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

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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).

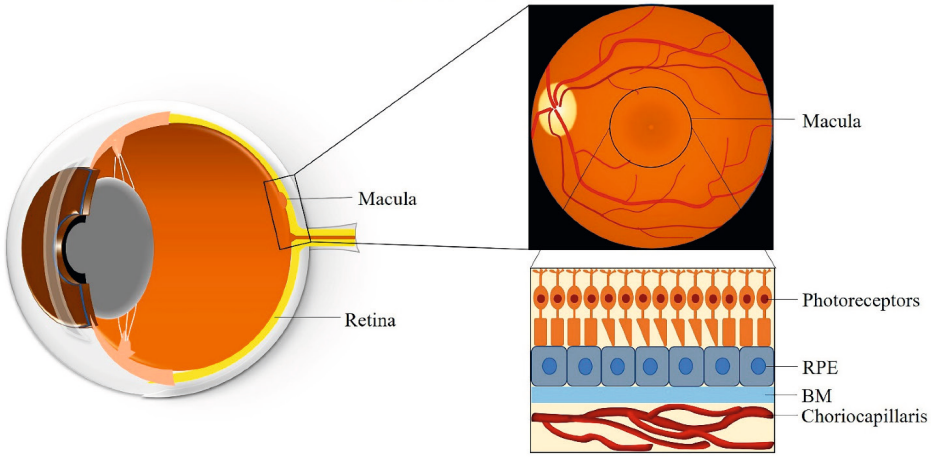


Figure 1. Anatomy of the human eye and a simplified schematic overview of the neuroretina. Abbreviations: RPE, retinal pigment epithelium; BM, Bruch's membrane (Ruan et al, 2021 [204]).

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.[3] These complaints are caused by a detachment of the neurosensory retina in the macula due to an accumulation of subretinal serous fluid (SRF).[4-6] As a result of the serous detachment of the neurosensory retina, the physiological connection between the photoreceptors and the underlying RPE cells is disturbed.[7, 8] 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.[7] 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.[9, 10] 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.[7]

The clinical presentation of CSC is heterogenous 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.[11] 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.[12, 13] Men are affected up to 7 times more often than women.[14] Women with CSC tend to be older at the time of first presentation.[15] Besides the older age of onset, CSC specific findings on multimodal imaging techniques, and disease progression show similar patterns between males and females.[16] CSC is more prevalent in the Caucasian and Asian population and somewhat less frequent in the African populations.[17]

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.[12, 18] 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.[18-20] Thus far, no direct dose-dependent association has been found.[21] However, a more chronic and extensive

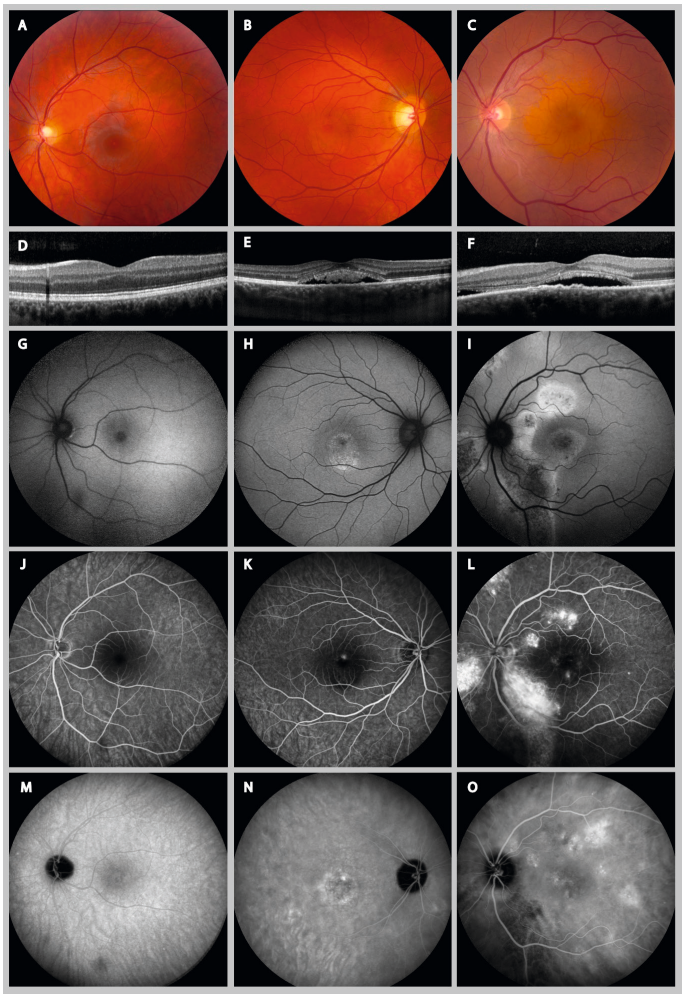


Figure 2. An overview of findings on multimodal imaging in a 27-year-old healthy male (A, D, G, J, M), a 41-year-old male with acute central serous chorioretinopathy (aCSC) (B, E, H, K, N), and a 59-year-old male with chronic CSC (cCSC) (C, F, I, L, O). There are barely any differences noticeable on 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.[22] Furthermore, steroid-associated CSC is often found bilaterally.[23] 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.[19] 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.[23]

