthalmologist. These settings included: half-dose (3 mg/m² verteporfin (Visudyne®, Novartis international AG, Basel, Switzerland)), or half-time (a treatment duration of 42 seconds), or half-fluence (25 J/cm²) compared to the original PDT settings described for neovascular age-related macular degeneration. PDT was performed with a standard PDT laser wavelength of 689 nm. All subjects in this study were treated when there was no spontaneous resolution of SRF. Here, we studied the effect of the first (initial) PDT treatment after manifestation of criteria of severity in the case group, and the first (initial) PDT treatment after diagnosis of cCSC in the control group.

**Definition of clinical outcome measures**

The primary outcome measures included post-PDT BCVA and final BCVA, as well as complete resolution of SRF as observed on OCT. For a longitudinal overview of the disease progression, relevant outcome measures were monitored at different moments throughout follow-up: at disease diagnosis, prior to the first PDT treatment, at the first visit after PDT treatment, and at final available follow-up visit. Information regarding the use of steroid-containing medication (through all possible modes of administration) and endogenous hypercortisolism was collected.

**Statistical analysis**

Statistical analysis was performed using IBM SPSS software for Windows, version 23 (IBM Corp, Armonk, NY, USA). Either a paired samples t-test or an unpaired t-test was used for continuous numerical data. Categorical data were analyzed using a Chi-square test. A survival analysis was performed and a Kaplan-Meier survival plot was generated comparing cases with controls in terms of resolution of SRF. The following event was used: the moment of complete resolution of SRF on OCT after initial PDT. A log-rank test was used to compare the period of time until this event was first documented among cases and controls. A univariate analysis was performed using Pearson’s correlation to evaluate the characteristics that associated with final visual outcome. A value of $p < 0.05$ was considered significant in all performed tests.

**RESULTS**

**Patient characteristics**

After retrospectively reviewing medical records of 650 CSC patients from the participating centers, 66 cCSC patients (81 eyes) were included in the case group who met the criteria of severity, and 35 cCSC patients (37 eyes) were included in the control group who did not exhibit any of the aforementioned severity criteria. An overview of patient characteristics is provided in Table 1. The distribution of the criteria of severity was as follows: 48 eyes (59%) showed DARA, 36 eyes (44%) showed multifocal “hot spots” (range: 2-6 “hot spots”),
25 eyes (31%) showed PCRD, and 13 eyes (16%) showed diffuse leakage on FA. Most cases (50 eyes, 62%) manifested multiple criteria of severity (Figure 1). All cases and controls were treated with PDT. However, only 63 eyes (78%) in the case group were treatment-naive before the studied PDT treatment was performed (Table 2). Moreover, 25 eyes among the cases (31%), and 6 eyes among the controls (16%) received additional treatments after initial PDT and before the final visit (Table 3).

Table 1 Demographic characteristics in severe chronic CSC patients (cases) and non-severe chronic CSC patients (controls)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (eyes)</td>
<td>66 (81)</td>
<td>35 (37)</td>
<td>n/a</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>69 (85)</td>
<td>28 (76)</td>
<td>0.210</td>
</tr>
<tr>
<td>Caucasian ethnicity, n (%)</td>
<td>72 (89)</td>
<td>27 (73)</td>
<td>0.029</td>
</tr>
<tr>
<td>Mean age at diagnosis in years (range)</td>
<td>49 (29-78)</td>
<td>47 (30-72)</td>
<td>0.243</td>
</tr>
<tr>
<td>Mean time from CSC diagnosis to final visit in years (range)</td>
<td>6 (0-30)</td>
<td>2 (0-7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subjects with recent use of steroids, n (%)</td>
<td>17b (21)</td>
<td>13 (35)</td>
<td>0.110</td>
</tr>
</tbody>
</table>

Notes: aWithin 3 months prior to the diagnosis. bOne patient was diagnosed with Cushing syndrome

Abbreviations: BCVA, best-corrected visual acuity; CSC, central serous chorioretinopathy; n/a, not applicable

Table 2 Treatment specifications in severe chronic CSC (cases) and non-severe chronic CSC (controls)

<table>
<thead>
<tr>
<th>PDT</th>
<th>Treatment characteristics</th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before study PDT treatment</td>
<td>Treatment-naive eyes (%)</td>
<td>63 (78)</td>
<td>37 (100)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Eyes with previous treatments (%)</td>
<td>9 (11)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>conventional thermal laser</td>
<td>4 (5)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>anti-VEGF injections a</td>
<td>1 (1)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>PDT</td>
<td>2 (2)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Regarding study PDT treatment</td>
<td>PDT settings (%)</td>
<td>72 (89)</td>
<td>31 (84)</td>
<td>0.454</td>
</tr>
<tr>
<td></td>
<td>half-dose</td>
<td>5 (0-234)</td>
<td>31 (3-354)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>half-time</td>
<td>7 (9)</td>
<td>5 (13)</td>
<td>half-time</td>
</tr>
<tr>
<td></td>
<td>half-fluence</td>
<td>2 (2)</td>
<td>1 (3)</td>
<td>unknown</td>
</tr>
</tbody>
</table>

Notes: a None of treated eyes had evidence of choroidal neovascularization, and injections were given before referral

Abbreviations: CSC: central serous chorioretinopathy; n/a: not applicable; PDT: photodynamic therapy; VEGF: vascular endothelial growth factor
Figure 1. Multimodal imaging of a 71-year-old male patient with severe bilateral chronic central serous chorioretinopathy (A-F: right eye, G-L: left eye). On color fundus photography, atrophic retinal pigment epithelial (RPE) alterations were seen in the inferotemporal quadrant of the left eye (G). Multifocal “hot spots” of leakage (H) and extensive areas of atrophy were seen on fluorescein angiography (B, H). Fundus autofluorescence showed large areas of hypo-autofluorescent and hyper-autofluorescent abnormalities corresponding to the RPE changes, extending to outside the macula (D, J). Indocyanine green angiography images (C, I) showed multifocal areas of diffuse choroidal abnormalities and leakage. Optical coherence tomography (OCT) revealed in both eyes epiretinal membrane and subretinal fluid centrally in the macula (E, K). Posterior cystoid retinal degeneration was seen in the outer nuclear layer of the nasal macula of the left eye (K). Ten weeks after half-dose photodynamic therapy which was only performed in the left eye, both subretinal fluid and posterior cystoid retinal degeneration had disappeared (L). The black arrows on the colour fundus photography images correspond to the scanning plane on the OCT scans (E, F, K, L).
**Table 3** Additional treatments after initial PDT in severe chronic CSC (cases) and non-severe chronic CSC (controls)

<table>
<thead>
<tr>
<th>Treatment characteristics</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of eyes that received additional treatments (%)</td>
<td>25(a) (31)</td>
<td>6(a) (7)</td>
</tr>
<tr>
<td>Number of eyes that received additional PDT treatments (%)</td>
<td>25(b) (100)</td>
<td>6(b) (100)</td>
</tr>
<tr>
<td>Number of eyes that received additional conventional laser (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Reason for additional treatment (%)</td>
<td>11 (44) recurrence of SRF 14 (56) insufficient response to PDT</td>
<td>1 (17) recurrence of SRF 5 (83) insufficient response to PDT</td>
</tr>
</tbody>
</table>

Notes: \(a\) Some eyes received more than one type of additional treatment; \(b\) Range of extra PDTS needed in cases: 1-2, and in controls: 1

Abbreviations: CSC: central serous chorioretinopathy; PDT: photodynamic therapy; SRF: subretinal fluid

**Best-corrected visual acuity**

Baseline BCVA before initial PDT was 66±19 ETDRS letters in cases, which was significantly lower in comparison with controls with 78±11 ETDRS letters \((p = 0.001)\). After initial PDT, BCVA increased significantly in comparison with the baseline to 72±18 ETDRS letters in cases \((p < 0.001)\), and to 82±9 ETDRS letters in controls \((p = 0.002)\) at first control visit (on average 7 weeks after initial PDT). The final available BCVA (on average 90 weeks after initial PDT) was 72±21 ETDRS letters in the case group and 82±11 ETDRS letters in the control group. Patients in the case group had a significantly lower BCVA at the final follow-up visit compared to the control group \((p = 0.001)\) (Table 4). A Pearson correlation analysis demonstrated that a statistically significant positive correlation existed between final BCVA outcome and the baseline BCVA before PDT \((r=0.8, p < 0.001)\). Other characteristics such as age, gender, Caucasian ethnicity, and the mean time from CSC diagnosis to final visit did not show any significant correlation with the final BCVA outcome.

**Resolution of subretinal and intraretinal fluid**

At the first visit after initial PDT, a complete SRF resolution was achieved in 56 eyes (70%) among cases and 28 eyes (78%) among controls \((p = 0.386)\). At final visit, SRF had resolved in 71 eyes (88%) among cases, and in 35 eyes (95%) among controls \((p = 0.247)\). When comparing the treatment-naive severe cases with the treatment-naive controls, a similar pattern was observed (Table 4). A survival analysis (event was defined as complete resolution of SRF) showed a moderate trend for subjects in the control group to attain a complete resolution of SRF faster (Figure 2). The estimated median duration to achieve complete resolution of SRF after treatment initiation in cases was 8 weeks [95% CI: 7-9], compared to 7 weeks in controls [95% CI: 7-8] \((p = 0.281)\). In the case group, PCRD was
observed in 25 eyes (31%). A complete resolution of PCRD after initial PDT was observed in 11 of these eyes (44%) at first visit (Figure 3). In 12 eyes (48%), PCRD was clearly reduced but not absent, and in 2 eyes (8%) PCRD remained unchanged after initial PDT. At final visit, on average after 96 weeks of follow-up, 13 eyes (52%) had persistent PCRD after previous PDT treatment.

Figure 2. Kaplan-Meier curve showing the cumulative fraction of patients treated for chronic central serous chorioretinopathy (cCSC). Endpoint: ‘Complete resolution of subretinal fluid (SRF) after photodynamic therapy’; the median duration to SRF resolution in cCSC patients with a severe phenotype of the disease (cases) was 8 weeks [95% CI: 7-9]. In cCSC patients who did not meet the criteria of severity (controls), the median duration was 7 weeks [95% CI: 7-8], (log-rank test, \( p = 0.281 \).
Figure 3. Clinical features on multimodal imaging of the right eye of a 63 year-old female patient with severe chronic central serous chorioretinopathy (A-C). Black arrow on color fundus photography image (A) showing the scanning plane which is depicted on the spectral-domain optical coherence tomography (SD-OCT) scans (D, E). B. Fundus autofluorescence imaging (FAF) shows multiple speckled hyper-autofluorescent changes in the macula together with an irregular surface of hypo-autofluorescence, expanding from the fovea to the superior and inferior vascular arcades. Fluorescein angiography imaging (C) revealed a limited area of fluorescein leakage with a clear central focus. The areas of hypofluorescence were located more temporal from the fovea, and were smaller than on FAF. An SD-OCT scan (D) at first presentation and prior to treatment revealed a subretinal serous fluid accumulation together with a posterior cystoid retinal degeneration in the outer nuclear layer of the retina. At approximately 2 months after half-dose photodynamic therapy, both subretinal fluid and intraretinal fluid on OCT had resolved completely (E).

