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Statement of the Professional Association of German Ophthalmologists (BVA), the German Society of Ophthalmology (DOG) and the German Retina Society (RG) on central serous chorioretinopathy

Situation January 2018

Key messages

Definition

- Central serous chorioretinopathy (CSC) is a unilateral or bilateral macular disease associated with the accumulation of subretinal fluid (SRF).

Incidence

- The frequency of CSC is not precisely known, but is put at an incidence of 1:10,000, primarily in males aged 30–50 years.

Pathogenesis

- The pathogenesis of CSC is multifactorial and is based on a complex interaction between environmental and genetic risk factors, with hyperpermeability of the choroidal vessels and subsequent changes to the retinal pigment epithelium (RPE) assumed to be the central pathogenetic factor.

Classification

- CSC is classified on the basis of temporal course (acute/chronic) and morphological findings. Both forms are characterized in the treatable phase by neurosensory detachment.
- Acute CSC: acute CSC exhibits SRF and one or multiple well-circumscribed pigment epithelial detachments, which may be striking on fluorescein angiography (FLA) as "leakage points." It can recur and transition to a chronic course.
- Chronic CSC: chronic CSC shows flat RPE changes of varying extent and associated photoreceptor degeneration with or without SRF. It may be an etiologically heterogeneous group of diseases that share a similar clinical appearance.
- In rare cases, choroidal neovascularisation (CNV) occurs as a complication.

Clinical symptoms

- Symptoms of acute CSC include often mild visual impairment, reduced contrast sensitivity ("gray disc"), blurred vision, metamorphopsia, micropsia, dyschromatopsia, and relative scotomas.
- Symptoms of chronic CSC include slow loss of visual acuity, often following recurrent acute episodes, and impaired contrast sensitivity, both in color vision and in the visual field.

Patient history

- At initial diagnosis, a targeted drug and disease history should be taken in order to adjust medication if

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necessary and treat risk factors in collaboration with the general practitioner. In particular, steroid treatment should be discontinued if possible.
Grade of recommendation: ⇑⇑

Diagnosis

- To diagnose and monitor acute CSC, best corrected visual acuity should be determined, as well as fundoscopy and optical coherence tomography (OCT) performed. FLA should additionally be performed in the case of an equivocal differential diagnosis or in order to localize and document leakage points. This should be performed prior to targeted laser therapy or photodynamic therapy (PDT), as well as in the case of suspected CNV. Indocyanine green (ICG) angiography may also be helpful.
  Grade of recommendation: ⇑⇑

Spontaneous course

- The literature puts spontaneous remission of SRF at 68% within 4 months and 84% within 6 months of initial diagnosis [19]. Recurrent accumulation of SRF in the further course is seen in approximately 50% of cases.

Treatment

- Due to the good spontaneous remission rates for CSC, it should only be monitored in the first 4 months and not treated, unless CNV is present.
  Grade of recommendation: ⇑
- If SRF persists for longer than 4 months and no clear trend toward resolution is seen, the following approaches can be used as treatment options in acute or chronic CSC:
  - Drug treatment approaches:
    - Due to positive evidence in recent studies on mineralocorticoid antagonists, the use of these substances can be considered, whereby eplerenone should be preferred due to its better side effects profile. Potassium levels should be monitored during this treatment.
      Grade of recommendation: ⇔
    - Since proof of efficacy is lacking in randomized controlled trials with sufficient patient numbers, carbonic anhydrase inhibitors should not be used and non-steroidal anti-inflammatory drugs and antioxidants must not be used.
      Grade of recommendation: ⇓
  - Laser therapy: extrafoveal leakage points can be treated with laser coagulation. Central leakage points can be treated with micropulse laser treatment.
    Grade of recommendation: ⇔
  - PDT: Half-dose or half-fluence PDT can be used in areas of leakage.
    Grade of recommendation: ⇔
- Secondary CNV in CSC should be treated with intravitreal administration of a VEGF inhibitor (see position paper on CNV not in age-related macular degeneration [nAMD])
  Grade of recommendation: ⇑⇑
- In all other cases, anti-VEGF therapy should not be used for CSC.
  Grade of recommendation: ⇑⇑

Introduction

Central serous chorioretinopathy (CSC) is a unilateral or bilateral macular disease that is initially associated with thickening of the choroid and the accumulation of subretinal fluid (SRF). In chronic forms, secondary degeneration of the retinal pigment epithelium (RPE) and photoreceptors occurs, as well as choroidal neovascularization (CNV) in rare cases.

Epidemiology

CSC most commonly occurs between the ages of 30 and 50 years [38, 80] and is the most frequent cause of irreversible macular damage after age-related macular degeneration (AMD), diabetic retinopathy, and retinal vascular occlusion [18]. The evidence on the incidence of CSC is poor. One study puts the incidence at 1:10,000/year, with males being predominantly affected and females six times less frequently affected [38]. There is controversy in the literature regarding an ethnic predisposition for the development of CSC. Although a higher incidence of CSC has been postulated among Caucasians, Hispanics, and Asians compared with African Americans [92], other studies have called this into question [21]. CSC is bilateral in up to 45% of cases [9, 26].

