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Central Serous Chorioretinopathy

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Abstract

Central serous is an atypical form of macular edema with mostly accumulation of fluid under the retina. It contitutes a pure phenotype of retinal pigment epithelium barrier breakdown. Another particularity is the good visual preservation despite important fluid volume increase in the macula.

Definition and Epidemiology

Central serous chorioretinopathy (CSCR or CSC) is a chorioretinal disease affecting predominantly middle-aged men and characterized by serous retinal detachments (SRD) frequently involving the macular area and associated with focal pigment epithelial detachments (PED). CSCR is often unilateral, but variable contralateral involvement has been detected in up to 40% of cases (Gäckle et al., 1998)[1]. A population-based study reported an annual incidence of 9.9 per 100,000 for men and 1.7 for women, confirming the male predilection (Kitzmann et al., 2008)[2]. The mean age at disease onset has been estimated between 39 and 51 years (Kitzmann et al., 2008; Spaide et al., 1996; Tsai et al., 2013)[2–4].

Clinical Presentation

The term 'CSCR' covers two distinct entities classically defined as acute and chronic. This distinction is ambiguous because it relies either on the duration of SRD (4–6 months), or on the presence of severe retinal pigment epithelium (RPE) alterations. The term 'nonresolving' or 'persistent' CSCR may be more appropriate to describe cases with long-lasting SRD, and thus avoid confusion with the chronic form characterized by a diffuse pigment epitheliopathy (Loo et al., 2002)[5].

Acute CSCR

In acute CSCR (fig. 1), patients report symptoms related to the detachment of the macula: blurred vision, relative central scotoma, variable meta-

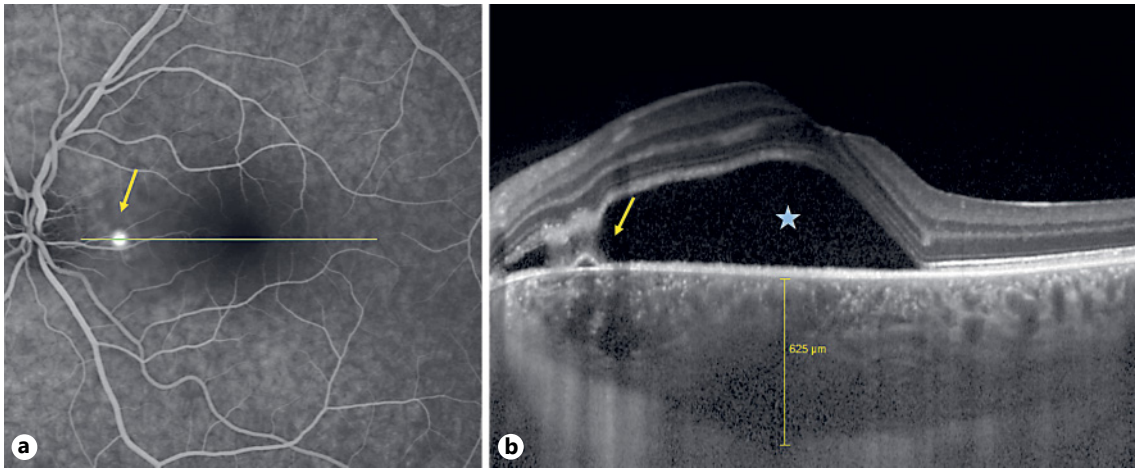

Fig. 1. Acute CSCR. Thirty-five-year-old man who reported blurred vision in his left eye for 4 days. Midphase fluorescein angiogram (**a**) revealed a single leaking point (yellow arrow). **b** SD-OCT identified a pigment epithelium detachment (yellow arrow) at the level of the leaking point, confirmed the presence of a subretinal detachment involving the fovea (blue star), and revealed an increased choroidal thickness (625 µm).

morphopsia, dyschromatopsia, hypermetropization, micropsia, and reduced contrast sensitivity (Wang et al., 2008)[6]. In addition to SRD visible on fundus examination, spectral domain optical coherence tomography (SD-OCT) may show limited RPE alterations, such as small PEDs. A leakage site through the RPE is frequently identified on fluorescein angiography (FA). The SRD usually resolves within 3–4 months, without sequelae (Baran et al., 2005)[7].