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.[24-26] 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.[27-30] Similar discrepancies exist on the role of intrinsic testosterone levels and the risk of CSC development.[25, 29, 31] 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.[18] In these women, CSC was suggested to be related to hormonal disturbances, since CSC occurred especially in the third trimester of the pregnancy.[32, 33] 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.[32, 33]

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.[34] However, CSC cases have been reported in highly myopic patients with a relatively thin choroid.[35]

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.[36, 37] 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.[37-39] Furthermore, systemic conditions such as hypertension, autoimmune disease, intestinal H. pylori infection, and sleeping disorders may also contribute to the risk of CSC development.[18, 37, 39, 40] On the other hand, there are also risk reducing factors.

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

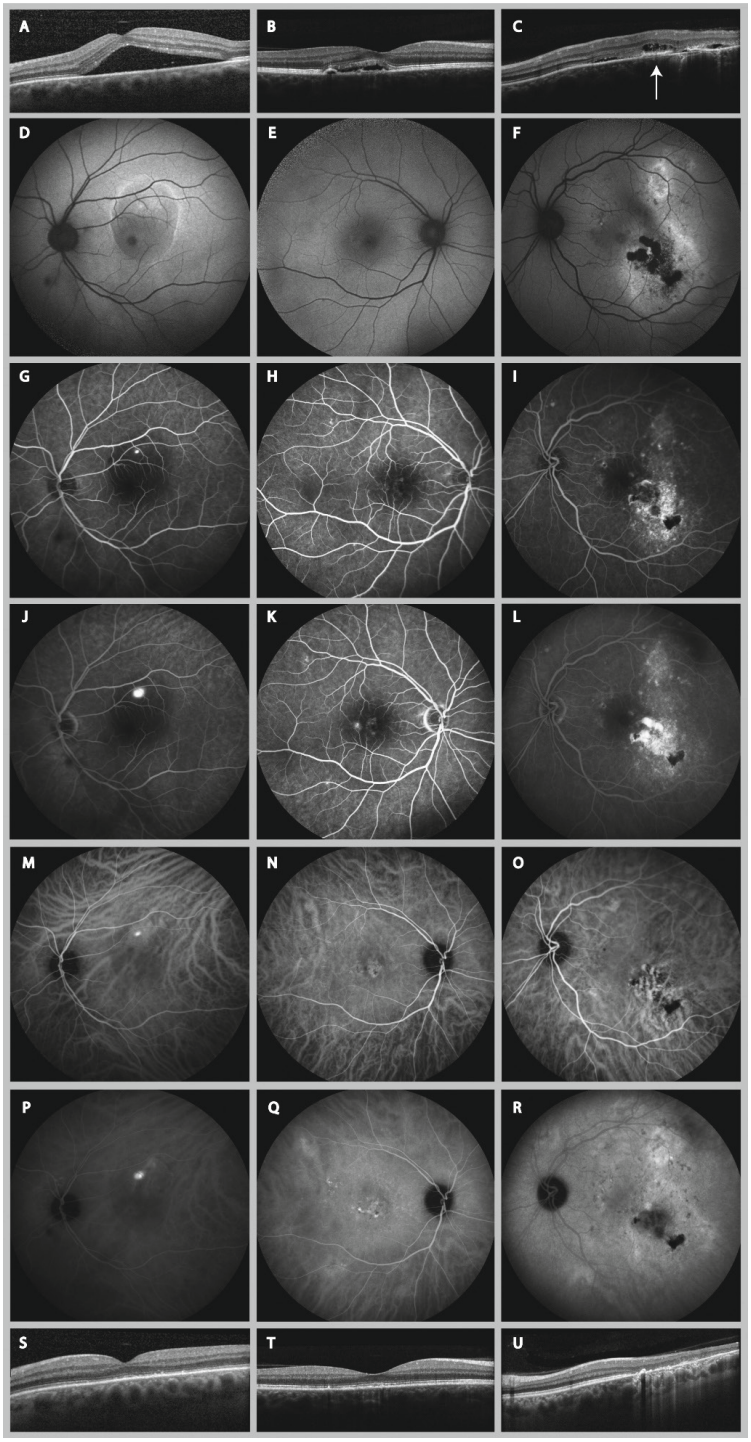
There is still much unknown about the pathophysiology of CSC, despite the increasing amount of literature.[60] It is currently thought that there is an elevated fluid pressure from the choroidal vasculature into the subretinal space.[1, 9, 10, 61] The mechanism may be explained as follows: An abnormally increased blood flow from the congested choroidal vessels causes serous leakage into the interstitial space.[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.[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.[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.[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.[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.[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 dependent photoreceptor (rods and cones) cells.[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.[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.[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,[72] subretinal debris accumulation as a sign of chronicity,[73] the aspect of RPE detachment, detecting irregularities suspicious for sub-RPE neovascularization and choroidal thickness and structure (Figure 3A, B, C).[8, 74] For instance, enhanced depth imaging OCT (EDI-OCT) has shown that choroidal thickening in CSC is mostly due to dilation of deep Haller's layer vessels, while the superficial choriocapillaris layer and medium-sized Sattler's layer vessels are abnormally thinned.[61, 62, 75]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<- Figure 3. This figure depicts multimodal imaging in a 47-year-old male with acute central serous chorioretinopathy (aCSC) (A, D, G, J, M, P, S), a 55-year-old female with non-severe chronic CSC (cCSC) (B, E, H, K, N, Q, T), and a 42-year-old male with severe cCSC (C, F, I, L, O, R, U). Optical coherence tomography (OCT) in the aCSC patient shows a large dome-shaped neurosensory detachment due to subretinal fluid (SRF) (A). OCT in non-severe cCSC shows a relatively shallow SRF accumulation and small retinal pigment (RPE) detachments (B). OCT in the severe cCSC shows multiple areas of SRF, a broad but shallow RPE detachment with a RPE break, and an area with posterior cystoid retinal degeneration (PCRD, white arrow) (C). Fundus autofluorescence (FAF) imaging in aCSC clearly demarcates the area with SRF (D). Only a small hypofluorescent spot can be seen on the FAF in the non-severe cCSC patient (E), while the severe cCSC shows large areas of mixed hypofluorescent and hyperfluorescent RPE changes (F). Early-phase (1 minute) fluorescein angiography (FA) in aCSC shows only a small well-defined hyperfluorescent spot (G), which enlarges in the mid-phase FA and corresponds with the leakage area (J). Early-phase FA (H) and mid-phase FA (K) in non-severe cCSC show a more diffuse and mottled hyperfluorescent area in the macula. FA in severe cCSC shows extensive areas of multifocal leakage and RPE atrophy visible as hyperfluorescent window defects (I, L). Findings on indocyanine green angiography (ICGA) in aCSC (M, P) are almost identical to the FA images revealing the leakage spot. ICGA abnormalities in non-severe cCSC (N, Q), and severe cCSC (O, R) are larger than the RPE leakage areas on FA, showing the underlying multifocal areas of choroidal hyperpermeability and leakage. OCT images at final visit show complete recovery in all the three patients (S-U). SRF resolution happed spontaneously in two months in the aCSC patient (S). SRF in non-severe cCSC resolved completely after half-dose photodynamic therapy (PDT) (T), and in the severe cCSC both SRF and PCRD resolved after half-dose PDT (U).