Risk factors

There are no clear risk factors for the development of CSC. The high number of investigations with sometimes contradictory results reflects the lack of understanding to date of the disease's pathogenesis. In their meta-analysis, Liu et al. evaluated possible risk factors for CSC [47]. According to their analysis, risk factors for the development of CSC include systemic or local corticosteroid treatment (odds ratio (OR): 4.2; 95% confidence interval (CI): 2.0–9.1), autoimmune disorders (OR: 3.4; 95% CI: 1.9–6.2), *Helicobacter pylori* infection (OR: 3.1; 95% CI: 1.8–5.4), psychopharmacological drug use (OR: 2.6; 95% CI: 1.6–4.4), type-A personality (OR: 2.5; 95% CI: 1.0–5.9), sleep disorders (OR = 1.9; 95% CI: 1.2–1.8), and arterial hypertension (OR: 1.7; CI: 1.2–2.2). Psychological stress, gastroesophageal reflux, gastric ulcers, pregnancy, systemic lupus erythematosus, multiple myeloma, and the use of antacids, antihistamines, and alcohol are also associated with the development of CSC. However, it should be borne in mind that psychosocial stress can cause a number of psychosomatic disorders, such as sleep disorders, gastroesophageal reflux, and gastric ulcers, all of which are associated with the development of CSC and are thus more likely to be epiphenomena rather than independent risk factors. A link between coronary heart disease and CSC has been postulated, but not confirmed in the meta-analysis [47].

Genetic analyses suggest that single nucleotide polymorphisms in the complement factor H, ARMS2 [35], and cadherin 5 genes increase the risk for the development of CSC [71]. However, the

pathophysiological significance of these genetic alterations remains unclear.

Pathophysiology

The pathogenesis of CSC appears to be multifactorial and is based on a complex interaction between environmental and genetic risk factors, which cause hyperpermeability of the choroidal vessels and subsequent changes to the RPE. The underlying pathophysiological changes have not been elucidated as yet.

Current evidence points to a particular role for corticosteroids [54] and over-activation of the choroidal mineralocorticoid receptor (MR) [18]. These receptors have two natural ligands, cortisone and aldosterone, with the former being more highly concentrated in blood. Preclinical studies show that over-activation of MRs by aldosterone or corticosterone causes vasodilatation and increased permeability of choroidal vessels [18]. Intravitreally administered aldosterone in particular induced choroidal vasodilation in animal models, as well as increased production of sodium (ENaC-α), potassium (Kir4.1), and water channels (aquaporin 4), which promote pigment epithelial detachment and SRF accumulation [18]. Other attempts to explain the pathogenesis of the disorder postulate a dysfunctional RPE and aberrant ion pumping function, which lead to reverse chorioretinal flow and the accumulation of SRF [82].

Classification and symptoms

CSC is classified on the basis of the temporal course of the disease (acute/chronic). The literature proposes an arbitrary limit of 4–6 months for disease duration to differentiate the acute from the chronic form [18].

The acute form of CSC is characterized by the accumulation of SRF and one or more mostly small, well-circumscribed serous pigment epithelial detachments, which are often localized in areas of choroidal vasodilation and hyperpermeability [76]. Symptoms of acute CSC include mild visual impairment, reduced contrast sensitivity ("gray disc"), blurred vision, metamorphopsia, micropsia, dyschromatopsia, and relative scotomas. Neurosensory detachment can also lead to hypermetropization. The spontaneous course of CSC is favorable and SRF absorbs within 4 months of initial diagnosis in 68% of cases and within 6 months in 84% [19]. Despite remission of SRF, patients may experience long-term metamorphopsia, reduced contrast sensitivity, and altered color vision [88]. Recurrent accumulation of SRF in the further course is seen in approximately 50% of cases. Subfoveal choroidal swelling, mild fluorescein leakage on angiography, hyperreflective foci in spectral-domain optical coherence tomography (SD-OCT), and shift work are discussed as independent risk factors for CSC recurrence [44, 50].

SRF that persists for a period of more than 4 months is referred to as acute CSC with persistent fluid. On fundoscopy, small yellowish precipitates are observed in the area of SRF; these are striking on SD-OCT as hyper-reflective structures in the outer granular layer or on the RPE [49]. The symptoms of this form are the same as those of acute CSC.

The chronic atrophic form of CSC was formerly referred to as "diffuse retinal pigment epitheliopathy" and is characterized by extensive RPE destruction and associated photoreceptor degeneration with or without SRF. Symptoms include moderate to severe vision loss and reduced light sensitivity, the severity of which depends on the extent of photoreceptor degeneration. This form is characterized by reduced autofluorescence on fundus autofluorescence [83] and by areas of granular hyperfluorescence with mild leakage that increases only slowly on fluorescein angiography (FLA) [93]. On SD-OCT, chronic atrophic CSC may also show intraretinal edema formation, which is believed to be secondary to RPE degeneration [33]. Whether acute CSC with persistent SRF can transition into chronic atrophic CSC or whether these are two distinct disease entities is the subject of controversy in the literature. Evidence of a continuum between the two forms has been described in case reports and case series [8, 36], but not validated in large prospective studies.