Recurrent CSCR is defined as a new episode of acute CSCR following a previous resolved episode. Recurrences are estimated to occur in 15–50% of cases (Daruich et al., 2015)[8]. The evolution to recurrent or persistent CSCR has been identified as a risk factor of visual acuity worse than 20/40 (Loo et al., 2002)[5].

Chronic CSCR

The chronic form was initially named 'diffuse retinal epitheliopathy' (Yannuzzi et al., 1992)[9]. It presents with widespread tracks of RPE atrophy associated with decreased fundus autofluorescence (FAF) (fig. 2) (Imamura et al., 2011; Teke et al., 2014)[10, 11]. Symptoms are permanent with moderate-to-severe visual acuity loss and decreased light sensitivity depending on the extent of photoreceptor damage (Ooto et al., 2010; Piccolino et al., 2005)[12, 13]. SD-OCT shows variable chronic SRD, multifocal RPE atrophy, and irregular RPE detachments. Intraretinal cystoid cavities can also be observed (Iida et al., 2003; Piccolino et al., 2008)[14, 15], more frequently with disease duration longer than 5 years (fig. 2) (Piccolino et al., 2008)[16].

Choroidal neovascularization (CNV) may complicate CSCR, either as the natural course of the disease (prevalence: 2–9%) or as a complication of focal treatments (Spaide et al., 1996; Loo et al., 2002)[3, 5].

Diagnosis: Multimodal Imaging of Central Serous Chorioretinopathy

SD-OCT is instrumental for the diagnosis and follow-up of CSCR. FA identifies the origin of leakage. FAF noninvasively detects RPE altera-

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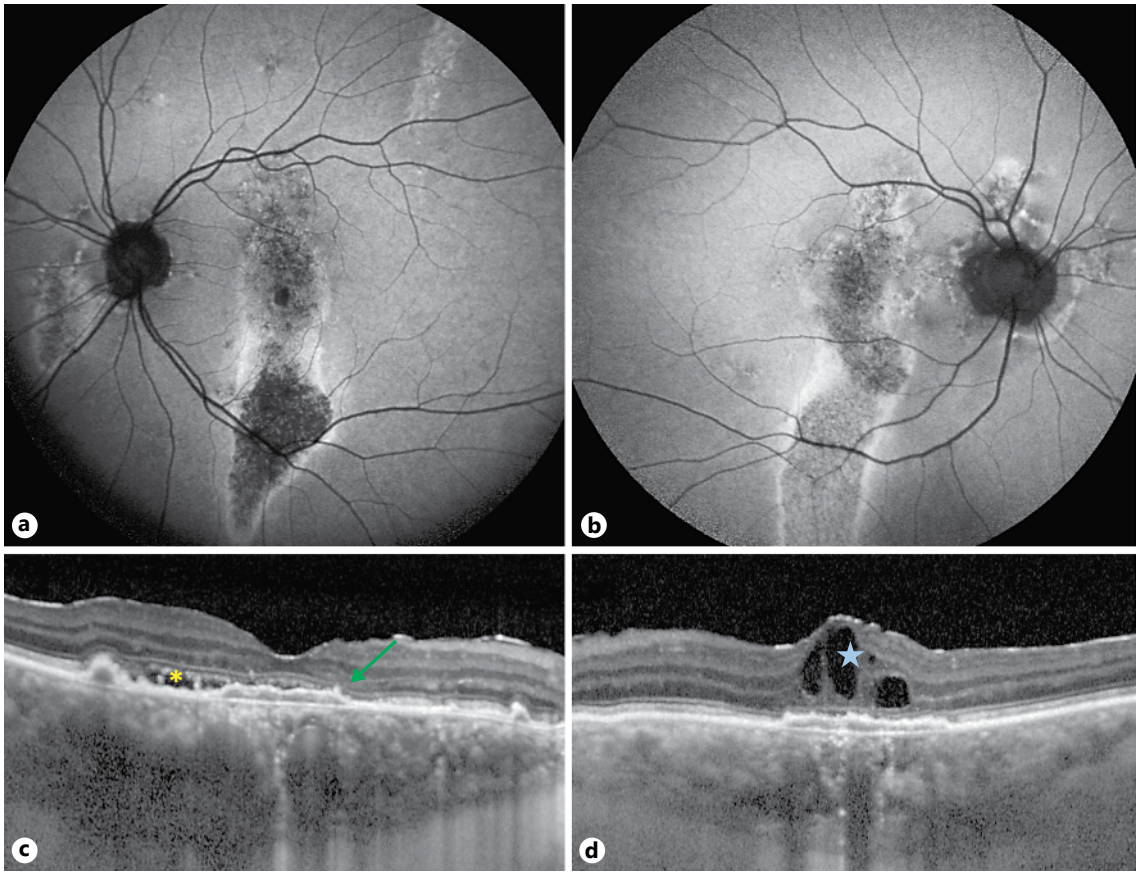