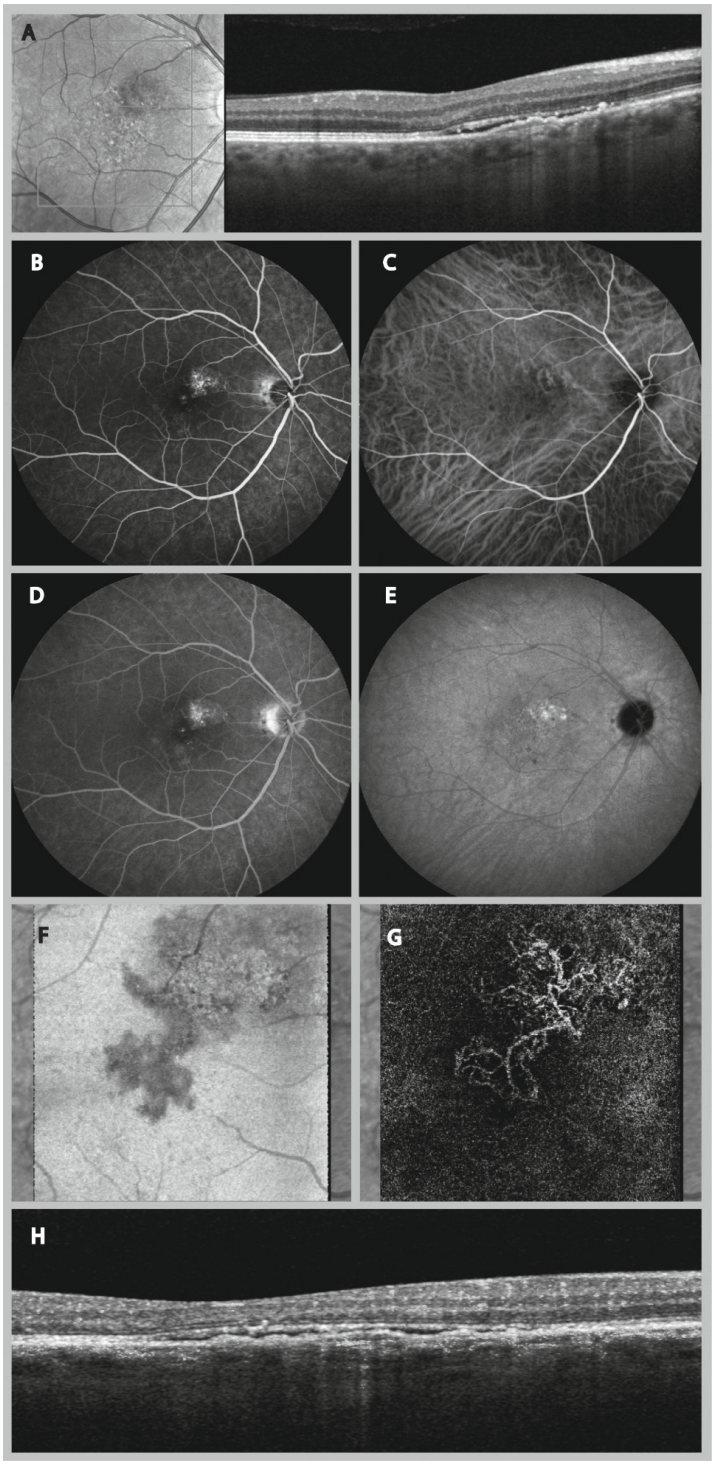
OCT angiography combines the abilities of conventional (structural) OCT with the possibility to evaluate the choroidal and retinal vasculature in a noninvasive manner.[76] Although vessel leakage and subretinal fluid leakage through the RPE cannot be visualized on OCT angiography, this technique may 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.[77, 78] 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).[77, 79]