CNV may occur as a "complication" of CSC—presumably as a result of lesions in the region of the RPE/Bruch's membrane. Clinical signs include subretinal bleeding and extensive, clearly demarcated early hyperfluorescence with leaks ("classic" or type-2 CNV) on FLA. CNV is rare in young patients with the clinical picture of CSC and needs to be differentiated from idiopathic CNV in this patient group. Secondary CNV appears to occur more frequently in the chronic form of CSC and primarily in the area of irregular pigment epithelial detachments [5, 7]. In older patients (aged 50 years and over), the diagnosis of exudative AMD is also an important differential diagnosis.

Aggressive bullous serous retinal detachment with massive exudation and subretinal fibrin deposition is a rare special form of chronic CSC seen mainly in Asians or as an exacerbation following systemic corticosteroid therapy [28].

Differential diagnoses

Differential diagnoses of CSC include AMD (see above), polypoidal choroidal vasculopathy, CNV of other etiology, optic pit, choroidal hemangioma, metastasis, melanoma, uveitis, vitreomacular traction, papilledema, optic neuritis, and dome-shaped maculopathy associated with posterior staphyloma and high myopia.

Test methods

A targeted drug and disease history should be taken at initial diagnosis in order to adjust medication and treat risk factors, if required, in collaboration with the general practitioner. In particular, steroid treatment should be discontinued if possible. To diagnose and monitor acute CSC, best corrected visual acuity is determined and macular lesions investigated by means of fundoscopy and SD-OCT.

Optical coherence tomography

OCT characteristically reveals SRF and possibly focal pigment epithelial detachments, as well as an increase in choroidal thickness in the area of the macula [18]. It also shows an elongation of photoreceptor segments [51] and hyper-reflective

dots in the retina and subretinal space, the number of which increases with disease duration and which correlate with poor visual acuity [18]. Similarly, changes in the ellipsoid zone, regeneration of the photoreceptor layer, and loosening of the RPE layer can be detected by means of OCT and are associated with poor visual acuity [91]. OCT may also show intraretinal fluid in cases of chronic CSC, particularly when CSC persists for more than 5 years [33, 59].

Fluorescein angiography

FLA can be used in the case of an equivocal differential diagnosis or in order to localize and document leakage points. It is required for the precise planning of focal leakage point lasering or photodynamic therapy (PDT).

In the early phase of acute CSC, patients exhibit areas of focal hyperfluorescence, which go on to expand in a circular manner (inkblot pattern) or spread vertically and horizontally in about 15%; this is referred to as the smokestack phenomenon [10]. In chronic forms, FLA shows areas of granular hyperfluorescence with only mild leakage that increases slowly [93]. Fluorescence angiography also reveals pooling of the dye in the area of SRF and window defects in chronic cases.

Indocyanine green angiography

As an adjunct to FLA, indocyanine green angiography (ICG-A) provides additional information on the localization and extent of pathological choroidal vessels and can be performed prior to planned leakage point laser treatment or PDT. ICG-A initially shows hypofluorescent filling delays of the arteries and choriocapillaris, which can be found up into the late stage [37]. In the intermediate phase, one also sees dilated choroidal veins, map-like areas with increased fluorescence and indistinct contours, as well as smokestack phenomena, which are classically discussed as choroidal hyperpermeability and represent the goal of PDT [81]. Early staining with late hypofluorescence is observed in chronic CSC. ICG-A can also provide important information to aid the diagnosis of CSC in equivocal cases and help in its differentiation from atypical exudative AMD. Typically, ICG-A also reveals areas of hyperfluorescence in extramacular areas that cannot be seen on FLA.

Fundus autofluorescence

Fundus autofluorescence is mainly caused by lipofuscin granules in the RPE and provides additional information on structural and metabolic changes there [20]. Acute CSC shows a focal reduction in fundus autofluorescence in the area of exudation, indicating a focal RPE defect and early RPE detachment [2]. Fundus autofluorescence shows reduced autofluorescence in the area of SRF, which normalizes again as SFR decreases and is interpreted as a shadow phenomenon caused by the fluid and elongation of the outer photoreceptor segments [32]. In the case of a chronic course, one sees focal granular areas with increased autofluorescence, which might be explained by an accumulation of fluorophores in the photoreceptor outer segments [51] or by a subretinal accumulation of phagocytic microglia [53]. Patients with chronic atrophic CSC are characterized by long fundus autofluorescence gravitational tracks, which originate in the optic nerve and macular region in particular and are accompanied by a fine border of increased fundus autofluorescence [79]. However, the importance of autofluorescence is unclear at present.

OCT angiography

Although OCT angiography has no clear relevance in the diagnosis of CSC in clinical routine as yet, it may be able to provide additional information in the future [7].

