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

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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).[18-20] 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.[18]

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.[21]

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.[20] In CSC patients, thickened vessels in Haller's layer with congested overlying capillaries and a thinned choriocapillaris are common features in all patients.[22, 23] 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.[24] Brinks et al. have proposed that there may also be a role for abnormal arteriovenous anastomoses in causing these choroidal abnormalities and their consequences.[25] Ultimately, these structural changes cause dysfunction of the RPE, thereby damaging the integrity of the outer blood-retina barrier formed by the RPE.[26, 27] The increased choroidal permeability may subsequently lead to a local elevation of the overlying RPE, and a subsequent serous RPE detachment.[28] Sub-RPE serous fluid may break through the RPE and leak in the subretinal space, causing a serous neuroretinal detachment.[26] 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. [29, 30] 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.[27, 31]

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,[32] whereas others suggest a duration of 6 months.[33-35] 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

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,[40] 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.[38, 41-44] 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.

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.[45] 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).[46] 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.[46] 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.[47] The auteurs also emphasized on the necessity of availability of both affected and fellow eyes information in the process of classification.[47]

Reasons to differentiate phenotypes

Recognizing specific landmarks in the clinical presentation of CSC phenotypes is important not only for an accurate diagnosis,[17] 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,[45] as well as preferences for treatment.[48] 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.[45] 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.[48] Many physicians consider treatment only when a CSC patient develops (or presents with) chronic disease.[49, 50] 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.[10, 29, 35] 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.[9, 51] 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,[1, 13, 32, 39] and may occasionally even lead to legal blindness.[12] In addition, cCSC patients have a worse vision-related quality of life.[11] 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.[46] 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.[48] When there is no spontaneous resolution, treatment is often considered to prevent (further) vision loss.[33, 52] However, an early treatment may be desirable also in aCSC because even a short period of SRF accumulation may cause damage to retinal photoreceptors,[53] and also to attempt to reduce the risk of disease recurrence, as we have shown in Chapter 2.1.[54] 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.[54, 55] However, while one trial reported an improvement of visual outcome in the treated group,[54] in the other trial the final visual outcome was similar between the different groups.[55] 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.[56, 57] 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).[49, 58-61] 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.[61] Our research group showed in the SPECTRA trial that half-dose PDT was markedly superior over oral eplerenone.[58] Finally, in the PLACE trial half-dose PDT was proven to be markedly superior over high-density subthreshold micropulse laser treatment.[59] 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.[49]

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.[62] 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.[38] 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.[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).[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.[1, 6] However, these definitions are still subject to variable interpretation and have not been sufficiently validated.[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,[40] to extensive end-stage variants with extensive RPE atrophy (DARA) and PCRD, to even bullous retinal detachment, and many more variations in between.[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.[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.[64] 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.[43,65] 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.[38]

Fortunately, only a minority of CSC patients has a severe form at first presentation.[38, 42, 43, 66, 67] 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.[36, 68] 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.[69-72] 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.[72-80] 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.[74, 76] 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

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.[80] 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.[81-83] 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.[74, 76, 80] However, in contrast to AMD, no systemic complement abnormalities are found in CSC patients.[84, 85] Therefore, complement system effects may be more localized in CSC. 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.[76] 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.[76, 86] 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.[74, 76] 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.[87] 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.[88-90] Previous studies in animal models have suggested involvement of the mineralocorticoid receptor in the pathogenesis of choroidal changes in cCSC.[91] 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.[79] However, in our analysis of the *rs2070951* SNP in *NR3C2* gene in aCSC, non-severe cCSC, and severe cCSCS 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.[74, 76, 79] 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.[74, 76] 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.[74, 76] 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.[92-94] A similar mechanism might explain the larger genetic predisposition among aCSC patients, who are generally younger than cCSC patients.[62] 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.[48, 49, 95] 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.[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.[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.[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.[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.[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.[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.[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.[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. [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.[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 de 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.[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.[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.[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.

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.[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%.[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.[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.[19, 44, 127] This PCRD without CNV should be differentiated with multimodal imaging from CSC cases complicated by CNV, which is also relatively common.[128, 129] In such cases with CNV, anti-VEGF treatment would be required.[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,[134] 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.[19, 135] 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.[136]

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.[39, 56, 134, 137-139] Others reported no clear association between visual outcome and symptom duration, baseline CRT, and the pattern of FA leakage.[140] However, almost all studies agree that a higher baseline visual acuity before treatment is an important prognostic factor for a better final visual outcome.[56, 105, 107] 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.[138] Poorer visual outcome was also related to greater dimensions of SRF (specially higher SRF), and thinning of the foveal outer nuclear layer on OCT.[141] Chan and coworkers reported in a prospective study that PDT was less effective in CSC eyes with

a central RPE detachment, possibly due to a less effective laser penetration.[137] 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.[108, 142] 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.[11, 40, 59]

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.[143] 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.[144] 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.[145] 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.[146] 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.[147] 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.[46] 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.[49] 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.[49, 58-60, 111, 116, 148]

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).[49] 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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