Fig. 2. Chronic CSCR. **a**, **b** FAF in a 70-year-old man showing bilateral oblong descending hypoautofluorescent tracks, a pathognomonic feature of a severe chronic CSCR with diffuse atrophy of the RPE. **c**, **d** SD-OCT revealed a small subretinal detachment (asterisk), a shallow PED (arrows) and the presence of intraretinal cysts (star).

tions. Recurrent, nonresolving, and chronic CSCR should benefit from multimodal imaging with SD-OCT, FAF, FA, and indocyanine green (ICG) angiography to guide treatment, follow extension, and detect neovascular components.

Spectral Domain Optical Coherence Tomography

Retinal Findings

In acute CSCR, retinal layers are preserved despite the presence of subretinal fluid. Elongation of photoreceptor outer segments above the SRD is frequent (fig. 3a) (Matsumoto et al., 2008)[17]. Intraretinal cysts and loss of photoreceptor outer segments are seen in very long-standing cases. Hyperreflective dots (fig. 3a) can be observed in the subretinal space (Kon et al., 2008; Maruko et al., 2011; Spaide and Klancnik, 2005)[18–20] and within the neuroretina (Kon et al., 2008; Ahlers et al., 2009; Yalcinbayir et al., 2014)[18, 21, 22]. Variable alterations of RPE, as PEDs, areas of RPE atrophy, or hypertrophy, may be observed in all CSCR subtypes (fig. 1, 2) (Piccolino et al., 2008; Yalcinbayir et al., 2014; Lim and Wong, 2008; Yang et al., 2013)[15, 22–24].