Location of leakage sites in severe cCSC
The active leakage spots on FA in severe cCSC cases were located inside the largest hyperfluorescent and/or hypofluorescent area of RPE abnormalities in 57 eyes (70%). In 12 eyes (14%), the leakage was located on the edges of this largest region of RPE changes, and in 4 eyes (5%) the leakage came from outside the largest hyperfluorescent and/or hypofluorescent area of RPE changes. In 8 eyes (10%) of cases multiple locations of leakage were observed (Figure 4). In 3 cases (4%) of severe cCSC, hard exudates were seen on fundus photography without evidence of (neo)vascular abnormalities on FA and/or ICGA. These exudates resolved after a single PDT treatment in all cases. Geographic atrophy was not observed in any of the cCSC cases.
Figure 4. Four categories of eyes with severe chronic central serous chorioretinopathy with active fluorescein leakage on fluorescein angiography. This figure illustrates different fluorescein leakage locations (arrows) in relation to the largest area of diffuse atrophic retinal pigment epithelium (RPE) alterations (DARA, dotted line). A. Category 1 concerns a leakage point inside the largest area of RPE alterations. B. Category 2 concerns one or more leakage points located on the edges of the largest region of RPE alterations. C. In category 3, leakage points causing macular subretinal fluid are outside the largest zone of RPE alterations. D. Category 4 concerns cases with multifocal leakage points in several of the aforementioned locations in relation to the area of RPE alterations.
Table 4. Clinical outcome after PDT with reduced settings in severe chronic CSC (cases) and non-severe chronic CSC (controls)

<table>
<thead>
<tr>
<th>Clinical outcome measures</th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA before initial PDT in ETDRS letters ± SD</td>
<td>66 ± 19</td>
<td>78 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BCVA at first follow-up in ETDRS letters ± SD</td>
<td>72 ± 18</td>
<td>82 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BCVA at final follow-up in ETDRS letters ± SD</td>
<td>72 ± 21</td>
<td>82 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>Resolution of SRF at first follow-up, n (%)</td>
<td>56 (70)</td>
<td>28 (78)</td>
<td>0.386</td>
</tr>
<tr>
<td>Resolution of SRF at final follow-up, n (%)</td>
<td>71 (88)</td>
<td>35 (95)</td>
<td>0.247</td>
</tr>
<tr>
<td>Resolution of SRF in treatment-naive eyes at first follow-up, n (%)</td>
<td>43 (70)</td>
<td>28 (78)</td>
<td>0.368</td>
</tr>
<tr>
<td>Resolution of SRF in treatment-naive eyes at final follow-up, n (%)</td>
<td>55 (87)</td>
<td>35 (95)</td>
<td>0.241</td>
</tr>
<tr>
<td>Presence of PCRD before initial PDT, n (%)</td>
<td>25/81 (31)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Resolution of PCRD at first follow-up examination, n (%)</td>
<td>11/25 (44)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Resolution of PCRD at final follow-up examination, n (%)</td>
<td>13/25 (52)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Notes: 'The average time between initial PDT and first follow-up was 7 weeks. 'The average time between initial PDT and final follow-up was 90 weeks. 'Posterior cystoid retinal degeneration was only present in the case group.

Abbreviations: BCVA, best-corrected visual acuity; CSC, central serous chorioretinopathy; ETDRS, Early Treatment of Diabetic Retinopathy Study; n/a, not applicable, PCRD, posterior cystoid retinal degeneration; PDT, photodynamic therapy; SD, standard deviation; SRF, subretinal fluid

**DISCUSSION**

In this multicenter study of severe cCSC, PDT with reduced settings showed a similar therapeutic effect in comparison to a control group of non-severe cCSC with regard to resolution of SRF. Although visual acuity did increase after PDT, the final outcome was less favorable in the severe cCSC cases. This group also had a worse pretreatment baseline BCVA presumably due to a long-standing active disease. Therefore, an early PDT treatment may reduce the chance of an irreversible decline of visual acuity in severe cCSC.

In the present study, severely affected chronic CSCs and non-severe chronic CSCs showed mostly comparable baseline characteristics before PDT-treatment (Table 1). However, in severe cCSC the mean time from the first CSC diagnosis to the final visit was 4 years longer than in controls. This may reflect the referral pattern in more complex cCSC cases to a tertiary medical center, and the follow-up pattern in these cases. A longer follow-up duration was also described by Otsuka and co-workers in their study on 25 cCSC cases with a severe variant of the disease. The mean follow-up in this study was 10.6 years.25

Despite the fact that baseline BCVA was significantly lower in the present severe cCSC cohort compared to the controls, the post-PDT BCVA increased significantly compared to baseline in both cases and controls. However, this improvement was larger in the control group at short-term and long-term follow-up. Furthermore, we showed that a better
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baseline BCVA correlated significantly with a better final visual outcome. We postulate that pre-existing photoreceptor and RPE damage in severe cCSC may be the primary cause of suboptimal BCVA improvement after PDT. However, Loo and co-workers reported no association between reduced visual acuity and any degree of macular RPE atrophy, although they did not specify the surface of the studied RPE atrophy in their cohort.\textsuperscript{26} Balaratnasingam and co-workers described a cohort of 14 patients with a bullous retinal detachment variant of cCSC with diffuse hypo-autofluorescent and hyper-autofluorescent retinal abnormalities, descending tracts, and PCRD, which showed similarities with our severe cases, although we did not observe bullous retinal detachments. In contrast to our findings, these authors reported that the mean BCVA at baseline did not differ from final visit BCVA after various treatment strategies.\textsuperscript{27} Future prospective studies should analyze if other parameters besides low baseline BCVA are also predictive for visual outcome, such as microperimetry and chorioretinal imaging characteristics.

In our study, a complete resolution of SRF was achieved in 70\% of severe cases at the first follow-up visit after PDT treatment. Previous reports have found similar rates of 71-87\%, for a general cCSC population.\textsuperscript{28, 29} At final follow-up (on average 90 weeks after PDT), a complete resolution of SRF was seen in as much as 88\% of severe cCSC patients. This observation of SRF resolution was comparable to available literature for a general cCSC population.\textsuperscript{28-30} However, 31\% of our severe cases needed additional treatments, mostly a single additional PDT treatment, due to insufficient treatment effect or SRF recurrence. We found that PDT treatment could be effective even in patients with PCRD. In this study, PCRD resolved completely after initial PDT in 44\% of severe cCSC cases with PCRD. This proportion remained stable until the final follow-up, which is in contrast with findings in previous smaller studies. For instance, Silva and co-workers reported that 10 out of 46 cCSC patients in their study showed PCRD on OCT, and in this study a complete resolution of intraretinal fluid was reported after treatment with full-settings PDT in all of these cases after 4 years of follow-up.\textsuperscript{31} In our study, we did observe a trend of further decrease in number and volume of intraretinal cystoid fluid abnormalities during follow-up after PDT. However, this tendency did not lead to a higher rate of complete PCRD resolution at final follow-up.

The most prominent abnormalities in CSC are choroidal dysfunction, choroidal congestion and hyperpermeability of the choriocapillaris, which appear to be the primary underlying abnormalities in CSC. The combination of a dysfunctional RPE outer blood-retinal barrier, the insufficient RPE pump function, and a positive pressure gradient from the underlying leaking choroid appears to be a prerequisite for active SRF leakage in CSC.\textsuperscript{7, 32} However, it is unclear if the atrophic RPE changes and choroidopathy result from a common pathway.\textsuperscript{7} With regard to the diffuse atrophic RPE alterations, for which we propose to use the abbreviation DARA, it is unclear if these changes always result from chronic overlying SRF or if RPE atrophy can also develop directly from an underlying choroidal dysfunction that directly affects the adjacent RPE without the presence of overlying SRF. In our study,
DARA areas often did not correspond with the areas of “hot spot(s)” of SRF leakage on FA. We postulate that atrophic RPE changes in severe cCSC may not only occur in areas of prolonged SRF but can also gradually develop primarily as a result of a dysfunctional, leaky underlying pachychoroid.\textsuperscript{33}

Although it has been estimated that only 16\% of patients with acute CSC may gradually develop a chronic type of disease,\textsuperscript{34} the majority (73\%) of patients that develop a severe phenotype shows signs of chronicity at very first presentation.\textsuperscript{22} Therefore, a timely diagnosis and a proper treatment appears crucial, since chronic SRF leakage can cause irreversible damage to the neuroretina and RPE, leading to a severe and extensive disease phenotype with a resulting suboptimal vision-related quality of life.\textsuperscript{5, 6, 34} In the present study, we suggested a definition for severity by taking into account a spectrum of previously described retinal abnormalities including extensive areas of diffuse atrophic RPE alterations (DARA), multiple foci of recurrent leaking spots, and degenerative intraretinal cystoid abnormalities (PCRD) without evidence of choroidal neovascularization.\textsuperscript{18, 25, 35} There is currently no consensus on the definition of ‘extensive’ and ‘large’ areas of atrophic RPE abnormalities.\textsuperscript{2, 7} Therefore, we somewhat arbitrarily chose a cumulative area of 5 optic disc diameters of atrophic RPE changes in the macula to define DARA. The definition of DARA, and also the definition of multifocal “hot spots”, and diffuse leakage must be validated in future studies. Another limitation of the present study is the variety in PDT settings, although half-dose PDT was most frequently used (Table 4). As previous comparative studies have demonstrated that PDT with different reduced settings may be equally effective in treating CSC case, we may assume that the efficacy of PDT was not significantly affected by the specific PDT settings used, But further studies are needed to address this issue more thoroughly.\textsuperscript{36, 37}

**CONCLUSION**

This study has outlined the clinical spectrum of severe cCSC. It is currently unclear whether aCSC and the spectrum of cCSC manifestations, such as a severe phenotype described in this study, are part of a continuum with the same pathophysiological background, or if they are essentially different diseases. This study shows that patients with severe cCSC respond favorably to PDT treatment with regard to SRF resolution, and that pre-PDT baseline visual acuity is strongly associated with a final BCVA outcome. We therefore suggest that an early PDT treatment in patients with severe cCSC phenotypes may improve BCVA more effectively and may prevent further vision loss due to persistent SRF leakage.

**Ethics approval**

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical
PDT treatment in severe cCSC

standards. The local institutional review boards in all participating centers (‘Medisch Ethische Toetsingscommissie’ (METC) in Leiden University Medical Center, The METC in the Radboud University Medical Center, and the ‘Wetenschapscommissie’ in the Rotterdam Eye Hospital) did not require written consent from the participants for reviewing their medical records, as all data were anonymized upon collection.

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Disclosure

The authors report no conflicts of interest in this work. An abstract version of this manuscript was presented at the 2016 annual meeting of the Association for Research in Vision and Ophthalmology.
REFERENCES


Chapter 4.2

CHAPTER 5
General discussion
Although central serous chorioretinopathy (CSC) is the fourth most common cause of fluid leakage in the macula, after age related macular degeneration (AMD), diabetic macular edema, and branch retinal vein occlusion,1 our understanding of its pathophysiology, clinical spectrum and classification, and the best treatment strategy, is still subject of debate. In this thesis, we provide new clinical and genetic insights into this mysterious eye disease. Our aim was to delineate the broad clinical spectrum of CSC, to describe the clinical differences and the similarities within this phenotypic spectrum, to investigate the possible role of genetic factors within the clinical phenotypes, and to evaluate treatment outcomes within these subgroups.

5.1. CLINICAL SPECTRUM OF CSC

Clinical symptoms
The visual complaints in CSC patients are attributed to the disturbance of the visual cycle and photoreceptor dysfunction due to fluid leakage below the neurosensory retina in the macula. This macular subretinal fluid is caused by fluid leakage from congested and hyperpermeable blood vessels of the choroid to the subretinal space, through a damaged outer blood-retina barrier of the RPE.2-4 This process appears to lie at the basis of all CSC phenotypes. Thus far, CSC has been roughly classified in an acute or a chronic phenotype, although this classification and its definition has long been subject of controversy.1 Acute CSC (aCSC) has a sudden onset, often with a unilateral clinical presentation, and is associated with mild visual complaints including metamorphopsia, micropsia or macropsia, a disturbed perception of colors, or contrast sensitivity.5, 6 Visual acuity may be affected only mildly.7-9 The condition is self-limiting in many patients, although the disease may recur, often with no necessity for treatment, and has a favorable prognosis with (near-)complete visual recovery in many cases.10 In contrast, chronic CSC (cCSC) is a more severe phenotype with often an indolent and prolonged disease course that persists for months to years unless treated, and has a worse long-term prognosis.6, 11, 12 Disease severity and visual impairment is widely variable in cCSC cases, depending on the active disease duration, and the extent of chorioretinal damage.13

The underlying abnormal choroid
CSC, as the term suggests, is a disorder of the retina and the choroid, and is generally characterized by a strikingly thickened choroidal layer (pachychoroid), which is best observed on enhanced-depth imaging optical coherent tomography (EDI-OCT).14 The concept of pachychoroid as a thickened choroid with dysfunctional choroidal vasculature is of great importance in the understanding of the underlying pathophysiology of CSC.15, 16 Also, this concept helps to discriminate CSC from the broad spectrum of other conditions that are associated with serous fluid in the macula.17 Upon the identification of the phenomenon of pachychoroid, it was shown that a number of different diseases were associated with a "pachychoroid disease spectrum".15 Besides CSC, this spectrum includes additional entities
such as: pachychoroid pigment epitheliopathy (PPE), peripapillary pachychoroid syndrome (PPS), and pachychoroid neovasculopathy (PNV). Furthermore, PPE is suggested to be the ‘forme fruste’, or precursor of CSC, as all CSC patients show retinal pigment epithelium (RPE) alterations comparable to PPE cases.