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).[80] This technique made it possible to visualize disturbed or damaged RPE.[81] Different patterns of FAF abnormalities are distinguishable.[14] 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.[82] 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).[83]

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).[1] A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<- Figure 4. Multimodal imaging of a 49-year-old male with chronic central serous chorioretinopathy (A-H). Patient was successfully treated with micropulse laser and had complete resolution of subretinal fluid (SRF). Patient returned six years after recovery with a mild central SRF recurrence and a shallow retinal pigment epithelium (RPE) detachment, as shown on optical coherence tomography (OCT) (A). Also, an accumulation of greyish hyperreflective material is visible in the area between the RPE and the Bruch's membrane (double-layer sign), which is suggestive for neovascular tissue (A). Early-phase (up to 3 minutes) (B) and mid-phase (3 to 8 minutes) fluorescein angiography (FA) (D) show a growing area of diffuse macular leakage and RPE alterations. Indocyanine green angiography (ICGA) imaging also shows a demarcated area of choroidal leakage suggestive for an occult choroidal neovascular membrane (C, E). OCT angiography imaging clearly shows the neovascular network at the double-layer sign, and when the OCT segmentation is adjusted to cover the space between the RPE and the Bruch's membrane (F-H).

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.[66] 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.[85] 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).[86] 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

an ischemic component due to choriocapillaris thinning, Bruch's membrane damage, and an increased level of vascular endothelial growth factor.[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.[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.[12, 60] The clinical presentation of CSC is highly variable, and the different terminology used to classify CSC is subject of controversy.[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.[60, 96] Alternative classifications have been suggested that also include non-resolving CSC, recurrent CSC, multifocal CSC, and inactive CSC.[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.[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.[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.[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.[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.