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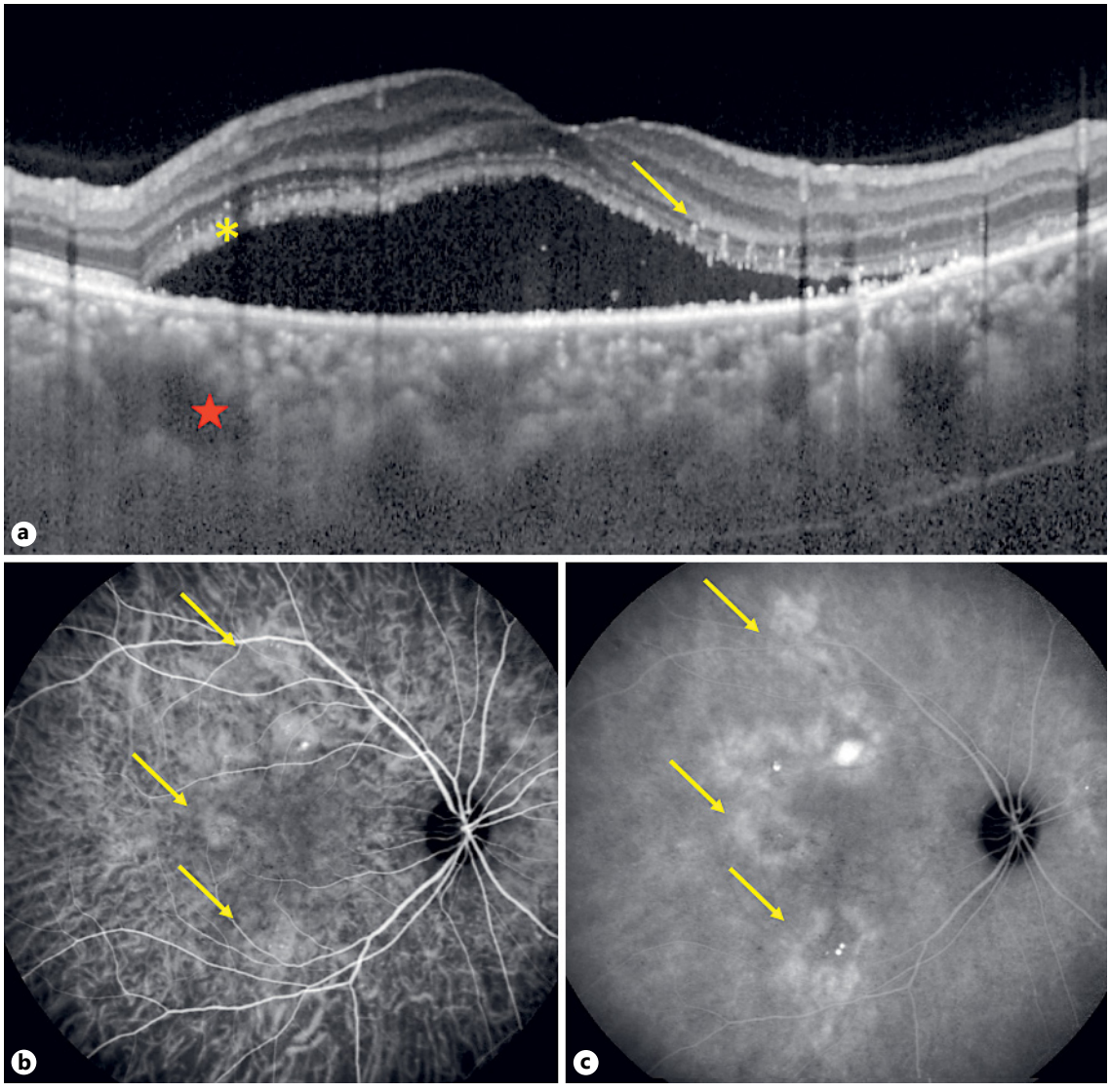

Fig. 3. Imaging of the choroid in CSCR. Forty-year-old woman presenting a first episode of CSCR. **a** SD-OCT identified a subretinal detachment associated with elongation of photoreceptor outer segments (asterisk). The enhanced-depth imaging acquisition mode visualized enlarged choroidal vessels (star) and the classical aspect of pachychoroid. Hyperreflective dots were visible in the neuroretina (arrow). ICG angiography showed multifocal hyperfluorescence areas with blurred contours during midphase, indicating choroidal vascular hyperpermeability (arrows) (**b**) that evolved into persistent hyperfluorescence, or peripheral extension forming hyperfluorescent rings at the late phase (arrows) (**c**).

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Choroidal Findings

Increased choroidal thickness (>395 μm) (Lehmann et al., 2015)[25] is often observed in affected (Yang et al., 2013; Imamura et al., 2009; Jirarattanasopa et al., 2012; Kim et al., 2011; Kuroda et al., 2013)[24, 26–29] and contralateral eyes of CSCR patients (Goktas, 2014; Maruko et al., 2011; Yang et al., 2013)[30–32]. Choroidal thickening (pachychoroid) can result from focal or diffuse dilatation of large choroidal vessels (fig. 1b, 3a). These dilated vessels are commonly localized within areas of increased choroidal vascular permeability on ICG angiography (Yang et al., 2013; Jirarattanasopa et al., 2012; Kuroda et al., 2013; Maruko et al., 2011; Razavi et al., 2014)[24, 27, 29, 31, 33].

Fundus Autofluorescence

FAF imaging reflects RPE status. In chronic CSCR, FAF is pathognomonic with oblong descending hypofluorescent tracks, originating from the optic disc or the macula, and described as 'gravitational tracks' (fig. 2a, b).