The human choroid consists, from anterior to posterior, of the following structures: 1) Bruch’s membrane, which is a thin connective tissue layer located under the RPE; 2) the highly anastomosed and fenestrated vascular network called choriocapillaris, which forms the innermost part of the choroid; 3) the Sattler’s layer consisting of medium sized vessels which feed and drain the choriocapillaris; 4) the Haller’s layer of large vessels, and; 5) the suprachoroidal layer, which forms the transition zone between the choroid and sclera.

In the pachychoroid disease spectrum, besides a thickened choroid, other (presumably subsequent) changes to the choroidal anatomy can be observed including: choriocapillaris attenuation, pronounced Haller vein dilation (so-called pachyvessels with a large lumen), choroidal hyperpermeability on indocyanine angiography imaging, and strongly varying spatial differences in choroidal thickening. In CSC patients, thickened vessels in Haller’s layer with congested overlying capillaries and a thinned choriocapillaris are common features in all patients. Spaide and co-workers have postulated that the dilation of Haller’s layer vessels originates from ‘venous overload’, which is thought to be caused by abnormal venous outflow, presumably at the vortex veins. Brinks et al. have proposed that there may also be a role for abnormal arteriovenous anastomoses in causing these choroidal abnormalities and their consequences. Ultimately, these structural changes cause dysfunction of the RPE, thereby damaging the integrity of the outer blood-retina barrier formed by the RPE. The increased choroidal permeability may subsequently lead to a local elevation of the overlying RPE, and a subsequent serous RPE detachment. Sub-RPE serous fluid may break through the RPE and leak in the subretinal space, causing a serous neuroretinal detachment. This detachment of the neuroretina from the RPE disturbs the function of the most outer layer of the retina, the photoreceptor layer. The fluid in the subretinal space results in disturbance of normal photoreceptor-RPE interaction, and compromises photoreceptor dysfunction. Furthermore, a dysfunctional RPE-cell pump function fails to adequately remove subretinal fluid, causing persistence of the serous detachment. This condition continues until the choroidal congestion diminishes, the leakage through the RPE decreases or stops, restoring the equilibrium at the interface of the neuroretina, RPE-Bruch’s membrane and choroid.

Ongoing debate on definitions and classification
CSC is often roughly divided in aCSC and cCSC, although there is currently no consensus regarding the exact period of time after which CSC should be considered chronic. Some authors suggest that aCSC resolves spontaneously within 2-4 months, whereas others suggest a duration of 6 months. This time period clearly appears a grey area that is not strictly definable. The precise definition of disease onset is also unclear and might be
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proposed as either the onset of patient’s subjective complaints, or the objective diagnosis after ophthalmological examination and/or by imaging techniques (i.e. OCT).

Furthermore, despite what these terms may indicate, we show in Chapter 2.2 that cCSC is not necessarily preceded by an acute episode. A patient may present with widespread and multifocal areas of chorioretinal damage, consistent with a long-persisting (presumably subclinical) disease. In Chapter 2.3 we reported that the majority (73%) of patients that develop a severe disease phenotype show signs of chronicity, including RPE detachments, RPE atrophy, and/or multifocal hot spots or diffuse leakage on multimodal imaging, at the very first presentation. Previously, the term diffuse retinal pigment epitheliopathy (DRPE) was also used to address the condition of widespread chorioretinal abnormalities in CSC, independent of a clinically evident prior acute episode. 36,37

The current classification of acute versus chronic is also inadequate when based on clinical examination, for example when extensive chorioretinal abnormalities in absence of subretinal fluid are observed in the fellow non-symptomatic eye. For these reasons, classifying CSC remains problematic when merely based on the disease duration.

Alternative to the time frame used to differentiate acute from chronic CSC, others have suggested to use fundoscopic examination and retinal imaging techniques to distinguish between both disease entities, since there are remarkable differences between aCSC and cCSC (Chapter 1). These different clinical characteristics are crucial to discriminate aCSC with very limited chorioretinal abnormalities, from the chronic cases with large and multifocal areas of serous leakage, and chorioretinal atrophy. However, there is no consensus on the maximum extent of chorioretinal abnormalities (e.g., the number of leakage sites, or the area of chorioretinal atrophy) as a cut-off value in discriminating aCSC from cCSC.

Even when considering duration of disease and multimodal imaging characteristics combined, there remain situations where the present dual classification in acute and chronic phenotypes may be unsatisfactory. For instance, 43-51% of aCSCs, and 30-52% of cCSCs can have a recurrent disease course,38,39 and are often difficult to distinguish from each other, when only focusing on the recurrent character. This is because patients, both in aCSC and cCSC, can experience multiple consecutive episodes with variable disease-free intervals. It is also debatable how to classify a CSC case with subretinal fluid (SRF) present for over 4 months without other characteristics of chronicity on multimodal imaging such as extensive atrophic RPE changes. Should this be classified as an aCSC, a non-resolving CSC, or a cCSC case? Also, when the serous fluid leakage is outside the fovea, disease activity can be present for several months until it is finally noticed when the central macula becomes involved, while funduscopic examination may show signs of a chronic disease. Furthermore, while there are clearly overlapping clinical and pathophysiologic features within the spectrum of CSC, we show in Chapter 2 that cCSC is a non-homogenous
phenotype, that encompasses a wide spectrum of chorioretinal abnormalities. While some cCSCs present with atrophic RPE alterations limited to a small localized area adjacent to the focal leakage, other cases display multifocal and large atrophic RPE areas, covering almost the entire posterior pole, showing a bullous retinal detachment, or posterior cystoid macular degeneration. Still, there is no universal consensus on the definition of ‘extent’ or ‘severity’ of cCSC.

In this thesis, we suggested and utilized relatively strict definitions for CSC phenotypes, which, in our view, represents real-life clinical practice most accurately. In these definitions, characteristics on multimodal imaging, especially the cumulative area of RPE atrophy, were of greater influence for the classification than the disease duration until (spontaneous) SRF resolution. CSC was considered an acute episode when SRF presumably persisted no longer than 6 months, and when all of the following criteria were applicable: 1. documented presence of SRF on OCT; 2. only one area of focal leakage (“hot spot”) on fluorescein angiography (FA); 3. limited RPE alterations including RPE detachments of less than one optic disc diameter; and 4. Absence of any sings of other possible causes of SRF accumulation (e.g., choroidal neovascularization) (Chapter 2.1). CSC was considered chronic when cCSC-related visual symptoms were present for more than 6 months, in the presence of chronic SRF on OCT for more than 3 months, RPE alterations including RPE detachments of larger than one optic disc diameter with at least 1 “hot spot” and/or diffuse leakage on FA, and corresponding hyperfluorescent areas on indocyanine angiography (ICGA) when available.

cCSC patients were further subcategorized as having a ‘severe’ or a ‘non-severe’ cCSC. A chronic case was considered non-severe when symptoms were present for 6 months, or when SRF was detected on OCT for more than 3 consecutive months, together with FA and ICGA changes as described above. A chronic case was considered severe when at least one of the following abnormalities was present: 1. a cumulative area of >5 optic disc diameters of diffuse atrophic RPE alterations (DARA) as visualized on mid-phase FA; 2. at least 2 “hot spots” of leakage on mid-phase FA (multifocal “hot spots”); 3. an area of diffuse fluorescein leakage larger than one disk diameter on mid-phase FA, without an evident leaking focus; 4. presence of posterior cystoid retinal degeneration (PCRD) assessed on OCT (Chapter 2.2).

We realize that our definitions are subject to limitations as some phenotypes of CSC cannot be categorized using the suggested definitions. For instance, CSC with prolonged leakage but without extensive RPE alterations cannot be categorized as aCSC, severe, or non-severe cCSC. Also, the suggested terms in the definition of severe cCSC including: DARA, multifocal hot spots, and diffuse fluorescein leakage are somewhat arbitrarily chosen. However, we did so in order to distinguish retinal phenotypes that are differentiated in daily clinical practice, ranging from a mild CSC phenotype without significant visual consequences, to a potentially blinding disease, and to facilitate reproducibility. Future research must establish the validity of the chosen criteria of severity.
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The large variety in the clinical presentation of CSC, as also illustrated in this thesis, results in a remarkable disagreement in CSC classification among the experts. Recently, an international expert panel introduced a diagnostic flow chart in an attempt to cover almost all phenotypes of CSC, by using clinical findings identifiable on OCT, FA, ICGA, and fundus autofluorescence (FAF). In this method, two major criteria (both must be present) and three minor criteria (at least one must be present) were used to classify CSC. The major criteria include: 1. presence or evidence of prior SRF documented on OCT in posterior pole; and 2. more than one area of RPE alteration on OCT, FAF, or infrared imaging. The minor criteria include: 1. mid-phase hyperfluorescent placoid areas on ICGA; 2. more than one focal leak on FA; and 3. subfoveal choroidal thickness larger than 400 µm. By applying these criteria, CSC could be classified as simple or complex, and subdivided further in 3 groups of primary, recurrent, or resolved CSC. So far, this nomenclature system seems most comprehensive compared to previous classification (acute / chronic). A recent cross-sectional study, which was performed to validate this classification by assessing the level of agreement among international retina experts, reported a fair-moderate intergrader agreement in classifying CSC using this new nomenclature system. The auteurs also emphasized on the necessity of availability of both affected and fellow eyes information in the process of classification.

Reasons to differentiate phenotypes

Recognizing specific landmarks in the clinical presentation of CSC phenotypes is important not only for an accurate diagnosis, but also to gain better insight into potential differences in the natural history, vision prognosis, and treatment outcome in different phenotypes within the spectrum of CSC. Chhablani and coworkers assessed the agreement rate in diagnosis of CSC phenotypes in an international group of retina specialists, and illustrated the variety in physicians’ phenotype assessment, as well as preferences for treatment. The authors observed a high discordance among retina specialists in describing CSC, and reported as many as thirty-six different terms, which were used by experienced retina specialists to categorize CSC patients. With regard to treatment, the authors reported that 79% of the retina specialists preferred a wait-and-see strategy for aCSC. In cCSC cases, 67% offered photodynamic therapy as first line treatment. Many physicians consider treatment only when a CSC patient develops (or presents with) chronic disease. The decision to treat may also be influenced by the severity of visual symptoms and the impact on the patient’s daily working life (i.e. pilots, truck drivers), the experience of the treating physician, and the accessibility of different treatment methods. Therefore, a systematic classification for CSC may help in comparing studies and objectify treatment outcome in order to come to a global treatment guideline.

In terms of disease prognosis, current literature suggests that visual symptoms in aCSC can recover completely in 3-6 months. In Chapter 2.1, we reported our findings in a well-defined cohort of typical aCSC patients, and showed that all cases had a complete resolution of SRF, of which 52% spontaneously, and 48% after early treatment, mostly
PDT with reduced settings. An important finding was that recurrent risk was significantly lower in the early treated aCSC cases, as will be discussed later on. The final best corrected visual acuity (BCVA) in this cohort was as high as 86 ETDRS (Early Treatment of Diabetic Retinopathy Study) letters. Other authors have shown that up to 50% of aCSC patients may have multiple disease recurrences of variable duration, which may or may not recover spontaneously. In our aCSC cohort we observed a recurrence rate of 29%, which could be partly explained by the early treatment policy in a large portion of cases, as will be discussed in the following paragraphs.

Visual impairment in cCSC is generally more severe compared to aCSC patients, and may occasionally even lead to legal blindness. In addition, cCSC patients have a worse vision-related quality of life. We observed a similar pattern among all cCSC patients reviewed in our studies. The cCSC cases that were phenotypically classified as non-severe showed an average visual acuity of 78 ETDRS letters at baseline (Chapter 4.2). The severe cases of cCSC showed the worst baseline BCVA of 66 ETDRS letters prior to treatment (Chapter 4.2). Finally, baseline BCVA in a subgroup of steroid-associated cCSC patient was 69 ETDRS letters (Chapter 4.1). In our criteria to differentiate between severe and non-severe cCSC however, BCVA was not taken into consideration. The concept of disease severity remains subject of debate and our definitions, although established by a group of experienced CSC specialists, are to a certain degree subjective, also given the marked international variability in CSC phenotype interpretation and classification.