Treatment

Despite decades of research, there is still no form of CSC treatment supported by a high grade of evidence. Due to the low incidence of CSC, its heterogeneous course, and its relatively frequent spontaneous resolution, large-scale, multicenter, randomized double-blind studies that adequately prove or refute the efficacy of treatments are lacking. After analyzing a total of 25 randomized controlled trials, a Cochrane study published in 2015 concluded that none of the treatment options available to date had sufficient evidence due to a lack of randomized studies with high case numbers [69].

Observation and modification of risk factors

Due to the good rates of spontaneous CSC remission, treatment should not be performed in the first 4 months following onset and the further course should be monitored, assuming CNV is not present. In the case of CSC remission, a slow improvement in morphological findings is usually seen first, while functional recovery takes longer [16].

Treatment with systemically or locally administered corticosteroids should—if possible and following consultation with the family practitioner—be discontinued or replaced, e. g., by non-steroidal immunomodulators [74].

Due to the link between elevated blood cortisol levels and the occurrence of CSC, stress prevention is discussed as a therapeutic option, particularly in type-A individuals. Having said that, the characterization of individuals into certain types, as it was popular in the 1980s, no longer plays a significant role in psychology today. Yanuzzi introduced this characterization in 1986 [92], basing it on a case report by Lipowski and Kirikos as well as even older literature from 1971 [46]. The hitherto unconvincing psychological therapeutic approaches make the significance of a stress hypothesis appear somewhat questionable. Moreover, there are no clinical studies with a high grade of evidence that validate stress prevention as a therapeutic option with confidence [53].

The treatment of concomitant sleep apnea and *Helicobacter pylori* infection, as well as the discontinuation of 5-phosphodiesterase inhibitors (e. g., sildenafil), to treat CSC is discussed in the literature, despite the fact that there is insufficient evidence to make a treatment recommendation [25, 34, 64].

Interventional treatment approaches

If SRF persists for longer than 4 months and no clear trend toward resolution is seen, the following approaches can be used as treatment options in acute or chronic CSC: Prior to treatment initiation, patients should be informed about the available evidence, possible side effects, and the off-label use of the treatment forms in question.

Drug treatment approaches

Antiglucocorticosteroid drugs

Due to the elevated blood cortisol levels in CSC patients [30], a number of treatment studies have been conducted using drugs that modulate the cortisol signal pathway. These drugs include, e. g., ketoconazole [52], mifepristone [56], finasteride [24], rifampin [78], and antiadrenergic drugs [31]. Despite the in part positive effects on the absorption of SRF and visual acuity, treatment with these drugs is currently not recommended due to a lack of randomized controlled trials and scant evidence.

Mineralocorticoid receptor antagonists

Spontaneous or corticosteroid-induced overactivation of the MR in choroidal vessels is assumed to be a central factor in the development of CSC (see above). MR antagonists such as spironolactone and eplerenone bind to MR, thereby preventing MR overactivation. However, since spironolactone has low selectivity and also interacts with progesterone receptors, it can cause hormonal side effects, such as gynecomastia, erectile dysfunction, and menstrual disorders. Although eplerenone has an approximately 10–20 times lower affinity to MR than does aldosterone [27], it is more selective and produces fewer side effects. Hyperkalemia is the most frequent side effect seen following treatment with aldosterone antagonists [41]. Even under the carefully controlled conditions of the EPHESUS study, hazardous hyperkalemia (values of 6.0 mmol/l or higher) occurred in 5.5% of patients treated with eplerenone compared with 3.8% of patients treated with placebo [62]. It is likely that hyperkalemia occurs even more frequently in routine practice. In addition, somewhat more gastrointestinal symptoms (diarrhea, nausea) were observed under eplerenone in the EPHESUS study compared with placebo (21.5% vs. 17.6% in the placebo group, $p = 0.06$) [57]. Thanks to eplerenone's selectivity, endocrine side effects (gynecomastia, erectile dysfunction, and menstrual disorders) are rare.

MR antagonist treatment is generally off-label. The recommended oral dose of spironolactone and eplerenone is 25 mg/day for 1 week and, if potassium levels are normal, 50 mg/day from the following week onwards. Patients with hypersensitivity to the active substance, a serum potassium value > 5.0 mmol/l, and severe kidney or liver insufficiency should not receive eplerenone therapy. Combing eplerenone with an angiotensin converting enzyme inhibitor, an angiotensin receptor blocker, lithium, cyclosporine, or tacrolimus should be avoided. In the case of concomitant treatment with weak to moderate CYP3A4 inhibitors, e. g., amiodarone, diltiazem, and verapamil, a dose of 25 mg once daily should not be exceeded.