Fluorescein Angiography

By identifying single (fig. 1a) or multiple leakage points, FA confirms the diagnosis and guides laser treatment (for extrafoveal leakages) (Yannuzzi et al., 2000)[34]. In acute cases, leakage sites (Burumcek et al., 1997)[35] present as a pinpoint of increasing fluorescence along the sequence, with a possible 'ink-blot' (progressive circular expansion), or 'smokestack' aspect (ascending expansion). In the mid- and late phases, a circular hyperfluorescence appears within the SRD. PED are characterized by early fluorescein pooling with hyperfluorescence persisting in late phases.

In chronic forms, diffuse RPE defects provoke multifocal leakage points visible in the mid- and late phases as patchy, granular hyperfluorescence (Yannuzzi et al., 1984)[36].

Indocyanine Green Angiography

ICG angiography has become the gold standard to analyze the choroidal vasculature. It helps differentiate other CSCR from differential diagnoses and identifies CNV when complicating CSCR (Spaide et al., 1996; Yannuzzi, 2011)[3, 37].

The choroidal modifications observed by ICG angiography in CSCR eyes are:

- Early phase: delayed filling of arteries and coriocapillaris (Prünte, 1995)[38], hypofluorescent areas corresponding to decreased choriocapillaris filling (persisting in the mid- and late phases) (Kitaya et al., 2003)[39]
- Midphase: dilation of large choroidal veins, geographic areas of hyperfluorescence with blurred contours described as choroidal vascular hyperpermeability, one of the hallmarks of CSCR (fig. 3b) (Piccolino and Borgia, 1994; Spaide et al., 1996)[40, 41]
- Late phase: midphase hyperfluorescent areas evolve into persistent hyperfluorescence, wash-out, or a peripheral extension forming hyperfluorescent rings (fig. 3c) (Tsujikawa et al., 2010)[42]

Pathogenesis

Risk Factors

Corticosteroids

The systemic or local administration of corticosteroids [inhalation (Haimovici et al., 1997; Kleinberger et al., 2011)[43, 44], epidural (Iida et al., 2001; Kao, 1998; Pizzimenti and Daniel, 2005)[45–47] or intra-articular injections (Hurvitz et al., 2009; Kassam et al., 2011; Mondal et al., 2005)[48–50], topical dermal (Ezra et al., 2011; Fernandez et al., 2004; Karadimas and Bouzas, 2004; Romero et al., 2005)[51–54], and periocular injections (Baumal et al., 2004)[55]] has been associated with the triggering, prolongation, aggravation, and recurrences of CSCR (Khairallah et al., 2012)[56].

Endocrine Changes

The risk of CSCR is higher during pregnancy (Haimovici et al., 2004)[57] and may resolve spontaneously after delivery (Chumbley and Frank,

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1974; Errera et al., 2013; Schultz et al., 2005)[58–60]. CSCR develops in up to 5% of patients with endogenous Cushing syndrome (Bouzas et al., 1993; Carvalho-Recchia et al., 2002)[61, 62]. Morning serum cortisol levels (Garg et al., 1997; Zakir et al., 2009)[63, 64] and 24-hour urine cortisol levels (Garg et al., 1997; Kapetanios et al., 1998)[63, 65] are higher in acute CSCR patients than in healthy subjects.

Psychopathology

An association was suggested between CSCR and 'type A' personality, characterized by a competitive drive, a sense of urgency, and an aggressive and hostile temperament (Yannuzzi, 1986)[66]. Antipsychotropic medication use and psychological stress were described as independent risk factors for CSCR (Tittl et al., 1999)[67]. Depression has been associated with an increased risk of recurrence (Fok et al., 2011)[68].