A more in-depth CSC classification may also allow for better decision making on whether or not to treat CSC, and if so, when, and how to treat. Recent initiatives attempt to achieve more uniformity in such classification. To date, when a clinician establishes the diagnosis of aCSC, spontaneous resolution of SRF is often awaited during follow-up ranging from 6 weeks to 6 months. When there is no spontaneous resolution, treatment is often considered to prevent (further) vision loss. However, an early treatment may be desirable also in aCSC because even a short period of SRF accumulation may cause damage to retinal photoreceptors, and also to attempt to reduce the risk of disease recurrence, as we have shown in Chapter 2.1. Two relatively small randomized controlled trials indicated that early treatment with PDT may result in a significantly higher percentage of SRF resolution, and also a faster SRF resolution in aCSC, as compared to a wait-and-see strategy. However, while one trial reported an improvement of visual outcome in the treated group, in the other trial the final visual outcome was similar between the different groups. In this thesis, we confirmed in a large retrospective cohort of well-defined aCSC cases that SRF resolution occurred significantly faster after early treatment of aCSC (Chapter 2.1). Interestingly, we also found that there was a significantly lower rate of SRF recurrence in the aCSC patients who were treated early, mostly with PDT, as compared to untreated cases (4% vs. 24%, respectively). Although the final visual outcome was not significantly different between the two groups, recurrences of SRF may repeatably affect photoreceptors and eventually lead to progressive and irreversible vision loss. Also,
there may be circumstances in which fast visual recovery is desirable, taking for instance patient preference, socioeconomic impact and professional visual requirements (e.g. pilots and bus drivers) into account. Therefore, a wait-and-see policy in aCSC may not always be the best option.

SRF leakage lasting for more than 4 months has been associated with retinal atrophic changes and irreversible visual loss. Therefore, treatment may thus be required in order to prevent further retinal damage and vision loss in cCSC cases with persistent SRF, or in cases when spontaneous resolution is not expected, for instance when a patient has a history of severe vision loss in an earlier disease episode. However, there is currently no universally accepted treatment for the spectrum of CSC phenotypes, despite large retrospective studies and a number of large prospective randomized trials (the PLACE, REPLACE, VICI, SPECTRA, and SPECS trials). The VICI trial, an investigator-initiated prospective trial from United Kingdom, showed that oral eplerenone treatment was not an effective treatment in cCSC as compared to placebo. Our research group showed in the SPECTRA trial that half-dose PDT was markedly superior over oral eplerenone. Finally, in the PLACE trial half-dose PDT was proven to be markedly superior over high-density subthreshold micropulse laser treatment. Therefore, PDT is increasingly considered the first choice treatment in cCSC.

In this thesis, we specifically looked at the outcome of PDT in phenotypic subgroups of CSC, including aCSC (Chapter 2.1), non-severe cCSC (Chapter 4.2), severe cCSC (Chapters 2.2, 2.3, 4.2), and steroid-associated CSC (Chapter 4.1). We confirmed that PDT treatment resulted in anatomical recovery (complete SRF resolution) in all of these CSC groups, with corresponding improvement in BCVA. A proper and timely treatment of cCSC, and possibly aCSC, aimed at a complete resolution of SRF, will improve the prognosis, or at least prevent further visual decline.

The CSC spectrum: a continuum or separate entities?
In spite of the differences in the clinical presentation of aCSC and cCSC, it is still unclear whether these diseases should be considered separate entities, or are closely related members of the same clinical spectrum. Patients with typical aCSC (focal leakage, few RPE abnormalities, spontaneous resolution) are generally young, while severe and complicated chronic cases are seen almost exclusively in patients above the age of 50 years. The mild and transient character of aCSC versus the recurrent and persistent character of cCSC may suggest that CSC starts as an acute disease which may show a recurrent clinical character due to certain risk factors, and in some cases end-up in a chronic condition. However, evidence for this theory is meagre, and so far no long-term study is available describing the transition of aCSC into cCSC. CSC cases with frequent disease recurrences and prolonged disease episodes show more similarities to the typical cCSC phenotype rather than the aCSC phenotype, and therefore may be seen as an intermediate stage toward a chronic disease. According to some reports, aCSC patients with a thicker choroid, a non-intense fluorescein
leakage on FA, a history of psychiatric illness, and a history of shift work (outside daylight hours 7 AM to 6/7 PM) are more prone to have disease recurrences.\textsuperscript{7, 51, 63} Furthermore, a longer aCSC episode duration has been associated with older age (above 40 years), the height of the RPE detachment (higher than 50 µm), and a thicker choroid (larger than 500 µm).\textsuperscript{9} In our large study in typical aCSCs patients, we found that SRF recurrence was only associated with younger age (Chapter 2.1). We also found a significant correlation between an increase in RPE alterations during follow-up in the affected aCSC eyes and the presence of RPE alterations in the unaffected contralateral eyes. This progression of RPE alterations could be interpreted as evidence of an evolution towards a more chronic disease process. Interestingly, the risk of SRF recurrence in our study was not correlated with these progressive RPE alterations as it might be expected (Chapter 2.1), despite follow-up of at least 12 months. Due to lack of convincing evidence, it is questionable if the CSC spectrum should be considered a continuum and that it is only a matter of time for its clinical transition, or if these diseases should, to certain extent, be considered different entities.

Some authors have proposed five categories, or stages, of CSC including: acute, non-resolving, recurrent, chronic, and inactive CSC.\textsuperscript{1, 6} However, these definitions are still subject to variable interpretation and have not been sufficiently validated.\textsuperscript{46} Others view CSC disease process as a gradient scale, suggesting that different clinical presentation follow one another, as mentioned in the previous paragraph. Chronic CSC can vary in presentation from mild but relatively persistent focal chorioretinal abnormalities,\textsuperscript{40} to extensive end-stage variants with extensive RPE atrophy (DARA) and PCRD, to even bullous retinal detachment, and many more variations in between.\textsuperscript{41, 43, 44} Pachychoroid pigment epitheliopathy (PPE), which is characterized by a certain degree of RPE alterations without (previous) SRF accumulation, has been suggested to be the ‘forme fruste’ precursor stage of CSC in all its forms.\textsuperscript{18} In general, RPE alterations are considered the common thread in CSC, which may vary from a single small RPE change or detachment to DARA in severe cCSC (see figure 3 in chapter 1). Nevertheless, there is currently no prospective study available which reports on a cohort of CSC patients undergoing these presumably consecutive disease stages; from an acute episode to a chronic end-stage, emphasizing the questionability of the clinical continuum of CSC.

In Chapter 2.1 we reviewed clinical characteristics in a large cohort of typical aCSCs with long-term follow-up in order to study the risk of CSC transition from aCSC to a chronic disease. In our study 36% of the affected eyes and 37% of the fellow eyes showed substantial increase in subclinical RPE alterations after at least 12 months follow-up. This subgroup of aCSC patients had a tendency toward chronic disease, in terms of progression of RPE alterations. In this sense, this subgroup of aCSC may be considered to be part of a CSC continuum. This clinical overlap, as well as the genetic overlap (see Chapter 5.2), indicates that aCSC and cCSC are generally part of the same disease spectrum. However, interestingly, none of the included aCSC patients developed chronic SRF leakage and all study eyes had a...
complete anatomical recovery on follow-up, although 52% spontaneously and 48% after an early treatment (Chapter 2.1). In a long-term follow-up study by Levine et al., patients with a history of typical aCSC and spontaneous resolution of SRF were asked to return for examination 7-12 years after the initial episode. After repeating FA imaging in this cohort, new areas of RPE alterations, and/or enlargement of old areas were observed in 43% of the previously affected eyes, and in 50% of the healthy (non-symptomatic) fellow-eyes. These data suggests a process of a gradual and subclinical progressive disease in a strikingly large group of aCSCs.

When observing CSC from the other end of the spectrum with a focus on chronic cases, we found that a transition pattern from aCSC to cCSC may be less obvious. In our study, we found that 14% of the severe cCSC patients started with a documented acute episode with limited or no RPE damage and spontaneous resolution of SRF, and eventually developed more widespread chorioretinal abnormalities. As a matter of fact, 73% of the included severe cCSC patients already presented with this extensive, severe phenotype at first presentation (Chapter 2.2). Previous reports suggest that merely 8-16% of cCSC has a documented history of aCSC. Otsuka and coworkers reported a higher percentage (36%) in a severe cCSC patient cohort to have initially presented with features of “classic” (i.e. idiopathic acute) CSC that developed multifocal RPE alterations and even inferior bullous retinal detachment 7 months to 9 years later.

Fortunately, only a minority of CSC patients has a severe form at first presentation. Chronic systemic corticosteroid use is currently the only reported factor to increase the risk of transition to a more extensive and presumably severe chronic disease form. However, the exact pathway leading to severe chronic disease, and its risk factors are still unknown. In the current thesis, we suggested a set of criteria to define disease severity, and to scrutinize severe cases in more detail (Chapter 2.2). Our retrospective case-series study was not designed to point out the risk factors for a severe cCSC development. However, we were able to report that a worse visual prognosis in a severe phenotype of cCSC was significantly associated with presence of PCRD, a large total area of DARA, and location of DARA with regard to the fovea (Chapter 2.2). Additionally, patients with poor baseline visual acuity were less likely to show vision improvement, even after successful treatment. Although these clinical characteristics predict only up to 47% of the variance in final visual outcome, they provide quantitative and qualitative parameters for disease prognosis in clinical practice.

In summary, based on the findings in this thesis and current literature, we postulate that there is an overlap in the clinical presentation in different CSC phenotypes, and that no fundamental and etiological differences may exist, except for the period of time needed for CSC to deteriorate. However, most aCSC patients do not develop chronic disease. Conversely, the majority of severe cCSC cases already present with this severe phenotype at first presentation. Therefore, there are still uncertainties around the notion of CSC as a disease
continuum. For instance, why does only a small subgroup of the – generally relatively benign – aCSC patients develop a vision-threatening chronic disease, and which risk factors play a role in this transition? And why do some patients already have a severe cCSC phenotype, sometimes even with choroidal neovascularization (CNV), at presentation? One clue may lie in the potential of gradual, smoldering development of atrophic RPE changes in association with an underlying abnormal pachychoroid (pachychoroid pigment epitheliopathy). Future prospective clinical and experimental studies may shed light on whether these subgroups are definitely members of the same spectrum, and which exact pathophysiological and prognostic factors play a role in determining in which part of the spectrum the patient ends up, and also whether treatment may influence this.

5.2. Genetics characteristics of CSC phenotypes

Although CSC is not assumed to be a monogenetically heritable disease, previous pedigree analyses observed a familial pattern, which may support the involvement of genetic risk factors. Recent candidate gene approach studies and genome-wide association studies, many from the Netherlands but also from Asia, have reported on the role of a number of genetic variants such as single nucleotide polymorphisms (SNPs) in CSC. Genetic risks in these investigations were generally studied in unspecified CSC, while some genetic studies only focused on cCSC. In this thesis, we were interested in the possible genetic risk factors in acute, non-severe chronic, and severe chronic CSC phenotypes, and whether there were differences in the genetic risk profile between these subgroups. Therefore, we studied the presence of different known CSC-associated SNPs in these subgroups. After all, significant differences in genetic risk factors between these subgroups could be a genetic indication of these seemingly different (or at least variable) forms of CSC to also be pathogenetically different. In contrast, if a similar genetic background would be found, this could suggest pathogenetic overlap between these CSC subgroups. For this purpose, we studied the effect of several SNPs known to be associated with CSC in the complement factor H (CFH) and complement component 4 (C4B) genes, which encode proteins associated with the complement system as a part of innate immunity. Also, the possible association of the age-related maculopathy susceptibility 2 (ARMS2) gene, which is thought to interact with the extracellular matrix at the level of the choroid and RPE, and the nuclear receptor subfamily three Group C member 2 (NR3C2) gene which encodes for the mineralocorticoid receptor, were studied (Chapters 3.1 and 3.2).

Genetic overlap between different phenotypes

Our genetic analysis in all three clinically well-defined CSC subgroups (aCSC, non-severe cCSC, and severe cCSC) showed a similar risk-conferring role of three SNPs in the CFH gene, as well as the protective effect of two other SNPs in this gene (Chapters 3.1 and 3.2). These findings on the role of the five currently associated SNPs in the CFH gene were in line with literature. However, despite the clear clinical differences between the three studied CSC phenotypes, no statistically significant differences were observed when comparing allele frequencies of these five SNPs in the three phenotypes. Our results also
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showed that having three or more copies of the $C4B$ gene protected against all three CSC phenotypes, which was also in accordance with the current literature. The distribution of $C4B$ copy numbers was not significantly different between acute, non-severe chronic, and severe chronic CSC cases. These findings of overlap of genetic risk factors appear to be an indication of pathophysiologic overlap between these CSC subgroups.

