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

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## **CHAPTER 6**



## **CHAPTER 6.1**

### **English summary**

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

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

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

There is an ongoing controversy on the pathogenesis, classification, the prognosis and the best treatment options of CSC. Thus far, little was known about differences between CSC phenotypes, and whether they may have a different pathogenesis and clinical outcome. The aim of this thesis was to take a closer look at the strikingly variable clinical spectrum of CSC presentations, to evaluate treatment efficacy in these phenotypic subgroups, and to assess the possible role of genetic risk factors in disease development and clinical variability. In **Chapter 1**, we provided an introduction on CSC based on current literature.

**Chapter 2** addresses the clinical spectrum of CSC. In **Chapter 2.1**, we report on a proposed strict definition for aCSC, based not only on disease duration, but especially on clinical characteristics observed on multimodal imaging in both the diseased eye, and the fellow eye. We reported the long-term (>12 months) risk of recurrence and/or transition to cCSC in a typical aCSC cohort. All study eyes recovered from the first disease episode, with half of these eyes being treated and in the other half a wait-and-see strategy was followed. We reported that a significantly lower number of recurrence was seen in the cases that received early treatment (mostly photodynamic therapy (PDT), performed in 95% of patients) as compared to patients followed by a wait-and-see strategy (4% versus 24%, respectively). Despite this difference, the visual outcome was favorable in all cases and not different between both groups. We also observed an increase in atrophic RPE alterations in 36% of the aCSC eyes during follow-up, and 23% of the eyes had both an increase in RPE alterations and SRF recurrence. Based on these reports, we concluded that a tendency toward chronicity, in terms of gradual increase in RPE alterations and/or episodes of recurrent SRF may be expected in almost one third of typical aCSC cases, while early treatment may decrease the risk of recurrences. However, none of our aCSC cases developed a severe cCSC during the follow-up.

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

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

resolved completely. Visual outcome is also poor in cCSC with secondary PCRD, even after complete resolution of SRF and PCRD. Therefore, PCRD in cCSC patients can be considered a clinical sign for a poor prognosis.

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

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

In **Chapter 4.2**, we specifically assessed the efficacy of PDT in the most severe cCSC cases. Despite widespread abnormalities and chronic and recurrent SRF accumulation in these severe cCSC cases, PDT was able to restore the anatomy of the retina by resolving SRF in the majority (87%) of cases, comparable to cCSC cases that did not display characteristics of severity. We also confirmed that visual acuity improves after PDT treatment both in severe and non-severe cCSC cases. However, final visual acuity remained poor in severe cCSC cases. These severe cCSC cases generally have a worse baseline pre-treatment visual acuity compared to non-severe cCSC cases, presumably due to pre-existent permanent photoreceptor and RPE damage.



In **Chapter 5**, we summarize our findings and conclusions, and place them in a broader perspective and the context of current literature. There are still multiple unanswered questions on the pathophysiology of CSC, its classification, the role of genetic predispositions in CSC, factors contributing to a certain CSC phenotype, and treatment. These remaining questions should be unraveled further in future studies.