Genetic Predisposition

Several sporadic familial cases of CSCR have been reported (Amalric et al., 1971; Haik et al., 1968; Lin et al., 2000; Oosterhuis, 1996; Park et al., 1998; Wyman, 1963)[69–74]. Additional evidence comes from the observation of fundus atrophic lesions or pachychoroid suggestive of CSCR in relatives of CSCR patients (Lehmann et al., 2015; Weenink et al., 2001)[25, 75]. Genetic studies based on single nucleotide polymorphisms have been performed on CSCR subjects. An association between 5 common complement factor H polymorphisms (Miki et al., 2014)[76] and 4 common cadherin-5 single nucleotide polymorphisms have been identified (Schubert et al., 2014)[77].

Cardiovascular Diseases and Hypertension

Patients with hypertension have higher risk of developing CSCR (Tittl et al., 1999; Eom et al., 2012)[67, 78]. Men with CSCR have a significantly higher rate of coronary heart disease (Chen et al., 2014)[79]. CSCR is also an independent risk factor for ischemic stroke (Tsai et al., 2012)[80] and organic and psychogenic erectile dysfunction (Tsai et al., 2013)[81].

Sympathetic-Parasympathetic Activity and Reactivity

Based on cardiac monitoring, patients with CSCR have shown significantly decreased parasympathetic activity and increased sympathetic activity (Tewari et al., 2006)[82].

Gastroesophageal Disorders

A higher risk of gastroesophageal reflux and more frequent use of antiacid or antireflux medications were found in CSCR patients (Mansuetta et al., 2004)[83]. Additional studies reported that CSCR patients have a high prevalence of *Helicobacter pylori* infection (Ahnoux-Zabsonre et al., 2004; Cotticelli et al., 2006; Giusti, 2001; Mateo-Montoya and Mauget-Faÿsse, 2002; Roshani et al., 2014)[84–89].

Drug-Induced CSCR

CSCR episodes have been associated with the use of phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil) (Aliferis et al., 2012; Fraunfelder and Fraunfelder, 2008)[90, 91]. Up to 65% of patients under oral MEK inhibitors (binimetinib) for metastatic cancer develop transient bilateral SRD and moderately blurred vision suggestive of CSCR (McCannel et al., 2014; Urner-Bloch et al., 2014)[92, 93].

Sleep Disturbance

The role of obstructive sleep apnea in CSCR remains controversial (Eom et al., 2012; Kloos et al., 2008; Brodie et al., 2015)[78, 94, 95].

Mechanism of CSCR

Choroidopathy and Epitheliopathy

The major mechanistic steps involved in CSCR pathogenesis are choroidal vascular hyperpermeability and congestion (choroidopathy), damage of the overlying RPE (epitheliopathy), and abnormal movement of plasma proteins and water through the RPE into the subretinal space (SRD).

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Molecular Hypothesis: Involvement of the Aldosterone/Mineralocorticoid Receptor Pathway in CSCR

Recent evidence from clinical and animal studies supports the hypothesis that inappropriate activation of the mineralocorticoid receptor (MR) pathway involvement leads to choroidal vasodilatation in CSCR. Indeed, MR activation in the choroidal endothelial cells, either by its natural ligand, aldosterone, or by glucocorticoids that have a high affinity for MR, induces upregulation of the vasodilator potassium channel KCa2.3 (calcium-dependent channel) and smooth muscle cell relaxation in the choroidal vasculature (fig. 4) (Daruich et al., 2015; Zhao et al., 2012; Zhao et al., 2010; Bousquet et al., 2013)[8, 96–98].

Treatments

Since acute CSCR is a self-limited disease (Yannuzzi, 2010)[99], observation is the recommended first-line attitude.

For persistent CSCR, there is no consensus about the optimal treatment and timing. Classically, treatment is justified in case of persistent macular SRD for more than 4 months, a new episode with history of multiple recurrences, reduced visual acuity, history of CSCR in the fellow eye with poor visual outcome, and professional need of rapid recovery (Nicholson et al., 2013)[100].

Eviction of Risk Factors

Interruption of glucocorticoid treatment appears beneficial to facilitate the resolution of CSCR episodes (Polak et al., 1995; Sharma et al., 2004; Wakakura et al., 1997; Williamson and Nuki, 1970)[101–104]. Improvement after management of obstructive sleep apnea has also been reported (Jain et al., 2010)[105]. Psychological support associated or not with pharmacotherapy should also be discussed when a clear psychopathology is identified.