A number of randomized placebo-controlled studies published recently investigated the effect of spironolactone and eplerenone on SRF and visual acuity in CSC patients with SRF that failed to absorb within 3–4 months [6, 60, 65, 72]. Bousquet et al. report that 1 month of spironolactone therapy achieves a reduction in SRF and subfoveal choroidal thickness ($p = 0.04$), but does not change visual acuity compared with placebo controls [6]. However, the Bousquet study is a cross-over study on only 16 patients. In addition, a reduction within a 3-month period was deemed a positive result, but not complete absorption of the leakage on OCT. Comparable conclusions can be drawn on the results obtained by Pichi et al. [60]. These authors obtained similar results in the largest randomized placebo-controlled study to date (three groups of 20 patients each) and found that 1 month of spironolactone treatment resulted in a significant improvement in visual acuity and a reduction in SRF of around 94 µm compared with an increase in SRF of around 24 µm in the placebo control group. However, since the placebo group changed to the treatment arm after 4 weeks, there was no real control group for the full duration of the study. In view of the complex structure of this study with additional cross-overs in the other two arms, it is difficult to draw a reliable conclusion that stands up to statistical evaluation.

In another randomized placebo-controlled study, Rahimy et al. described a therapeutic effect for eplerenone involving a reduction in central retinal thickness of 81 µm after 2 months of eplerenone treatment compared with an increase in central retinal thickness of 35 µm in the placebo-treated control group. In all, 33% of eplerenone-treated eyes (5/15) and 17% (1/6) of placebo-treated eyes showed complete SRF absorption after 2 months of therapy. Eplerenone-treated patients also achieved a slight and statistically significant improvement in visual acuity at 2 months after therapy, whereas patients in the control group experienced a slight deterioration [65]. In their randomized controlled trial, Schwartz et al. also found a significant reduction of SRF in the eplerenone group at 1, 3, and 5 months following treatment initiation compared with baseline findings. The placebo group also showed a reduction in SRF, which, however, was not statistically significant. In all, 23% of eplerenone-treated eyes (3/13) and 33% (2/6) of placebo-treated eyes showed complete SRF absorption after 3 months of treatment. A comparison between the placebo and eplerenone groups revealed that there was no significant difference in the reduction of SRF, choroidal thickness, and visual acuity at 5 months following treatment [72]. None of the studies mentioned here reported significant side effects of eplerenone treatment. One patient developed gynecomastia under spironolactone treatment [60].

Although the previous data have failed to provide strong evidence that MR antagonists are an effective treatment option with a low side-effects profile for the treatment of CSC and non-absorbing SRF, they do point to a positive effect

on disease course in the absence of spontaneous absorption and can therefore be considered as a treatment attempt. More studies with larger case numbers are required to validate this effect, particularly with regard to the development of visual acuity, and this over a longer period of at least 1 year.

Antioxidants and lutein

A recently published randomized placebo-controlled study postulates a positive effect of oral antioxidants and lutein on SFR absorption in CSC patients. Further randomized placebo-controlled trials are needed to validate this effect as postulated for the Asian population, meaning that treatment cannot be recommended at present [77].

Non-steroidal anti-inflammatory drugs

There is currently insufficient evidence on the therapeutic benefit of non-steroidal anti-inflammatory drugs. Although treatment studies with acetylsalicylic acid [11], ketorolac [15], and nepafenac [1] postulate a positive treatment effect in CSC, no unequivocal treatment benefit has been demonstrated.

Carbonic anhydrase inhibitors

It has been suggested that the oral use of carbonic anhydrase inhibitors (e. g., acetazolamide) increases RPE absorption and improves retinal adhesion [87]. Pikkel et al. described faster absorption (3.3 vs. 7.7 weeks) with this treatment in the only prospective non-randomized trial in a small number of patients (15 treated and 7 untreated CSC patients) that had the same final visual acuity under this therapy [61]. Therefore, there is only scant evidence to support treatment with carbonic anhydrase inhibitors.

Anti-VEGF therapy

Although the intraocular level of vascular endothelial growth factor (VEGF) is normal in CSC patients [75], the intravitreal administration of anti-VEGF agents is discussed as a potential treatment method to reduce choroidal hyperpermeability in CSC [17]. However, small randomized controlled studies show that intravitreally administered bevacizumab has no effect on CSC [45] and that the intravitreal injection of ranibizumab is inferior to half-fluence PDT [3]. A meta-analysis of anti-VEGF treatment studies concluded that anti-VEGF therapy had no positive effect either on visual acuity or central retinal thickness after 6 months in patients with acute or chronic CSC [17]. Therefore, CSC patients without secondary CNV should not receive anti-VEGF therapy; this approach should only be considered in the presence of CNV (see below).

Other forms of drug treatment

In addition to the therapeutic agents mentioned above, other treatment studies with antibiotics (e. g., amoxicillin), proton pump inhibitors (omeprazole), antimetabolites (methotrexate), and diarylheptanoids (curcumin) have been conducted for the treatment of CSC, some of which had no or only a weak effect on CSC and cannot be recommended at present (see [53] for a detailed summary).