A range of variants in genes involved in the complement system have previously been identified in AMD. Involvement of similar genetic pathways in CSC is conceivable as CSC and AMD have similarities in certain clinical characteristics, such as macular fluid leakage and RPE abnormalities. Besides the similarities, there are considerable clinical differences between AMD and CSC as well, such as an absence of drusen in CSC, the prominent role of pachychoroid in CSC (whereas the choroid in AMD is usually normal-to-thin), steroid use as a risk factor for CSC, and younger age at disease onset in CSC. The proven association of the $CFH$ and $C4B$ genes in CSC patients suggest that complement system dysregulation may be a contributing factor in the CSC disease mechanism in a similar way as to AMD. However, in contrast to AMD, no systemic complement abnormalities are found in CSC patients. Interestingly, the aforementioned $CFH$ gene variants were shown to have opposite effects in CSC as compared with AMD, in terms of protection or a risk-conferring effect. This observation, which was also confirmed in this thesis (Chapters 3.1 and 3.2), could also indicate that the complement system may actually have decreased activity in CSC, in contrast to the increased activity in AMD. However, more studies are needed to further test this hypothesis.

One variant in the $ARMS2$ gene, which is a risk factor for AMD, was shown to be protective against the risk of cCSC. However, the studies on AMRS2 and cCSC did not make a distinction between severity in clinical presentation (non-severe and severe forms of cCSC) such as in the research described in this thesis. Although the mechanism of action of this gene is not fully understood, it may be related to the potential interaction of the ARMS2 protein with the extracellular matrix at the level of the choroid and RPE, the sites that are also primarily affected in CSC. However, in our current studies this protective effect of the $ARMS2$ gene could not be reproduced in the three clinical phenotypes of CSC, possibly due to small study cohorts.

Exogenous corticosteroids are a known important risk factor in CSC, and some studies have also reported enhanced levels of endogenous steroids in CSC without Cushing syndrome, although this is subject of controversy. Previous studies in animal models have suggested involvement of the mineralocorticoid receptor in the pathogenesis of choroidal changes in cCSC. It is conceivable that genetic variations in genes encoding the glucocorticoid and mineralocorticoid receptors may play a role in the risk of CSC development at a molecular level. Our group has previously shown that one SNP in the $NR3C2$ gene, encoding the mineralocorticoid receptor, increases the risk of cCSC as compared to
healthy individuals. However, in our analysis of the rs2070951 SNP in NR3C2 gene in aCSC, non-severe cCSC, and severe cCSC patients, no statistically significant association could be reproduced for this SNP. This is surprising because genetic analysis in both ARMS2 and NR3C2 genes were performed in well-designed studies, and the associations were proven by independent research groups. We assume that the lack of significant association in our investigation may be caused, in part, by a small sample size in the three phenotypic subgroups, and further studies in larger well-phenotyped cohorts are needed to analyze potential associations.

**Difference in effect size of relevant genetic variants**

Our findings suggest that the profile (i.e. presence or absence) of known genetic risk SNPs in the associated complement genes is roughly similar between phenotypically different CSC patients. However, the genetic effect size of the CFH gene variants in terms of protective or risk-conferring odds ratios (ORs) appeared to show a clear distinguishing pattern. The effect size of these variants appears the largest in the severe cCSC group compared to non-severe cCSC and aCSC groups in our study. This was also the case when comparing the genetic effect size in our severe cCSC cohort to the ‘general’ cCSC cohort in literature. The genetic effect size was also larger in aCSC patients as compared to non-severe cCSC in our study, and when compared to ‘general’ cCSC patients in literature. Therefore, similar gene variants in all CSC phenotypes may have the largest impact in severe cCSC phenotype, followed by aCSC, and have the least impact on the non-severe cCSC phenotype, but more research is needed to see if these observations can be replicated.

It has previously been shown that in multifactorial retinal diseases with genetic involvement such as AMD, patients who develop the disease at a younger age have a stronger genetic predisposition. A similar mechanism might explain the larger genetic predisposition among aCSC patients, who are generally younger than cCSC patients. Conversely, it is unclear why severe cCSC has the largest genetic effect size, as this does not rhyme the age argument. It is plausible that more genetic risk factors, or presence of genetic variants with a larger effect size, may correspond to a more severe clinical presentation and course. However, a better insight into the exact role and potential impact of genetic factors in CSC is required. Clearly, other non-genetic risk factors such as local anatomical and environmental factors also play a significant role and are likely to be as important for the pathogenesis and clinical course of CSC.

### 5.3. THE ROLE OF PDT AS TREATMENT OF CSC

There is currently no global consensus on the treatment of first choice for CSC patients and there is considerable worldwide variation in preferred practice patterns. This is partly due to a lack of knowledge on the exact pathophysiology of the disease. Multiple treatments including a number of pharmacological agents have been used as treatment of...
CSC, although with low level of evidence.\textsuperscript{95} In Chapter 1, we discussed the most frequently used treatments in CSC. Recent research including randomized controlled trials have repeatedly shown the superiority of PDT as an effective treatment for CSC, as will be discussed in the next paragraphs.\textsuperscript{49, 58, 59}

**Mechanism of PDT**

Photodynamic therapy (PDT) was initially utilized in ophthalmology to treat choroidal neovascularization in neovascular AMD, but subsequently PDT was also proven to be effective in the treatment of a number of other chorioretinal diseases including choroidal haemangioma, polypoidal choroidal vasculopathy, and CSC.\textsuperscript{96-98} PDT treatment in CSC is used in cases where no spontaneous resolution of subretinal fluid occurs within a few months, and in more extensive diseases.\textsuperscript{33, 49, 52, 99} In PDT treatment, verteporfin (6 mg/m$^2$, Visudyne®) is introduced intravenously and activated in the eye by a laser beam (689 µm, 50 J/cm$^2$, over 83 seconds) at the area of choroidal leakage.\textsuperscript{100} Although the mode of mechanism is not fully understood, it has been suggested that the free radicals which are formed upon illumination of the treatment affect the vascular endothelium, and may lead to vascular remodeling.\textsuperscript{49, 96, 101, 102} Nevertheless, the precise mechanism of PDT remains unclear. Currently, there are only a few randomized comparative trials available on PDTs safety and efficacy.\textsuperscript{54, 55, 58, 59} PDT with reduced settings (half-time (42 seconds), half-dose (3 mg/m$^2$), or half-fluency (25 J/cm$^2$)) is used in CSC and was shown to be safe, but also effective in achieving a complete resolution of SRF in 41-100% of the CSC patients, and to improve visual acuity and retinal sensitivity of microperimetry in many patients.\textsuperscript{54, 55, 58, 59, 103-111}

Side effects of full-dose PDT that have previously been reported in AMD, such as choroidal ischemia, RPE atrophy, and choroidal neovascularization (CNV) formation, but these are extremely rare in CSC.\textsuperscript{5, 98, 104, 112, 113} No such serious adverse effects were reported in a broad range of large prospective and retrospective studies on both full-dose and reduced-settings PDT, even with large PDT spot size involving the fovea.\textsuperscript{49, 58, 59, 114-118} A temporary increase in SRF and intraretinal edema, as well as an initial decline in vision may be seen in a small proportion of CSC patient in the first weeks after PDT treatment, with a final complete resolution and improvement of the OCT parameters, and visual function compared to the pre-PDT situation.\textsuperscript{119} This temporary effect, was hypothesized to be due to an inflammatory reaction, or an increase in vascular permeability after PDT-induced short-term choroidal hypoperfusion.\textsuperscript{119, 120} The reason why choroidal ischemia and side effects after PDT are so rare in CSC as compared to AMD may be that the choroid in CSC is often significantly thickened and hyperpermeable – which is effectively addressed by PDT, while the choroid and RPE in AMD is thinned and more degenerative and therefore more vulnerable to potential adverse effects of PDT.\textsuperscript{49, 121}
**PDT outcome in different CSC phenotypes**

It is important to carefully define treatment success when evaluating treatment. Multiple studies considered PDT effective when a reduction was observed in central retinal thickness (CRT, often measured automatically by the OCT machine), or merely a reduction of SRF but no complete resolution.\(^{105, 122, 123}\) This at least might partly explain the wide range of success rates of PDT reported in different studies. CRT measurement as an endpoint to evaluate treatment efficacy for example, may be deceptive because automated measurements often include SRF, but also the volume of an RPE detachment, or subretinal debris, which should not be considered part of the neuroretina.\(^{124}\) We argue in our studies that PDT can be considered successful only when SRF resolved completely. After all, only this anatomical endpoint of complete resolution of SRF enables a reconstitution of the normal photoreceptor–RPE relationship and physiology.

So far, the outcome of PDT was mostly evaluated for cCSC, and rarely for aCSC, as aCSC is generally assumed self-limiting. However, visual symptoms in aCSC may also be significant, and some patients also require a rapid resolution of SRF and normalization of vision, for instance for professional reasons (e.g. pilots, bus drivers). Therefore, in this thesis, we evaluated the outcome of PDT (among other treatments) in aCSC. Chan and coworkers reported in a relatively small randomized controlled trial that early treatment with half-dose PDT in aCSC resulted in a significantly higher percentage of SRF resolution with subsequent better final visual acuity, when compared to an untreated aCSC cohort.\(^54\) Another recent randomized clinical trial concluded that early half-fluence PDT treatment (within one week of presentation) resulted in a faster resolution of SRF in aCSC patients as compared to a wait-and-see strategy.\(^55\) However, performing PDT in all aCSC patient was not found cost-effective and necessary, also because the final visual outcome at 12 months was comparable in both groups.\(^55\) Two meta-analysis studies performed to evaluate efficacy of different treatments in CSC concluded that - based on the present level of evidence- early treatment for aCSC does not seem to have a clinical benefit.\(^{49, 50}\) Another recent comprehensive review performed to provide an evidence-based treatment guideline for aCSC recommended active monitoring without initial therapeutic intervention.\(^49\) In a case series where we reviewed 295 aCSC eyes, we also found that early treatment resulted in faster SRF resolution, but had no additive benefit for the final visual outcome. However, in our study, aCSC eyes receiving early PDT showed a statistically significantly lower risk of SRF recurrence as compared to eyes with a wait-and-see strategy (4% versus 24%, respectively). This was also reported by Ozkaya and coworkers, who found that the recurrence rate was significantly lower in aCSC patients treated with PDT as compared to patients with spontaneous resolution (25% versus 51%, respectively).\(^8\) Recurrence of SRF, hence a neurosensory detachment, adversely affects photoreceptors and this may eventually lead to progressive vision loss. The aforementioned findings, in combination with the favorable safety profile of PDT, indicate that early PDT may be considered in selected aCSC cases, although larger prospective randomized controlled trials are needed to lend further support to such a strategy.
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The majority of studies on PDT treatment in CSC have been performed in cCSC patients. In the PLACE, REPLACE, SPECTRA, and SPECS trials, up to 87% of the ‘general’ cCSC patients had a complete SRF resolution after half-dose PDT, and a significant increase in visual acuity as compared to baseline.\textsuperscript{58-60, 111} Other large retrospective studies with long-term follow-up after PDT in cCSC reported even higher SRF resolution rates, and up to 97%.\textsuperscript{105, 108, 125, 126} An interesting subgroup of CSC that had been under-studied thus far, was the group of cCSC with severe disease characteristics, such as large diffuse atrophic RPE alterations, large area of diffuse fluorescein leakage or multiple “hot spots” of leakage, and presence of posterior cystoid retinal degeneration (PCRD). Until recently, it was unclear whether PDT would also be effective in these patients with signs of severe and/or long-standing disease. That is why we performed large studies on patients with such signs of more severe disease, to assess whether comparable rates of treatment efficacy may be achieved in this subgroup. Our data suggested similar success rates for PDT in the most severe cCSC cases as compared to chronic cases with no severe criteria, as we found 70% complete SRF resolution in severe cCSC at first follow-up visit after PDT, and even 87% complete SRF resolution at final follow-up (Chapter 4.2). However, one third of severe cCSCs required multiple (PDT) treatments. In contrast to non-severe cCSC patients, baseline and final visual outcome was still relatively poor in this severe cCSC subgroup, without a statistically significantly visual improvement compared to pre-PDT, even after complete SRF resolution (Chapter 4.2). The reason for this is likely the profound and pre-treatment photoreceptor atrophy due long-standing disease. Still, achieving complete resolution of SRF even in such severe cCSC cases may help to at least stabilize remaining visual function by preventing further retinal damage related to prolonged SRF accumulation. These findings indicate that cCSC should preferably be treated early upon diagnosis to prevent further vision loss due to ongoing disease activity.\textsuperscript{49}

Up to one third of cCSC is complicated with macular and/or peripapillary posterior cystoid retinal degeneration (also referred to as PCRD), at some point during the disease course.\textsuperscript{19, 44, 127} This PCRD without CNV should be differentiated with multimodal imaging from CSC cases complicated by CNV, which is also relatively common.\textsuperscript{128, 129} In such cases with CNV, anti-VEGF treatment would be required.\textsuperscript{130-133} In this thesis, we performed the largest study thus far on clinical characteristics and treatment outcome in PCRD in cCSC (Chapter 2.3). We found that PCRD is accompanied by subretinal leakage in the majority (76%) of cases. Treatment resolved SRF completely in up to 82% of SRF in these cCSC cases with PCRD. However, the percentage of PCRD resolution after treatment was much lower. PDT was the most frequently used treatment with relatively the highest rate of complete SRF and PCRD resolution compared to other treatments (subthreshold micropulse diode laser, conventional thermal laser, intraocular anti-VEGF agents). Complete PCRD resolution was seen in 39% of the PDT-treated cases, which is a much lower success rate compared to previous reports on complete SRF resolution in a general cCSC cohort. Thus, PCRD seems to be more therapy-resistant than SRF. We hypothesize that the underlying mechanism in PCRD may consist of the contribution of two components: 1) a homeostatic fluid imbalance,
leading to intraretinal fluid (PCRD) and SRF. This component seems more responsive to (PDT) treatment; and 2) a degenerative component, leading to tissue loss and intraretinal cystoid-like cavity formation, which is resistant to treatment, as there are no active leaking (neo-)vessels. Final visual outcome in PCRD cases in our study showed, similar to severe cCSC cases, no overall changes during follow-up even after PCRD resolution. Morphologic studies suggested that in such severe cases there is already significant irreversible photoreceptor damage also after SRF resolution, which may explain the discrepancy between anatomical and visual recovery after PDT in both severe cCSC, and PCRD cases. We argue that accomplishing a complete SRF resolution is still an important endpoint in these patients, at least to reduce further photoreceptor loss.