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

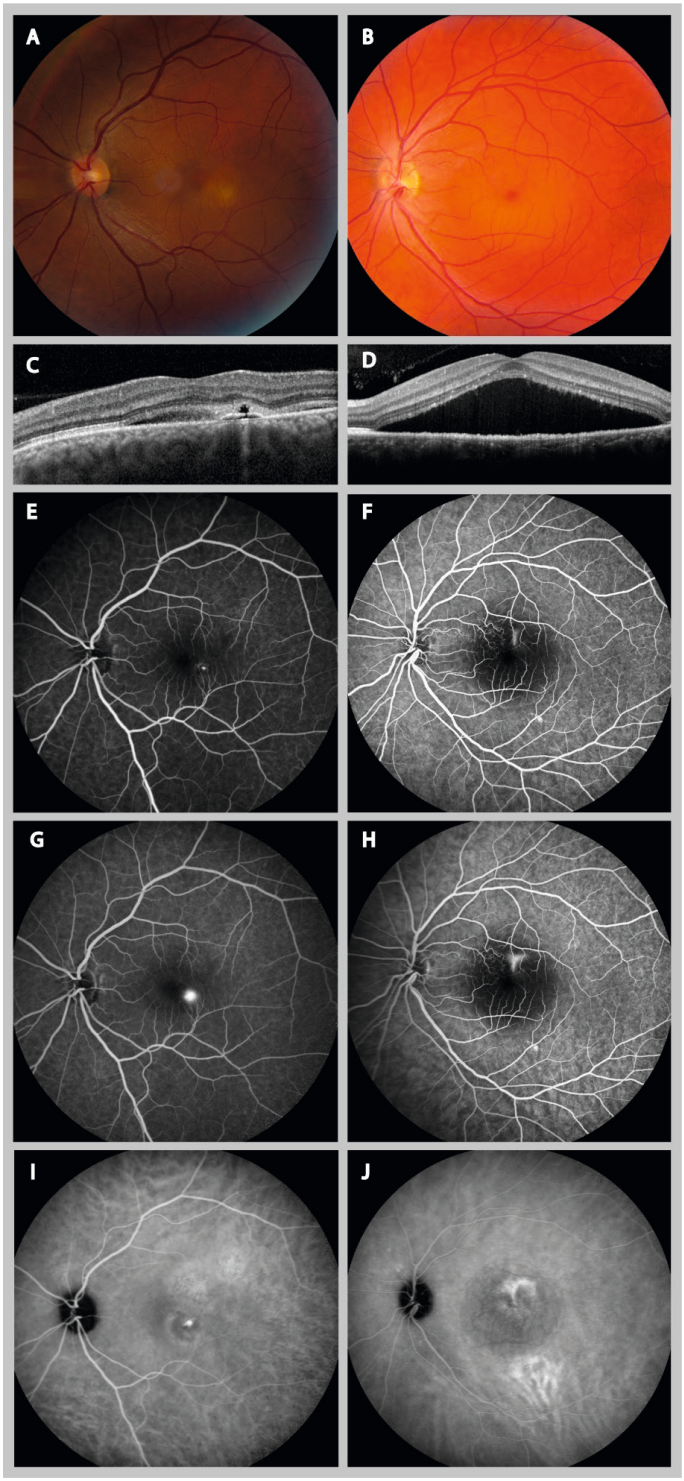
2.1 Acute CSC

General clinical characteristics

Acute CSC (aCSC) is characterized by a sudden onset of central vision loss.[12, 60] This CSC phenotype is more frequent among younger patients during their professionally active age (between 35 and 55 years), and rare among the elderly.[13] The clinical presentation of aCSC includes a unilateral dome-shaped serous retinal detachment in de macula as observed fundoscopically and on OCT imaging (Figure 3A).[103] 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.[104] 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.[8, 74] Gradual restructuring of these layers after SRF resolution was shown to be followed by visual recovery.[74, 105, 106] 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).[5, 103] 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).[107] 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 "ink-blot" (Figure 5E, G).[60] FA may also show minimal focal RPE alterations, sometimes even in the non-symptomatic contralateral eye,[108] but in absence of significant atrophy of the RPE, the latter being indicative of chronic disease.[5, 105] 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,[109] or slightly hyper-autofluorescent (Figure 3D).[83] 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).[110, 111] 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.[110]

Prognosis

Acute CSC is generally self-limiting with a (near) complete visual recovery.[12, 60] It has been estimated however, that between 20% to 50% of aCSC patients have disease recurence. Others will only experience one disease episode.[12, 60, 112] 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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<- Figure 5. Multimodal imaging showing an ink-blot versus a smokestack leakage pattern in two patients with chronic central serous chorioretinopathy (cCSC); a 40-year-old male with persistent cCSC for four months (patient one) (A, C, E, G, I), and a 42-year-old male with recurrent cCSC (patient two) (B, D, F, H, J). Optical coherence tomography (OCT) in patient one shows subretinal fluid (SRF) in the fovea and an adjacent small retinal pigment epithelium (RPE) detachment, with a small RPE break on the top (C). OCT in patient two shows only a large dome-shaped serous retinal detachment with SRF (D). In patient one an ink-blot leakage pattern can be seen, which starts as a small hyperfluorescent spot in the early-phase (up to 3 minutes) fluorescein angiography (FA) (E), and becomes larger and more intense in the late-phase (8 minutes) FA (G). This leakage spot corresponds accurately with the location of the RPE break on OCT (C). In patient two a smokestack leakage pattern can be seen, showing fluorescein dye gradually ascending from the RPE break in the early-phase FA (F), and forming a 'mushroom' shape in the late-phase FA (H). Indocyanine green angiography (ICGA) in both patient reveals more vast and multifocal hyperfluorescent areas of choroidal leakage (I, J).