Laser-assisted treatment approaches

Argon laser therapy

Focal argon laser treatment of leakage points has been used as a therapeutic option in CSC patients since the 1990s. A number of studies show that focal laser treatment of leakage points leads to faster SRF absorption, but has no effect on visual acuity, color vision, or the recurrence rate [23, 43, 67]. Heat-induced scarring of the RPE, expansion of the surrounding RPE, and the resulting improvement in RPE pump function are discussed as the mode of action of focal leakage point laser photocoagulation [18]. In contrast to PDT (see below), focal lasering is not assumed to have an effect on the choroid [49]. Focal laser therapy outside the fovea centralis is generally a safe treatment option, and there are only a handful of case reports on complications, such as secondary CNV or paracentral scotomas [23, 29]. It is important to note that treatment in all these very old case reports on secondary complications was performed with laser parameters that are no longer used today, or the presence of CNV was not sufficiently considered.

CSC patients with SRF that fails to absorb within approximately 4 months and a leakage point outside the fovea detected on FAG can be treated with focal argon laser coagulation (514 nm), diode-pumped solid-state laser (532 nm, 577 nm), or with the classic infrared diode laser (810 nm) in continuous wave (CW) mode. Depending on the size of the leakage point, a laser spot size of 50–200 µm and laser energy of 150–400 mW are selected and the site of leakage lasered for 20–200 ms [23, 43]. Leakage points within 500 µm of the foveal area should not undergo focal laser coagulation. Prior to focal laser coagulation, laser energy should be carefully titrated in the area of the vascular arcades and the laser energy selected should be so low that discrete retinal edema at the very most can be seen.

Micropulse laser and selective retina therapy

By using significantly shorter laser pulses, alternative laser strategies attempt to avoid the side effect of retinal damage associated with conventional laser coagulation due to large-scale heating. The exposure time of the single pulse in conventional laser coagulation is between 50–200 ms, whereas exposure times are shortened by a factor of more than 1000–30,000 in the case of exposure with short pulses. These methods include micropulse laser (MPL) treatment with diode-pumped green and yellow solid-state lasers (532, 577 nm) or infrared lasers (810 nm), and selective retina therapy (SRT) with an Nd:YLF laser (527 nm). Both methods apply these short pulses rapidly in succession for the entire duration of a single exposure (typically between 50 and 200 ms), usually at a frequency of 500 Hz, i. e., a single pulse every 2 ms. The duration of a single pulse in SRT is 1–2 µs, while a single pulse in subthreshold MPL is 50–100 µs [68]. However, since the single pulse duration in subthreshold MPL treatment is 100 times longer, MPL corresponds more closely to weak