Laser Photocoagulation

Laser photocoagulation has been attempted to 'seal' the RPE leakage site when located outside the macular area. Besides the direct thermal effect on the RPE, it is thought to increase fluid movements out of the subretinal space into the choroid (Robertson and Ilstrup, 1983)[106] or to allow the expansion of surrounding RPE cells after destruction of altered RPE cells (Lim et al., 2011)[107].

Laser photocoagulation accelerates the resolution of SRD without an impact on the final visual acuity (Burumcek et al., 1997; Robertson and Ilstrup, 1983; Leaver and Williams, 1979; Gilbert et al., 1984; Brancato et al., 1987)[35, 106, 108–110] or on the rate of recurrences. The few reported adverse effects include paracentral scotoma and iatrogenic CNV (Gilbert et al., 1984; Ficker et al., 1988; Verma et al., 2004)[109, 111, 112].

Verteporfin Photodynamic Therapy

Verteporfin photodynamic therapy provokes short-term choriocapillaris hypoperfusion and long-term choroidal vascular remodeling, thus reducing choroidal congestion, vascular hyperpermeability and extravascular leakage (Chan et al., 2003; Schlötzer-Schrehardt et al., 2002)[113, 114]. Complete resolution of subretinal fluid has been obtained in 80–90% of eyes after 12 months. Possible long-term complications of photodynamic therapy include choriocapillaris nonperfusion, secondary CNV (Reibaldi et al., 2010)[115], and RPE atrophy (Lim et al., 2014)[116]. Reduction of verteporfin dosage and laser fluence/dose have been attempted to reduce these adverse effects while preserving the benefits of treatment.

Oral MR Antagonists: Spironolactone and Eplerenone

Both drugs have been evaluated for the treatment of nonresolving CSCR and have led to a significant improvement of foveal SRF and visual acuity (Bousquet et al., 2013; Bousquet et al., 2015; Herold et al., 2014; Singh et al., 2015)[98, 117–119]. Possible side effects of spironolactone include

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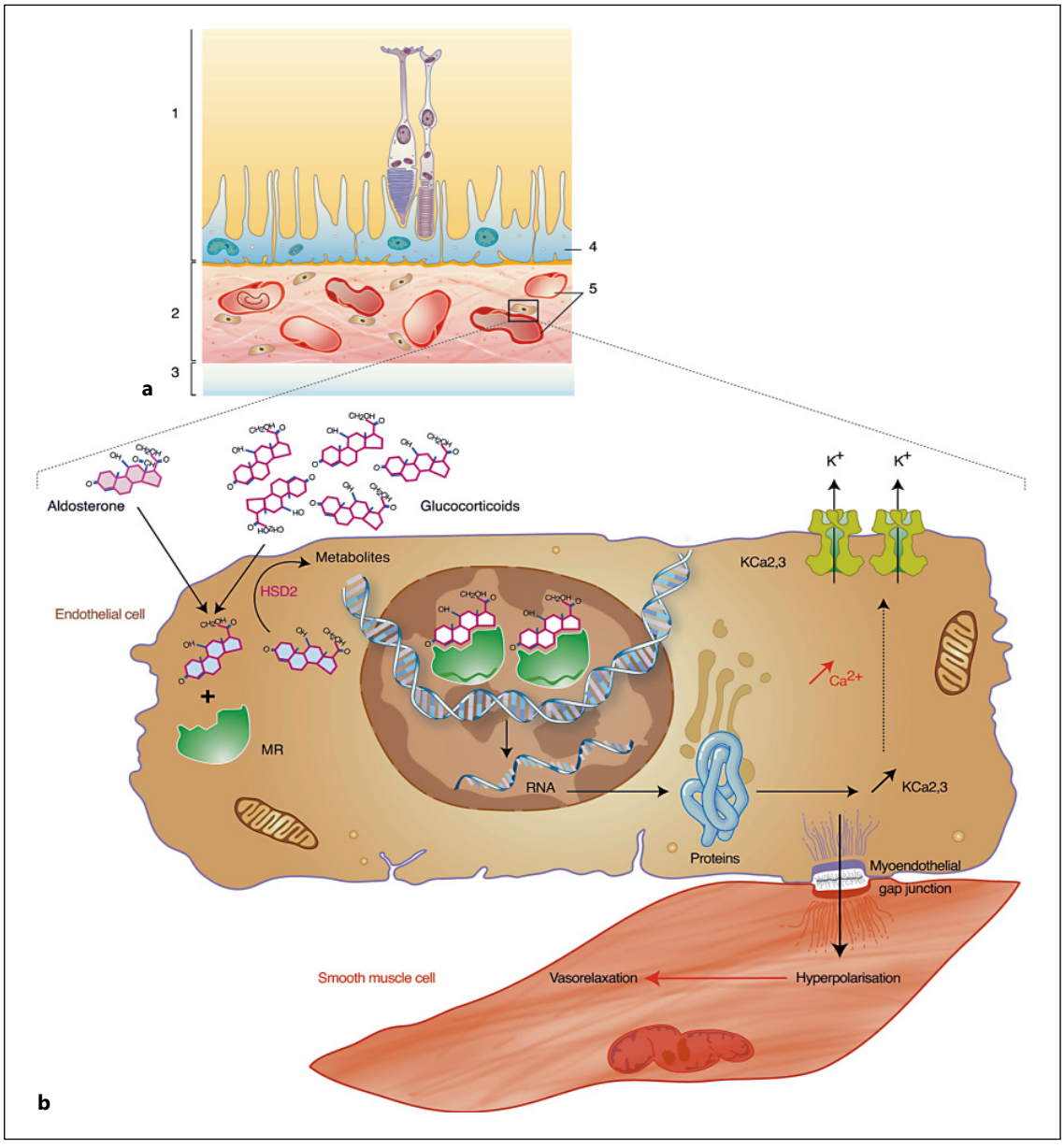