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.[112] 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.[113, 114] 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.[115] 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.[12, 96, 116] 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.[117] Currently, a spontaneous disease resolution is awaited for at least 3 months before treatment is considered.[116, 118] 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.[119] Also, earlier treatment may be considered in patients with a recurrent episode of aCSC.[116]

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.[96] 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.[14, 96, 120] Traditionally, conventional thermal laser is used to consolidate the leakage spot.[121, 122] 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

RPE, and stop subretinal leakage. This method may still be used when other treatments are not available.[123] 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.[12, 120] Also, functional outcome in terms of gain of visual acuity and reduced recurrence rate after this treatment modality is inconsistent.[124] 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.[125]

Photodynamic therapy (PDT), is increasingly considered as treatment of first choice in all CSC phenotypes.[96, 126-128] 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.[96, 129, 130] Subretinal leakage may stop when choroidal congestion is decreased, resulting in resorption of SRF, and eventually improvement of visual acuity.[126, 127] 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).[127] 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.[118]

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.[131, 132] 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.[96] 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.[96] 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.[133]

Occasionally, treatment with an intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents is reported,[134, 135] 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.[136, 137]

Currently, a few comparative RCT studies are available, discussing different treatments in aCSC.[118, 122, 127, 133, 138, 139] 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.[60, 119, 140] 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).[98] 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.[61, 106, 141] 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.[93, 142] 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).[143, 144] 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).[77, 78, 145]

Interpretation of 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).[83]

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.[12, 60] 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).[60] As mentioned earlier is FA used to study retinal vascular abnormalities, whereas ICGA is used to illustrate deeper choroidal abnormalities in cCSC.[146] 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).[12, 60] 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,[142] having an important role in directing treatment, as will be discussed in the following paragraphs.

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.[3, 141] 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.[14, 140] 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 pateints,[147] which may be informative in evaluating disease prognosis.

Treatment

The treatment approach for cCSC is not globally uniformed.[116, 148] Several relatively large prospective RCTs and retrospective studies have shed more light on the efficacy of the most commonly performed treatment options for cCSC.[96, 128, 149] 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.[12, 96, 150]

The role of cortisol and endogenous mineralocorticoid in CSC risk has been established.[18, 26] 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.[96, 151-153] However, the conclusions of different studies are not always coherent. 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.[149] Also, there was no significant difference in visual outcome between cCSC patients who were treated with eplerenone and those who received sham.[149] The SPECTRA trial compared the outcome of oral eplerenone treatment during three months with half-dose PDT.[154] 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).[154] 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.[154] There were also no major adverse events reported in both treatment groups, making PDT evenly safe as eplerenone treatment.[154] 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.[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.[96, 155] Subthreshold micropulse laser seems particularly effective in studies on cCSC eyes with focal leakage rather than diffuse leakage.[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).[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^2 verteporfin, 50 j/cm^2 energy for a duration of 83 seconds) in treatment of cCSC.[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^2), half-fluency (25 j/cm^2), or half-time (40 seconds)) in cCSC patient.[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.[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).[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.[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.[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.[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.[173] Recently the term peripapillary pachychoroid syndrome (PPS) was introduced to address a new entity within the pachychoroid disease spectrum, which also includes CSC.[92] 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.[92, 174] 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).[93, 142] Different types of CNV's exist.[175] 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.[143, 176] 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.[77, 177] It is estimated that secondary CNV formation may occur in approximately 2-15% of CSC patients,[142, 178] mostly in chronic cases, but occasionally in acute cases too.[178] 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.[179] A timely diagnosis of secondary CNV is of great importance as it may, when left untreated, damage the vision dramatically and permanently.[140, 178, 180] Monotherapy 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.[181-183] However, combination therapy seems the most sensible choice, as it deals with both thenon-VEGF driven cCSC, and the VEGF-driven CNV.[96]