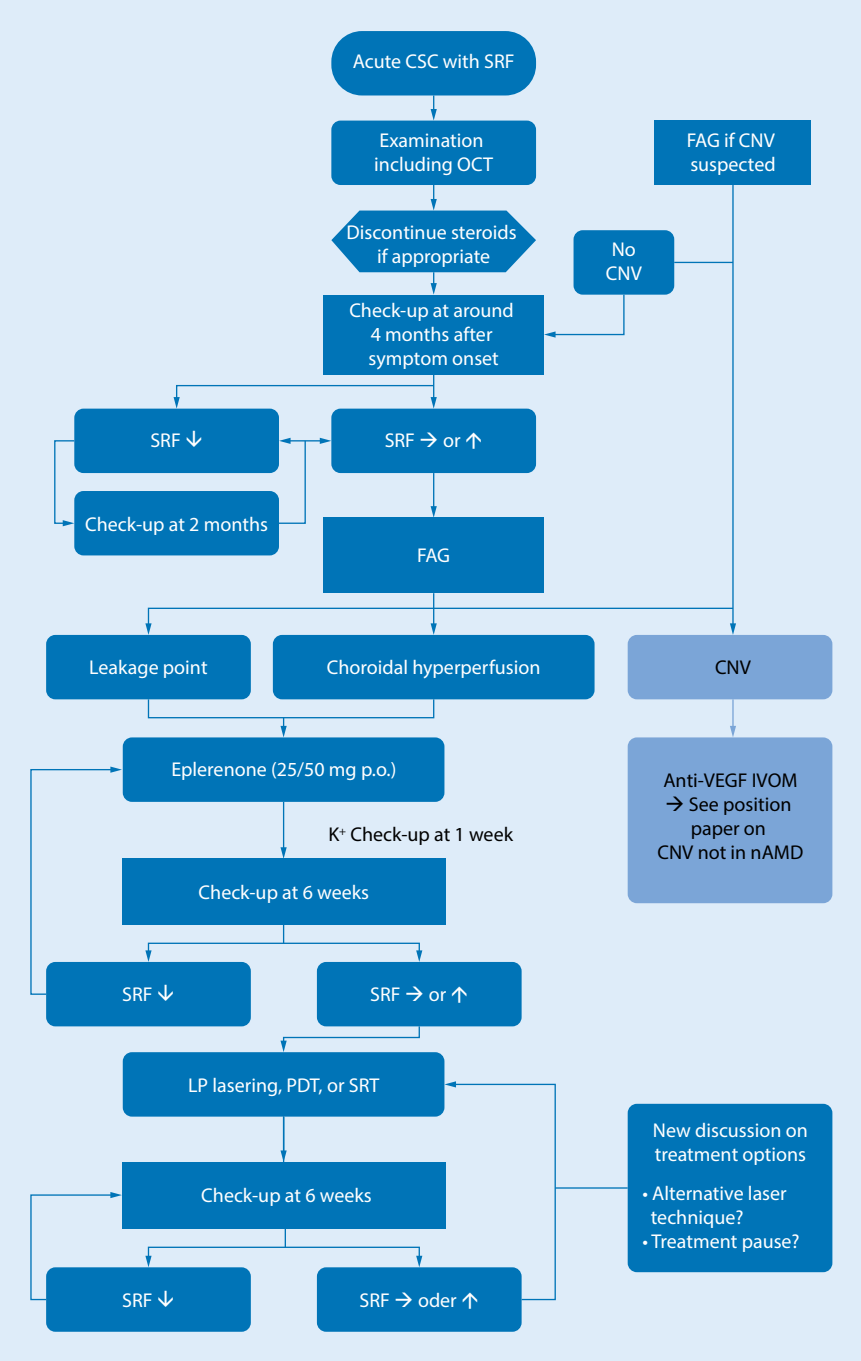

Fig. 1 ▲ Treatment algorithm. *CSC* central serous chorioretinopathy, *OCT* optical coherence tomography, *FAG* fluorescein angiography, *SRF* subretinal fluid, *CNV* choroidal neovascularization, *p. o.* per os, *VEGF* vascular endothelial growth factor, *IVOM* intravitreal operative medication, *nAMD* neovascular age-related macular degeneration, *LP* leakage point, *PDT* photodynamic therapy, *SRT* selective retina therapy

conventional laser coagulation, thereby bearing a slightly higher risk of thermal damage to the retina. Both methods are used as additional treatment options in CSC with persisting fluid.

The aim is to stimulate RPE function without causing thermal damage. As such, this technique is also suited to treating leakage points located in the subfoveal area and generally results in fewer complications compared with argon laser therapy [70].

In order to treat the leakage point with conventional lasers and conventional exposure duration while sparing the retina as much as possible, Lavinsky developed the "endpoint management algorithm" for the optimal titration of laser power in each patient, whereby the power is reduced to 30% based on a barely visible laser effect (=100%) [42]. All procedures treat the RPE with a varying number of single exposures depending on the surface area [89]. Clinical studies show that both subthreshold MPL procedures and SRT result in increased absorption of SRF and heightened visual acuity in patients with acute CSC compared with untreated control patients [22, 39, 68]. Subthreshold methods appear to be superior to conventional argon laser therapy in terms of contrast sensitivity and visual field recovery [86]. In their meta-analysis, Wood et al. summarized the evidence regarding subthreshold laser therapy and found that central retinal thickness decreased in 398 patients by 80% at 3 months following laser therapy and that visual acuity increased by nine letters. With the exception of slight RPE changes in a total of six patients due to excessive laser settings, no adverse side effects were observed [89]. Scholz et al. came to similar conclusions in their review article and postulated that subthreshold retinal laser therapy was superior to photodynamic therapy in reducing central retinal thickness and increasing visual acuity. While PDT is associated with a reduction in central retinal thickness of 85 µm (range, 76–109 µm) and an increase in visual acuity of 3.8 ETDRS letters (2–8), subthreshold retinal laser therapy achieves a central retinal thinning of 131 µm (69–204 µm) and an increase in visual acuity of 6.3 letters (–15 to 20) [70]. Although these observations need to be verified in large-scale randomized head-to-head studies with adequate patient numbers and a sufficiently long study period of at least 1 year, they suggest that subthreshold laser therapy is a treatment option in non-spontaneously absorbing CSC. There are no citable study data as yet on a nanosecond laser that is an already commercially available (2RT, Ellex Medical Lasers Ltd, Adelaide, Australia) for use in CSC; thus, like SRT, this treatment method should only be performed in the context of studies at present.

Photodynamic therapy

PDT involves the i. v. administration of a photosensitive drug (verteporfin, Visudyne®; Novartis, Switzerland) to the patient, followed by the application of a non-thermal laser at a wavelength of 693 nm to the area of choroidal hyperpermeability. The photoactivated verteporfin then releases radicals that damage the choroidal endothelial cells and lead to reduced blood flow and vasopermeability [12]. Damage to the healthy choriocapillaris and RPE, which can lead to ischemia of the outer retina and secondary CNV, is discussed as a side effect of PDT [12]. However, since these changes also occur in the natural course of the disease, no clear causal link to PDT has been demonstrated. In order to reduce potential damage to the choroid and RPE, PDT is performed nowadays as half-fluence PDT or half-dose PDT. In half-fluence PDT, light intensity is reduced to 25 J/cm^2, while in half-dose PDT, the drug dose is reduced to 3 mg/m^2. Since PDT is a photochemical process, there is no difference between these two approaches.