Fig. 4. Suggested mechanism leading to choroidal vascular dilatation by overactivation of the MR pathway in the choroidal vascular endothelial cells. Aldosterone and glucocorticoids bind to the MR. Permanent activation of the MR by glucocorticoids is prevented by the metabolizing enzyme 11-β-hydroxysteroid dehydrogenase type 2 (HSD2), which degrades the glucocorticoids into subproducts with a weaker affinity for the MR. However, the MR pathway can be activated by an excess of glucocorticoids or overexpression of the MR. MR activation increases the calcium-dependent, endothelial vasodilatory potassium channel KCa2.3. As a result, this leads to the hyperpolarization of endothelial cells and the underlying smooth muscle cells (via electric coupling through myoendothelial gap junctions), finally inducing choroidal vasodilation. K^+ = Potassium; Ca^{2+} = calcium. Adapted from Daruich (2015)[8].

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hyperkalemia, gynecomastia, erectile dysfunction, decrease in libido, and menstrual irregularities (Funder, 2013)[120]. Eplerenone has been designed to reduce these side effects.

Anti-VEGF Agents

A few case series indicate a beneficial effect of intravitreal anti-VEGFs (Chan et al., 2007; Konstantinidis et al., 2010; Broadhead and Chang, 2015)[121–123] on CNV complicating CSCR.

Central Serous Chorioretinopathy-Related Entities and Differential Diagnosis

Several entities may present with retinal or choroidal changes mimicking CSCR. Clinical history and multimodal imaging are crucial to distinguish them from CSCR:

- Type 1 CNV complicating age-related macular degeneration
- Polypoidal choroidal vasculopathy
- Cavitary optic disc anomalies: optic disc pit and optic disc coloboma
- Circumscribed choroidal hemangioma
- Dome-shaped macula with subretinal fluid
- 'Pachychoroid neovasculopathy'

Conclusion

CSCR is a chorioretinal disease with a wide presentation spectrum and different prognoses. Pathogenesis of CSCR is not fully understood but recent findings have suggested an overactivation of the MR pathway that opens new therapeutic perspectives in addition to laser/photodynamic therapy treatments. Despite the high prevalence of CSCR, the best treatment option and the ideal timing of intervention still need to be specified.

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