A new phenotypic description that has been reported after publication of our PCRD study is peripapillary pachychoroid syndrome (PPS), in which PCRD-like changes are associated with abnormalities that are typically seen in the pachychoroid spectrum, including cCSC-like abnormalities with SRF in some cases. However, there appears to be overlap with CSC with PCRD, and PDT may be effective in a sizeable proportion of these cases in terms of SRF resolution, while the cystoid changes seem more therapy-resistant.

Patient characteristics and PDT outcome

Given the differences in clinical presentations of CSC, it is relevant to know whether different clinical findings and patients’ characteristics may influence final visual outcome after PDT. Multiple studies are available on this topic, although the conclusions are not always coherent. Several, relatively small studies have shown that a less favorable final visual outcome is associated with long persistent SRF, older age (above 55 years), presence of baseline confluent RPE atrophy, focal RPE detachment, foveal degeneration and changes in foveal thickness, frequent SRF recurrence, and development of secondary CNV. Others reported no clear association between visual outcome and symptom duration, baseline CRT, and the pattern of FA leakage. However, almost all studies agree that a higher baseline visual acuity before treatment is an important prognostic factor for a better final visual outcome. In our study on long-term visual prognosis in 199 eyes with severe cCSC (Chapter 4.2), we found that a worse post-PDT visual outcome was associated with male gender, lower baseline visual acuity, a large surface of atrophic RPE (which we defined as diffuse atrophic RPE alterations (DARA)), and foveal location of DARA. In contrast, we found no association with disease duration, steroid use, age, location of hotspots of focal leakage on FA, or number of disease recurrences.

Findings on multimodal imaging may also help to predict treatment efficacy of PDT. For instance, Moon and coworkers reported that disintegrity of the foveal ellipsoid zone on OCT after treatment, and post-PDT progression of RPE atrophy were significantly associated with final visual outcome. Poorer visual outcome was also related to greater dimensions of SRF (specially higher SRF), and thinning of the foveal outer nuclear layer on OCT. Chan and coworkers reported in a prospective study that PDT was less effective in CSC eyes with...
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a central RPE detachment, possibly due to a less effective laser penetration. Our data from cCSC cases with secondary PCRD suggested that presence of SRF in combination with PCRD on OCT was significantly associated with a higher chance of PCRD (and SRF) resolution after PDT, as compared to PCRD cases with no active SRF leakage on OCT (Chapter 2.3). Also, an intense hyperfluorescent leakage area on ICGA was strongly associated with higher chance of a complete resolution of SRF after PDT treatment. Presumably, if the choroid still shows active leakage and congestion, it is also likely more receptive to the desired remodeling effect of PDT, with subsequent resolution of SRF. ICGA is a helpful tool to assess the true extent of active underlying (choroidal) disease, especially in cCSC patients in whom the area of choroidal hyperpermeability on ICGA is often larger than the area of leakage on FA.

Steroid use is the most important known risk factor for CSC, and stopping steroid use is generally the first recommendation for patients with potentially steroid-associated CSC. However, this might not be possible due to certain medical conditions, for example for post-transplantation patients. Severe visual impairment has been described in literature in cCSC cases associated with chronic systemic corticosteroid therapy. In this thesis, we present a retrospective case-control study in which we reported that current or recent use of corticosteroids did not seem to adversely affect the efficacy of PDT, when compared to the outcome in non-steroid associated cCSC (Chapter 4.1). Lee et al. reported earlier in a smaller cohort of steroid-associated cCSC that 100% of the cases had a resolution of SRF with improvement of visual acuity after PDT treatment with full, or reduced settings. Baseline visual acuity in our steroid-associated cCSC cohort was significantly lower than the non-steroid associated cases. Nevertheless, a significant improvement after successful PDT was observed among steroid-associated cCSCs. In addition, we found no significant difference in the final visual outcome between steroid-associated cCSCs and non-steroid associated cases after PDT treatment. Therefore, we concluded that treatment with PDT shows an efficacy that is comparable between steroid-associated and non-steroid associated cCSC. Also, PDT may still achieve SRF resolution in cCSC cases where steroids cannot be omitted, and when performed early enough it may prevent further visual loss.

It has been postulated that PDT in cases with subfoveal fibrin accumulation may induce subretinal fibrosis and fibrotic scar formation, which in turn may deteriorate visual acuity. Until, recently, PDT was used with caution or deferred in these cases with subfoveal fibrin. However, more recently, Liang and coworkers reported in a relatively large case-control study on 48 patients with CSC and subretinal fibrin versus 125 controls, that PDT efficacy and visual outcome were not negatively influenced by central subretinal fibrin accumulation. Interestingly, in our studies on over 400 cCSC patients, who were mostly of Caucasian background, we did not observe any noteworthy subretinal fibrin accumulation or post-PDT subretinal fibrosis, although these findings were not part of our primary outcome measures.
5.4. Conclusions and future perspectives

The classification of CSC remains challenging and controversial, although there are attempts to reach consensus and evidence on a clinically relevant classification system. Nevertheless, we have shown in the studies presented in this thesis that differentiating CSC phenotypes can have important clinical implications for predicting disease progression and visual outcome. In this thesis, we suggested definitions for CSC phenotypes with more emphasis on characteristics on multimodal imaging rather than disease duration. Accordingly, we distinguished a typical aCSC phenotype with focal leakage and no significant atrophic RPE changes (Chapter 2.1). This aCSC subgroup has the best prognosis within the CSC spectrum. We have also shown that chronic forms of CSC encompass a heterogenous group arranging from relatively focal disease, to severe phenotypes with extensive DARA and PCRD, with consecutive disparate disease courses (Chapters 2.3 and 2.3).

We assessed whether CSC may consist of a continuum of clinical presentations (phenotypes) that may succeed each other by passage of time. In support of this theory, we found that the different clinical phenotypes of CSC did not show a fundamental difference in the known CSC-associated risk SNPs. However, intriguingly, we found that many aCSC patients did not show an evolution to more extensive cCSC with persistent SRF leakage. Presence of RPE alterations in the non-symptomatic contralateral eye seemed the only predictive risk factor for a tendency towards a more chronic disease in aCSC patients. Future long-term prospective studies must assess the validity of this finding. We also found that many patients with extensive and severe cCSC already had this advanced clinical picture at first presentation, without a clear history of one or more episodes of aCSC. Presumably, other nongenetic risk factors such as local anatomical factors in the choroid and RPE, environmental factors, or currently unknown genetic variants may play a role in the evolution towards a more self-limiting, localized disease, or more extensive chronic phenotypes.

To date, evidence is piling up on the efficacy and safety of PDT treatment with reduced settings as treatment of first choice in CSC, culminating towards an evidence-based treatment guideline. However, thus far, little evidence was available on the efficacy of PDT in different CSC subtypes. In this thesis, we investigated PDT treatment efficacy in aCSC, steroids-associated cCSC, severe cCSC, and cCSC complicated by secondary PCRD. We concluded that anatomical recovery in terms of resolution of subretinal and - to a lesser extent - intraretinal leakage is favorable after PDT treatment in all investigated CSC subtypes. Based on the current evidence presented in this thesis, as well as several pivotal prospective randomized controlled trials from our group (e.g. the PLACE, REPLACE, SPECTRA, and SPECS trials), the best treatment approach in CSC is ICGA-guided PDT with reduced settings, treating the hyperfluorescent leakage area on ICGA.
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So far, we can predict post-PDT anatomical recovery by a number of patients characteristics and findings on multimodal imaging techniques. Most importantly, the final visual outcome is determined by the pre-treatment baseline visual acuity. Therefore, early treatment of cCSC (and potentially aCSC) with PDT, before substantial and irreversible vision loss due to photoreceptor damage, appears crucial to optimize visual outcome. In addition, early treatment may reduce the number of recurrences (Chapter 2.1). Future prospective studies on the natural history and treatment outcome in different CSC subgroups will be essential to potentially replicate the findings in this thesis, which appear highly relevant for clinical practice.
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Chapter 5


Chapter 5


General discussion


CHAPTER 6
CHAPTER 6.1

English summary
Central serous chorioretinopathy (CSC) is a multifactorial disease of the retina and the choroid, which generally affects otherwise healthy and relatively young male patients (between their twenties and sixties) of all races. However, older and younger male and female patients may also be affected. The disease is characterized by a serous detachment of the neurosensory retina in the central macula, which causes visual complaints including blurred vision, a central relative (grayish) scotoma, metamorphopsia, and alterations in color and contrast vision. Due to its sudden onset and disturbance of central vision, CSC can have a large impact on the affected person.

Multimodal imaging techniques in CSC patients have revealed that abnormally thickened, leaking choroidal blood vessels (the vascular layer of the eye underlying the retina) cause an excessive fluid outflow into the interstitial space, which presumably causes the characteristic thickened choroid (also known as ‘pachychoroid’). This is best observed on optical coherence tomography (OCT). Another important layer in between the choroid and the retina is the retinal pigment epithelium (RPE), a pigmented one-cell-layer thick structure that forms the outer blood-retina barrier. Among an array of other functional properties, the RPE also facilitates the transport of oxygen and nutrients from the choroid towards the neuroretina, and prevents fluid passage by actively pumping fluid away from the neuroretina and subretinal space.

A persistently thickened, dysfunctional, leaky choroid affects the overlying RPE, and may cause atrophic RPE abnormalities and local RPE detachment (‘pachychoroid pigment epitheliopathy’). In the case of CSC, a focal RPE disruption and breakdown of the outer blood-retina barrier) causes leakage of subretinal fluid and neurosensory retinal detachment. The majority of patients present with the relatively milder acute form of CSC (aCSC), from which most cases (more than 90%) will recover spontaneously in several months, with a near-complete visual recovery. However, a substantial percentage of patients present with a recurrent, more persistent form with more extensive chorioretinal abnormalities, which may influence vision more profoundly and irreversibly. This form is generally referred to as chronic CSC (cCSC), although the definitions of aCSC and cCSC are still under debate. Furthermore, it is unclear whether aCSC and cCSC are different variants of the same disease, whether aCSC necessarily has to precede cCSC development, and if cCSC can be prevented, for example by (early) treatment of aCSC.