Ever since the first description of PDT in CSC [4], more than 100 articles have been published on the benefits of PDT in CSC patients. These include a number of larger case series with a follow-up period of several years, comparative treatment studies, and meta-analyses [48, 53, 69]. These studies report that both half-fluence PDT and half-dose PDT result in complete SRF absorption at 12 months following treatment in over 90% of cases [13, 14, 66], without the development of relevant side effects [73, 90]. PDT also appears to reduce the recurrence rate of SRF [84, 85]. However, although PDT appears to result in absorption of SRF in chronic atrophic CSC with cystoid retinal degeneration, it does not contribute to an improvement in visual acuity or a reduction in the recurrence rate [55].

In their meta-analysis, Ma et al. analyzed nine treatment studies involving a total of 319 patients with chronic CSC characterized by persistent SRF over a period of 3 months. They concluded that half-dose PDT represents an effective treatment option and has a positive effect on visual acuity and central retinal thickness at 12 months compared with untreated eyes. They also postulated that PDT is responsible for better SRF absorption compared with conventional argon laser therapy and anti-VEGF therapy [48].

Despite the lack of large-scale multicenter RCTs validating the benefits of PDT, half-fluence or half-dose PDT is a safe and effective treatment and can be offered to patients with chronic CSC and with acute CSC persisting for at least 4 months.

Treatment of secondary choroidal neovascularization

Secondary CNV occurs in rare cases in patients with acute CSC and somewhat more frequently in patients with chronic CSC [5, 7, 58, 63]. Results from the phase-3 MINERVA study clearly show that anti-VEGF therapy with ranibizumab improves central retinal thickness and visual acuity in patients with CSC-related CNV (+6.6 letters compared to +1.6 letters in the control group [40]). Therefore, secondary CNV in CSC should be treated with intravitreal administration of a VEGF inhibitor (see position paper on CNV not in nAMD). In all other cases, anti-VEGF therapy should not be used for CSC (**Fig. 1**).

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Compliance with ethical guidelines

Conflict of interests. See **Table 1** in the Appendix.

This article does not contain any studies with human participants or animals performed by any of the authors.

The supplement containing this article is not sponsored by industry.

Appendix

Table 1 A tabular summary of declarations of conflicts of interest. Statement on central serous chorioretinopathy (CCS)

	1	2	3	4	5	6	7	8	9	10
	Consultancy/appraisal activities or paid collaboration on a scientific advisory board of a company in the health industry (e. g., pharmaceutical industry, medical product industry), a commercially oriented contract research organization, or an insurance company	**Fees for lectures and training activities or paid authorships or co-authorships on behalf of a company in the healthcare industry, a commercially oriented contract research organization, or an insurance company**	**Financial support (third-party funding) for research projects or direct financing of employees of the institution by a company in the healthcare industry, a commercially oriented contract research organization, or an insurance company**	**Owner interest in drugs/medical products (e. g., patent, copyright, sales license)**	**Ownership of business interests, shares, funds involving companies in the healthcare industry**	**Personal connections to an authorized representative of a company in the healthcare industry**	**Member of relevant specialist societies/associations connected with the development of guidelines, mandate holder in guideline development**	**Political, academic (e. g., belonging to particular "schools"), scientific, or personal interests that could constitute possible conflicts**	**Current employer, relevant previous employers in the last 3 years**	**In your opinion, do all of the above points give rise to significant conflicts of interest for you or the guideline group as a whole?**
Bertram, Prof. Dr. Bernd	No	No	No	No	No	No	Yes BVA: 1. Chairman DOG: Member of the Executive Board, Spokesman for the DOGBVA Guidelines Commission	No	Independent ophthalmologist	No
Feltgen, Prof. Dr. Nicolas	No	No	Yes German Medicinal Products Act (AMG) studies with sponsors: Novartis, Bayer, Allergan, Roche	No	No	No	Yes BVA, DOG	No	Göttingen University, Germany	No'
Hoerauf, Prof. Dr. Hans	Yes Participation on advisory boards: Allegan, Alimera, Bayer, Novartis	Yes Lecture activities: Allergan, Alimera, Bayer, Heidelberg Engineering, Novartis	Yes Allergan, Alcon, Bayer, Boehringer Ingelheim, Formycon/Bioeq, Novartis, Ophthotech, Regeneron Pharmaceuticals, Roche, Lutronic	No	Yes Novartis, Roche, 3M, Johnson & Johnson	No	Yes Member of the board of the BVA, member of the executive board of the DOG, DRG	No	University Hospital Göttingen, Germany	No
Lange, PD Dr. Dr. Clemens	No	No	No	No	No	No	Yes DOG	No	Department of Ophthalmology, University Hospital Freiburg, Germany	No
Pauleikhoff, Prof. Dr. med. Daniel	Yes Novartis, Bayer, Roche	Yes Novartis, Bayer, Roche	No	No	No	No	Yes DOG, BVA, RG	No	Independent	No
Roider, Prof. Dr. Johann	No	No	No	No	No	No	Yes DOG, BVA	No	Schleswig-Holstein University Hospital, Kiel Campus, Germany	No
Treumer, PD Dr. Felix	No	No	No	No	No	No	Yes BVA and DOG	No	Schleswig-Holstein University Hospital, Kiel Campus, Germany	No

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