Polypoidal choroidal vasculopathy

Polypoidal choroidal vasculopathy (PCV) is considered a variant of type 1 macular CNV.[184, 185] 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.[186] 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.[187-191] 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.[192] 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.[12, 179] 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.[193, 194] Secondary PCV may occasionally complicate cCSC, and PCV may even present as a masquerader of CSC.[187, 188, 195] PCV may also independently of the occurrence of CSC be considered part of the pachychoroid disease spectrum, just like CSC,[90] as a thickened choroid (thickness above 395 µm) was also shown to be a frequent finding in PCV.[196] PCV, regardless of its background, always needs to be treated, just like any other type of subretinal neovascularization.[197] In PCV, full-settings PDT, usually in combination with intravitreal anti-VEGF medications, appears the most successful treatment.[198] This is in contrast to uncomplicated cCSC, in which PDT with reduced settings as monotherapy is effective and sufficient.[96]

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.[199] 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.[200] 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.[201]

Inferior bullous retinal detachments may be observed in rare cases of extensive and severe cCSC.[99, 202] These patients may also show multiple RPE detachments, RPE tears, and areas of non-perfusion on FA.[60] 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.[203] 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.[203] Future prospective studies are necessary to prove this theory.

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.*[205]).

	Disease	Clinical characteristics and differential diagnostic aspects	References
Ocular neovascular disease	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')	[179,206]
	Polypoidal choroidal vasculopathy	Older age; presence of polypoidal dilatations on OCT and ICGA, sometimes with concurrent non-polypoidal neovascularization on ICGA and OCT	[207-211]
	Neovascular age-related macular degeneration	Presence of drusen in combination with or without vitelliform lesion, neovascular lesion on OCT, OCTA, FA (and ICGA)	[212,213]
	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

	Disease	Clinical characteristics and differential diagnostic aspects	References
Vitelliform lesions	Autosomal dominant Best vitelliform macular dystrophy and autosomal recessive bestrophinopathy due to *BEST*1 gene mutations	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	221, 222
	Acute exudative polymorphous vitelliform maculopathy	Multiple, bilateral well-defined serous macular detachments, subretinal accumulation of yellow -white material; hyperautofluorescence on FAF; no focal leakage on FA/ICGA	223, 224
	Adult-onset foveomacular vitelliform dystrophy	Either unilateral or bilateral small (< 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	225-228
	Vitelliform lesions secondary to age-related macular degeneration	Presence of drusen in combination with surrounding vitelliform detachment, underlying confluent drusen	212, 213
	Vitelliform lesions in the context of other diseases	- Epiretinal membrane - Vitreomacular traction - Persistent SRF after retinal reattachment surgery	229, 230

Table 1 Continued

	Disease	Clinical characteristics and differential diagnostic aspects	References
Inflammatory diseases	(Vogt-Koyanagi-)Harada disease	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	231-233
	White dot syndromes (e.g., acute posterior multifocal placoid pigment epitheliopathy)	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	234
	Posterior scleritis	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	235, 236
	Sarcoidosis	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	237, 238
	Unilateral acute idiopathic maculopathy	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	239-242

Table 1 Continued

	Disease	Clinical characteristics and differential diagnostic aspects	References
Ocular tumors	Choroidal nevus and melanoma	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	[243, 244]
	Choroidal metastasis	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	[245-247]
	Circumscribed cavernous choroidal hemangioma	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	[248, 249]
	Choroidal osteoma	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	[250-254]

Table 1 Continued

	Disease	Clinical characteristics and differential diagnostic aspects	References
Hematological malignancies	Waldenström macroglobulinemia	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	255, 256
	Choroidal lymphoma	Presentation between fifth and seventh decade Multifocal, yellow-whitish choroidal infiltrates on fundoscopy, homogenous hyperreflective sub-RPE infiltration (primary vitreoretinal lymphoma) or deep choroidal infiltration (choroidal lymphoma) on OCT	257-259
	Leukemia	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	260, 261
Paraneoplastic syndromes	Bilateral diffuse uveal melanocytic proliferation (BDUMP)	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	262-264
	Paraneoplastic vitelliform maculopathy	Relationship with cutaneous and uveal melanoma; vitelliform lesions; anti-RPE and anti-retinal auto-antibodies in serum	265, 266

Table 1 Continued

	Disease	Clinical characteristics and differential diagnostic aspects	References
Genetic diseases	Best vitelliform macular dystrophy and autosomal recessive bestrophinopathy due to *BEST1* gene mutations	see 'Vitelliform diseases'	221, 222
	RP1L1-associated occult macular dystrophy	*RP1L1* gene mutation, autosomal dominant inheritance 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	267
	Central areolar choroidal dystrophy (CACD) due to *PRPH2* gene mutations	*PRPH2* gene mutation, autosomal dominant inheritance 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	268, 269
	Pseudoxanthoma elasticum and serous fluid	*ABCC6* gene mutation, autosomal recessive inheritance 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 Localized skin changes ('plucked chicken' appearance), premature atherosclerosis, gastrointestinal and cardiovascular complications	270, 271