There is an ongoing controversy on the pathogenesis, classification, the prognosis and the best treatment options of CSC. Thus far, little was known about differences between CSC phenotypes, and whether they may have a different pathogenesis and clinical outcome. The aim of this thesis was to take a closer look at the strikingly variable clinical spectrum of CSC presentations, to evaluate treatment efficacy in these phenotypic subgroups, and to assess the possible role of genetic risk factors in disease development and clinical variability. In Chapter 1, we provided an introduction on CSC based on current literature.
Chapter 2 addresses the clinical spectrum of CSC. In Chapter 2.1, we report on a proposed strict definition for aCSC, based not only on disease duration, but especially on clinical characteristics observed on multimodal imaging in both the diseased eye, and the fellow eye. We reported the long-term (>12 months) risk of recurrence and/or transition to cCSC in a typical aCSC cohort. All study eyes recovered from the first disease episode, with half of these eyes being treated and in the other half a wait-and-see strategy was followed. We reported that a significantly lower number of recurrence was seen in the cases that received early treatment (mostly photodynamic therapy (PDT), performed in 95% of patients) as compared to patients followed by a wait-and-see strategy (4% versus 24%, respectively). Despite this difference, the visual outcome was favorable in all cases and not different between both groups. We also observed an increase in atrophic RPE alterations in 36% of the aCSC eyes during follow-up, and 23% of the eyes had both an increase in RPE alterations and SRF recurrence. Based on these reports, we concluded that a tendency toward chronicity, in terms of gradual increase in RPE alterations and/or episodes of recurrent SRF may be expected in almost one third of typical aCSC cases, while early treatment may decrease the risk of recurrences. However, none of our aCSC cases developed a severe cCSC during the follow-up.

The clinical presentation of CSC can be very variable. For instance, in cCSC, the total area of atrophic RPE changes, the severity of vision loss, and the capacity of visual recovery may vary largely. To cover the whole spectrum of clinical presentations in CSC, we investigated a large cohort of extensive and severe cCSC. In Chapter 2.2, we proposed a definition for disease severity in cCSC, and we selected and studied a cohort of patients according to these criteria of presumed severe cCSCs. We found that only 14% of severe cCSC cases has a documented history of an acute episode as first presentation, whereas 73% already showed pre-existing features of chronicity (with multifocal areas of atrophic RPE alterations and/or multifocal areas of leakage) at first presentation. Treatment in severe cCSC (mostly PDT, performed in 60% of patients) resulted in SRF resolution in 76% of eyes at final visit, although 68% of severe cCSC patients still showed some enlargement of the area of diffuse atrophic RPE abnormalities (DARA), which is considered a potential sign of continuing disease activity despite an absence of subretinal fluid. Treatment success in severe cCSC is lower compared to aCSC and non-severe cCSC. However, treatment – especially with half-dose PDT, which appears to be the most effective treatment modality - is important in order to maximize the likelihood of subretinal fluid resolution and preserve long-term visual acuity.

In Chapter 2.3, we focused on severe cCSC patients who had a phenotype that was complicated by the presence of posterior cystoid retinal degeneration (PCRD), and reviewed the visual outcome and treatment efficacy in these cases. Chronic CSC with secondary PCRD is accompanied by SRF in 76% of cases. Patients who present with a combination of active SRF and PCRD seem more responsive to treatment. While SRF had resolved in 82% of cases at final available visit (mostly after PDT), only slightly over one third (37%) of PCRD had
resolved completely. Visual outcome is also poor in cCSC with secondary PCRD, even after complete resolution of SRF and PCRD. Therefore, PCRD in cCSC patients can be considered a clinical sign for a poor prognosis.

Chapter 3 focuses on the genetic characteristics of CSC phenotypes. In Chapters 3.1 and 3.2, we studied the role of genetic risk factors in CSC. The aim of the studies was also to determine possible genetic differences between seemingly distinct CSC phenotypes. In these chapters we assessed the role of previously reported single nucleotide polymorphisms (SNPs) in the \textit{ARMS2}, \textit{CFH}, and \textit{NR3C2} genes. Also, \textit{C4B} gene copy numbers were analyzed. Our data confirmed the role of the \textit{CFH} gene, and the \textit{C4B} gene copy numbers in CSC risk. Acute CSC, non-severe cCSC, and severe cCSC all showed a similar association with these genes, and the three phenotypes could not be distinguished based on the genotypes. This shows that despite the differences in clinical presentation and severity, there is an overlap in the genetic predisposition of different CSC phenotypes. Other genetic and/or nongenetic risk factors may be more influential in the differentiation toward an acute or a chronic phenotype of CSC.

Chapter 4 aims to evaluate the efficacy of photodynamic therapy in CSC, and to report on influential factors. Corticosteroid use is the most important known exogenous risk factor for CSC development. Patients with certain medical conditions (e.g. after organ transplantation) may not be able to cease steroid use even when they suffer from CSC. Thus far, it was largely unknown if PDT may also be effective in steroid-associated CSC. In Chapter 4.1 we report the efficacy of PDT with reduced settings in cCSC presumably associated with corticosteroid use, and compared it to the effect of PDT in patients who had not used corticosteroids. We found that PDT was efficacious in many cCSC patients despite corticosteroid use. Complete SRF resolution after PDT occurred in 69% of steroid-associated cCSCs, and increasing to 74% at longer-term follow-up. Continuation of corticosteroids at the time of PDT treatment did not seem to adversely affect PDT response. Also, significant vision improvement was observed after PDT treatment in steroid-associated cCSC. If possible, discontinuation of corticosteroids should be the first step in CSC, but our study has shown that PDT treatment can still be effective in disease management in cases with prior or continuous steroid use.

In Chapter 4.2, we specifically assessed the efficacy of PDT in the most severe cCSC cases. Despite widespread abnormalities and chronic and recurrent SRF accumulation in these severe cCSC cases, PDT was able to restore the anatomy of the retina by resolving SRF in the majority (87%) of cases, comparable to cCSC cases that did not display characteristics of severity. We also confirmed that visual acuity improves after PDT treatment both in severe and non-severe cCSC cases. However, final visual acuity remained poor in severe cCSC cases. These severe cCSC cases generally have a worse baseline pre-treatment visual acuity compared to non-severe cCSC cases, presumably due to pre-existent permanent photoreceptor and RPE damage.
In Chapter 5, we summarize our findings and conclusions, and place them in a broader perspective and the context of current literature. There are still multiple unanswered questions on the pathophysiology of CSC, its classification, the role of genetic predispositions in CSC, factors contributing to a certain CSC phenotype, and treatment. These remaining questions should be unraveled further in future studies.
CHAPTER 6.2
Dutch summary
Chapter 6.2

Centrale sereuze chorioretinopathie (CSC, oftewel serosa) is een multifactoriële ziekte van het netvlies (de retina) en het daaronder liggende vaatvlies (het choroïd). CSC komt voornamelijk voor in gezonde en relatief jonge (gemiddeld 39 tot 51 jaar) mannen van alle etniciteiten. Echter, individuen van andere leeftijden en vrouwen kunnen ook aangedaan zijn. Patiënten klagen over plots ontstaan wazig zicht vaak in één oog, een centrale grijze vlek (relatieve scotoom), vervorming van rechte lijnen (metamorfopsie) en verandering van kleuren- en contrastzien. CSC kan grote gevolgen hebben voor het (werkzame) leven van patiënten, met name vanwege het vaak acute ontstaan van de klachten en het beperkte zicht.

Momenteel is nog veel onbekend over de ontstaanswijze van de ziekte en meerdere risicofactoren zijn gerapporteerd. De belangrijkste, tot nu tot bekende, risicofactor is het gebruik van steroid-houdende substanties (anabole steroïden) en/of medicaties (corticosteroïden). In de loop van de jaren en door de ontwikkeling van nieuwe beeldvormende onderzoekmethoden is de pathofysiologie van CSC meer opgehelderd. Het is bekend dat de klachten ontstaan door een ophoping van sereus (waterachtig) vocht onder de retina waardoor er een loslating van de sensorische laag van de retina (neuro retina) ontstaat. Deze loslating bevindt zich meestal in het centrum (de macula).

Momenteel denkt men dat deze sereuze loslating van de neuro retina een gevolg is van de uittreding van vloeistoffen uit beschadigde en daardoor lekkende (hyperpermeabele) bloedvaten in het choroid, de anatomische laag onder de retina. Het overtollige vocht verspreid zich in de ruimte tussen de choroidale bloedvaten en zorgt voor de karakteristieke verdikking van het het choroid (zogenaamde pachychoroïd) welke goed waar te nemen is op de optical coherence tomography (OCT) scan. Er ligt nog een belangrijke structuur tussen het choroid en de retina; het retinale pigment epitheel (het RPE). Dit is een één-cellige dikke structuur die fungeert als een zogenaamde buitenste bloed-retina barrière. Dit betekent dat het RPE alleen zuurstof en voedingsstoffen afkomstig uit de choroidale bloedvaten toelaat richting de retina maar voorkomt de doorstroom van vocht richting de retina, namelijk door het actief terugpompen van het vocht. In CSC-patiënten is het RPE beschadigd, vermoedelijk door langdurige en aanhoudende lekkage van choroidale bloedvaten. Dit zorgt voor kleine scheuren in het RPE, een onderbreking van de bloed-retina barrière, een doorstroom van vocht in de ruimte onder de neuro retina, met een sereuze loslating van de retina tot gevolg. De meerderheid van CSC-patiënten presenteert zich met een relatief gunstige acute vorm (aCSC). In meer dan 90% van de gevallen zal spontaan herstel optreden binnen enkele maanden met een nagenoeg volledig herstel van het zicht. Er is echter een substantieel deel van de patiënten dat een terugkerend, langdurig en/of uitgebreider ziektebeeld laat zien, met ernstigere of permanente visusklachten. Deze vorm wordt doorgaans geduid als chronische CSC (cCSC). Wereldwijd bestaat er echter nog geen consensus over eenduidige definities voor aCSC en cCSC. Bovendien, het is niet bekend of aCSC en cCSC kunnen worden gezien als variaties van dezelfde ziekte, of CSC altijd met een
acute vorm begint welk in de loop van de tijd verandert in de chronische vorm, en of cCSC voorkomen kan worden, bijvoorbeeld door vroegtijdig behandelen van aCSC.

In de afgelopen decennia zijn er in toenemende mate onderzoeken naar de etiologie van CSC, en een klinische classificatie. Bovendien zijn er meerdere behandelmethodes beschreven voor het behouden van de visus, vooral in cCSC-patiënten. In dit proefschrift is er getracht om een overzicht te geven van verschillende klinische presentaties van CSC, de effectiviteit van verschillende behandelmethodes te evalueren en de mogelijke genetische risicofactoren in het ontstaan van CSC te bestuderen. **Hoofdstuk 1** bevat een algemene introductie over CSC gebaseerd op de belangrijkste literatuur.

**Hoofdstuk 2** is gewijd aan het klinische spectrum van CSC. In **Hoofdstuk 2.1** introduceren we een strikte definitie voor aCSC, niet alleen gebaseerd op de ziekteduur tot spontaan herstel, maar voornamelijk op anatomische veranderingen en klinische karakteristieken. We bestudeerden deze veranderingen en karakteristieken op verschillende beeldvormende onderzoeken, zowel in het aangedane oog als in het andere niet symptomatische oog. We onderzochten in een, zorgvuldig op basis van strikte criteria geselecteerd, aCSC cohort de lange termijn (>12 maanden) risico’s. We keken met name naar het risico op het ontwikkelen van een recidief van de ziekte na aanvankelijk herstel, en de kans op transformatie tot de chronische vorm. Dit cohort waarin alle patiënten volledig waren hersteld van de eerste aCSC episode, bestond uit twee groepen. Bij de helft van de gevallen was een spontaan herstel afgewacht en in de andere helft van de gevallen trad herstel op na een vroege behandeling. Opvallend genoeg is er geen significant verschil in visus uitkomst tussen beide groepen, terwijl we echter wel zagen dat in de groep met een vroege benadeling (95% fotodynamische therapie (PDT)) significant minder vaak een terugkeer van aCSC is waargenomen in vergelijking met de groep waarbij een afwachtend beleid is gevoerd (respectievelijk 4% versus 24%). Bovendien rapporteren we een toename in cumulatieve afwijkingen in het RPE in 36% van de aCSCs na meer dan 12 maanden follow-up tijd. In 23% van de aCSCs is er zowel een toename in RPE-afwijking waargenomen, als ook een terugkeer van een sereuze retina loslating. We beschouwen deze lange termijn veranderingen in het RPE tezamen met de terugkeer van een sereuze retina loslating als tekenen van een transformatie richting de chronische vorm van CSC. Deze bevindingen suggereren dat ongeveer een derde van alle aCSC patiënten de neiging heeft om op lange termijn te transformeren naar een chronische vorm. Bovendien lijkt een vroegtijdige behandeling de kans op een terugkeer van een sereuze retina loslating significant te verminderen in vergelijking met een afwachtend beleid. De visus uitkomst is echter vergelijkbaar in beide strategieën.

De klinische presentatie van CSC, en met name de chronische vorm, kan erg uiteenlopen. Zo is er binnen de cCSC een grote variatie in mate van visus verlies, uitgebreidheid van afwijkingen van het RPE en het herstellend vermogen van de visus. Deze variatie kan mogelijk invloed hebben op de prognose en het effect van therapie. We introduceren
in **Hoofdstuk 2.2** een definitie voor wat we een ernstige vorm van cCSC noemen en bestudeerden het ziektebeloop in deze patiënten. Wat opvalt in deze volgens onze definitie ernstige cCSC groep is dat 14% van de patiënten zich initieel presenteert met een typische aCSC, terwijl 73% van de nieuwe gevallen bij de eerste presentatie al anatomische kenmerken laat zien (zoals multifocale gebieden met RPE atrofie en/of lekkage) van een langer bestaande CSC en dus een chronische vorm. Behandeling (60% PDT) is in de meerderheid (76%) van de ernstige cCSC patienten succesvol en leidt tot volledig opdrogen van het vocht onder de retina. Echter, in 68% van de gevallen is er sprake van een geleidelijke toename van afwijkingen in het RPE en dus progressie van de ziekte gedurende follow-up, ondanks de goede respons op behandeling. Behandeling in ernstige cCSC lijkt minder effectief vergeleken met aCSC en niet ernstige cCSC, in termen percentage opgedroogd vocht onder de retina. Desalniettemin blijft een tijdige behandeling – met name halve dosis PDT, welk tot heden de meest succesvolle behandeling lijkt - in ernstige cCSC belangrijk voor het stabiliseren van de visus en het voorkomen van verdere visus verlies.

Een interessante minderheid binnen de ernstige cCSC groep betreft patiënten met een cystoïde degeneratie van de retina (posterior cystoid retinal degeneration (PCRD)). Deze cystevormende degeneratie is gelokaliseerd tussen de (met name diepgelegen) retinale lagen, is vaak secundair aan vocht onder de retina en vermoedelijk verantwoordelijk voor een deel van visus klachten. De studie in **Hoofdstuk 2.3** focust op deze subgroep van ernstige cCSC waarin klinische karakteristieken, behandel effectiviteit en visus uitkomst onderzocht is. In 76% van bestudeerde patiënten is er subretinaal vocht vastgesteld naast de PCRD bij presentatie, en in de resterende gevallen lijkt het subretinaal vocht afwezig (vermoedelijk opgedroogd) terwijl de PCRD persisteert. Behandeling (met name PDT) in patiënten met zowel subretinaal vocht als PCRD leidt in 82% van gevallen tot volledig opdrogen van vocht onder de retina, terwijl in slechts in 37% van de gevallen ook de PCRD verdwijnt. Bovendien is de visus uitkomst in deze subgroep van ernstige cCSC met PCRD slechter, zelfs na het volledig opdrogen van het vocht onder de retina en het verdwijnen van de PCRD. Op basis van onze bevindingen concluderen we dat PCRD als klinische kenmerk in het spectrum van cCSC een teken is van slechte prognose in termen van visus uitkomst.

**Hoofdstuk 3** focust op de genetica. De studies gepresenteerd in **Hoofdstukken 3.1 en 3.2** hebben de rol van genetische variaties als risicofactor in CSC als thema. Bovendien hebben we in deze studies getracht om de mogelijke genetische verschillen te bestuderen tussen de klinisch ogenschijnlijk verschillende CSCs; acute, ernstig chronische, en niet ernstig chronische CSC. We onderzochten in deze hoofdstukken de rol van eerder ontlede CSC geassocieerde genetische variaties (single nucleotide polymorphisms (SNPs)) in het ARMS2, het CFH, het C4B en het NR3C2 gen. Onze bevindingen tonen een statistisch significante correlatie tussen aanwezigheid van een aantal SNPs in het CFH gen en het risico op CSC. Bovendien is een statistisch significante correlatie aangetoond tussen een verlaagd risico op CSC en een genetische variatie waarin drie of meer kopieën van het C4B gen voorkomen. Hiermee bevestigen onze bevindingen de eerdere beschreven rol van het CFH en het
C4B gen in CSC, terwijl de rol van het ARMS2 en het NR3C2 gen in CSC niet kon worden gereproduceerd. Opvallend genoeg, in onze studies vertonen de acute CSC, niet ernstige cCSC en ernstige cCSC, als vermoedelijk klinisch verschillende fenotypes, een vergelijkbare genetische predispositie en waren de klinische beelden onderling niet te onderscheiden op basis van deze genetische variaties. We concluderen dat CSC-fenotypes ondanks hun klinisch uiteenlopende presentaties, een vergelijkbare genetische predispositie hebben in relatie tot het CFH en het C4B gen. Er zijn vermoedelijk andere tot heden onbekende (genetische) risico factoren die een rol spelen in het ziektebeloop van CSC.

Hoofdstuk 4 focust op de effectiviteit van PDT-behandeling in alle CSC fenotypes en evaluateert potentiële factoren die de effectiviteit kunnen beïnvloeden. Het gebruik van corticosteroïden is tot op heden de belangrijkste exogene risicofactor voor CSC. Een dilemma doet zich voor wanneer een patiënt met een corticosteroid-afhankelijke behandeling (bijvoorbeeld na een organaanplantatie) ook aan CSC lijdt, en het gebruik van corticosteroïden niet kan staken. Het is tot heden onbekend of PDT-behandeling effectief kan zijn in corticosteroid-geassocieerde CSC. In Hoofdstuk 4.1, beschrijven we het effect van de PDT-behandeling in corticosteroid-geassocieerde cCSC en vergelijken we dit behandeleffect met cCSC patiënten zonder corticosteroiden gebruik in de voorgeschiedenis. We laten zien dat PDT even effectief is in beide groepen en dat het effect onafhankelijk is van corticosteroid gebruik. Subretnaal vocht droogde volledig op in 74% van corticosteroid-geassocieerde cCSC en de visus steeg tevens significant na behandeling. Hoewel het staken van corticosteroïden het belangrijkste advies in behandeling van cCSC blijft, tonen wij dat een PDT-behandeling effectief is voor patiënten die corticosteroid gebruik niet kunnen staken door andere medische comorbiditeiten.

In Hoofdstuk 4.2 is de focus gelegd op het behandeleffect van PDT in ernstige cCSC. We rapporteren dat PDT-behandelingen in deze groep patiënten met de meest uitgebreide anatomische afwijkingen, langdurige ziekte en frequente terugkeer van vocht onder de retina, even effectief is in het anatomisch herstel (87%) en vergelijkbaar is met cCSC patiënten zonder kenmerken van een ernstige ziekte. Ook de visus verbetert in ernstige cCSC na PDT-behandeling. Echter dit visus herstel is beperkerd in vergelijking met niet ernstige cCSCs. Onze data laten zien dat een lage visus voorafgaand aan de PDT behandeling in de ernstige cCSC groep een voorspellende factor is voor een slechtere eind visus in deze patiënten. Vermoedelijk speelt een preéxistente permanente schade aan fotoreceptoren door langdurige ziekte een rol in dit beperkte visuele herstel.

In het concluderende Hoofdstuk 5 bespreken we onze belangrijkste bevindingen in een breder perspectief van de literatuur. Er blijven nog altijd meerdere vragen onbeantwoord in de pathofysiologie van CSC zoals nieuwe en nog onbekende genetische risicofactoren voor het ontstaan van CSC, evenals de rol van andere (genetische) risico factoren die bepalend kunnen zijn voor het ziektebeloop en hun invloed op de behandeling. Er is zodoende nog veel ruimte voor toekomstig onderzoek voor het verder ophelderen van deze hiaten in onze kennis van CSC.
CHAPTER 6.3

Acknowledgments (Dankwoord)
Chapter 6.3

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CHAPTER 6.4

About the author
CURRICULUM VITAE

Danial Mohabati was born on the 21\textsuperscript{st} of March 1987 in Gorgan, by the northern coast of Iran. In 2005 he graduated from the Sama high school in Tehran. In the same year Danial moved to the Netherlands to pursue higher education. After graduating from the preparation program and the language course at Leiden University in 2006, he attended the University of Applied Sciences (Hogeschool) in Leiden and studied ‘Biology and Medical Laboratory’ between 2006 and 2008. In September 2008 he was admitted to study Medicine at Leiden university. As a student Danial was also an active committee member of the International Federation of Medical Student Association, and organized multiple national events.

Danial’s interest and curiosity for ophthalmology were arisen during the senior internship in 2014 at the Department of Ophthalmology of the Leiden University Medical Center (LUMC). His enthusiasm in this field led to a research internship on the topic “chronic central serous chorioretinopathy and the influence of corticosteroid use on treatment outcome in this disease”, which was supervised by Prof. Dr. C.J.F. Boon. After obtaining his M.D. degree in 2015, he was offered to continue his research as a PhD-student on the project titled “The clinical spectrum of central serous chorioretinopathy” under supervision of Prof. Dr. C.J.F. Boon, Dr. S. Yzer, and Prof. Dr. G.P.M. Luyten at the department of ophthalmology of the LUMC. For this multicenter project Danial collected clinical data and genetic material to build a large database. This was done in three outpatient clinics of the LUMC in Leiden, the Radboud UMC in Nijmegen, and the Eye Hospital in Rotterdam. The results of his research project are presented in this thesis.

As a PhD-student Danial attended multiple national and international conferences including the ARVO, the EURETINA, the NOG, the DOPS, and presented his research results there. In 2016 he won the third prize at the Bayer Ophthalmology Research Award, and in 2018 was nominated for the best ARVO poster award. He started his residency training in ophthalmology at the LUMC in 2018, under the supervision of Prof. Dr. G.P.M. Luyten and Prof. Dr. N.E. Schalij-Delfos.

Besides his professional occupations Danial enjoys the family life with his partner Anne and their daughter Jasmin and their son Siebe. He also enjoys reading history, doing carpentry and cooking for friends and family.
CHAPTER 6.5

List of publications
**Efficacy of photodynamic therapy in steroid-associated chronic central serous chorioretinopathy: a case-control study.**
*Joint first authors

**Neovascular age-related macular degeneration without drusen in the fellow eye: clinical spectrum and therapeutic outcome.**

**Familial central serous chorioretinopathy.**

**Genetic risk factors in acute central serous chorioretinopathy.**
*Joint first authors
#Joint last authors
Retina. 2019 Dec;39(12):2303-2310

**Clinical spectrum of severe chronic central serous chorioretinopathy and outcome of photodynamic therapy.**

**Clinical characteristics and long-term visual outcome of severe phenotypes of chronic central serous chorioretinopathy.**

**Correlation between redefined optical coherence tomography parameters and best-corrected visual acuity in non-resolving central serous chorioretinopathy treated with half-dose photodynamic therapy.**
List of publications

Thomas J. van Rijssen, Danial Mohabati, Greet Dijkman, Thomas Theelen, Eiko K. de Jong, Elon H. C. van Dijk, Camiel J. F. Boon

Lipocalin 2 as a potential systemic biomarker for central serous chorioretinopathy.

Risk of Recurrence and Transition to Chronic Disease in Acute Central Serous Chorioretinopathy.
Danial Mohabati, Camiel J. F. Boon, Suzanne Yzer

Clinical characteristics and outcome of posterior cystoid macular degeneration in chronic central serous chorioretinopathy.
Danial Mohabati, Carel B. Hoyng, Suzanne Yzer*, Camiel J. F. Boon*  
*Joint last authors  
Retina. 2020 Sep;40(9):1742-1750.

Genetic risk factors in severe, non-severe, and acute phenotypes of central serous chorioretinopathy.
# Joint last authors  
Retina. 2020 Sep;40(9):1734-1741

The spectrum of polypoidal choroidal vasculopathy in Caucasians: clinical characteristics and proposal of a classification.
Elon H. C. van Dijk, Danial Mohabati, Simona Veselinovic, Wing H. Chung, Greet Dijkman, Camiel J. F. Boon

I’ve blown my nose!
Daan Schuur, Danial Mohabati, Bart van der Weerd

Fundus autofluorescence abnormalities can predict fluorescein angiography abnormalities in patients with chronic central serous chorioretinopathy.
Danial Mohabati, Camiel J. F. Boon, Carel B. Hoyng, Konstantine Purtskhvanidze, Johann Roider, Elon H. C. van Dijk
Central serous chorioretinopathy (CSC) is a multifactorial disease of the retina and the choroid, which generally affects otherwise healthy and relatively young male patients (between their twenties and sixties). The disease is characterized by a serous detachment of the neurosensory retina in the central macula, which causes visual complaints including blurred vision, a central relative (grayish) scotoma, metamorphopsia, and alterations in color and contrast vision. Due to its sudden onset and disturbance of central vision, CSC can have a large impact on the affected person.