Table 1 Continued

	Disease	Clinical characteristics and differential diagnostic aspects	References
Ocular developmental anomalies	Dome-shaped macula	Inward macular deviation with a thickened underlying sclera, together with relatively thin choroid, especially on vertical OCT scan	[272]
	Tilted disc with inferior staphyloma	Anterior position of the upper and temporal portion of the tilted optic disc, oblique axis of the optic disc with an inferonasal crescent, mild situs inversus of the retinal vessels, attenuation of the choroid and depigmented RPE in the staphylomatous inferior part of the eye SRF is visible on the horizontal and vertical OCT scan, but the vertical OCT scan shows the inferior staphyloma, in which SRF occurs in the watershed zone of thicker to thinner choroid; no focal leakage on FA/ICGA	[273, 274]
	Optic disc pit	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	[275, 276]
	Uveal effusion syndrome	Most often in middle-aged hyperopic men; localized areas of RPE hypertrophy and hyperplasia ('leopard spots') on examination, together with peripheral choroidal detachment and sometimes concomitant non-rhegmatogenous retinal detachment with shifting subretinal fluid; in the acute phase, 'leopard spots' correspond to hyperfluorescent areas on FA, which later become a mixture of hyper- and hypofluorescence, early granular hyperfluorescence on ICGA; choroidal detachment on ultrasonography	[277-279]
	Focal choroidal excavation with secondary serous subretinal fluid	Concavity in the choroid, with normal overlying retinal architecture	[280]
	Macular choroidal macrovessel	Large tortuous choroidal vessel temporally in the macula; no leakage on FA, early filling on ICGA	[281, 282]
	Torpedo maculopathy	Hypopigmented lesion of the RPE, temporally to the fovea with a tip pointing towards the fovea, some hyperpigmentation of edges; lack of autofluorescence on FAF and no leakage on FA	[283, 284]

Table 1 Continued

	Disease	Clinical characteristics and differential diagnostic aspects	References
Medication-related conditions and toxicity-related disease	MEK inhibitor associated serous retinopathy (MEKAR)	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	285, 286
	Checkpoint inhibitors causing birdshot-like chorioretinopathy (e.g. pembrolizumab)	Onset of SRF associated with checkpoint inhibitor treatment (for metastatic tumors); macular oedema, retinal vasculitis on examination	287-291
	Hair dyes containing aromatic amines (para-phenylenediamine and 5-diamine sulphate) causing serous retinopathy	Similar to MEKAR. Onset of SRF soon after the use of specific commercial hair dye containing aromatic amines; no pachychoroid or RPE detachments on OCT; no leakage on FA and no hyperfluorescent abnormalities on ICGA	292
	Poppers maculopathy	Either unilateral or bilateral yellow subretinal (foveal) deposit on fundoscopy, disruption of the ellipsoid zone and slight retinal elevation on OCT, no pachychoroid or RPE detachments on OCT, no leakage on FA	293, 294
Rhegmatogenous and tractional retinal detachment		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	295

Table 1 Continued

	Disease	Clinical characteristics and differential diagnostic aspects	References
Retinal vascular disease	Diabetic macular oedema	Diabetes mellitus in medical history; other features characteristic of diabetic retinopathy on examination (hemorrhages, microaneurysms, cotton wool spots, hard exudates)	[296-298]
	Retinal vein occlusion	Retinal hemorrhages, cotton wool spots, and vein occlusion on examination; non-perfusion on FA	[299, 300]
	Acute hypertensive retinopathy	Retinal hemorrhages, cotton wool spots, and blood vessel occlusion on examination, increased choroidal thickness on OCT in the acute phase A similar clinical picture may be observed in pregnant women with pre-eclampsia	[301, 302]
	Pregnancy-related serous maculopathy	Multifocal areas of SRF accumulation on OCT, together with intraretinal cystoid changes and outer retinal changes, hyperfluorescent changes corresponding to dye staining in the subretinal space on FA, choroidal filling defects on ICGA Hypertensive complications of pregnancy, e.g. (pre-)eclampsia	[303, 304]
Miscellaneous	Serous maculopathy with absence of retinal pigment epithelium (SMARPE)	SRF accumulates due to absence of RPE, no drusen; early hyperfluorescence on FA, no pronounced abnormalities on ICGA	[205]
	Serous maculopathy secondary to RPE dysfunction due to confluent drusen	Drusen, signs of age-related macular degeneration / drusen in other eye	[305]
	Serous maculopathy due to aspecific choroidopathy (SMACH)	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	[205]

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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