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phic altered RPE are hypoautofluorescent, while there is an absence of autofluorescence in places of RPE atrophy. At the outset these are generally hyperautofluorescent if subretinal fluid is present, but they progressively become hypoautofluorescent upon the gradual degradation of the RPE cells, up to their complete atrophy. Studies have demonstrated a relatively good correlation between the findings on FAF and retinal sensitivity quantified by microperimetry and VA, and FAF may therefore be used in order to estimate the degree of functional changes in eyes with CSC, as well as for the prognosis of the change of BCVA in connection with the therapeutic intervention [117].

Macular microperimetry

Macular microperimetry detects reduced macular sensitivity in patients with CSC, and may be a useful subjective examination method for evaluating response to photodynamic therapy. The results of clinical trials indicated that mere examination of VA alone may significantly underestimate changes to macular functions, which accompany successful treatment of CSC. Macular microperimetry has been demonstrated to be an appropriate method for precisely evaluating the sensitivity of the retina in patients treated with the aid of PDT or micropulse laser, in whom better sensitivity has been demonstrated in the central retinal region after therapy [117,118].

Multifocal electroretinography

Multifocal electroretinography (mfERG) serves for objective evaluation of functional changes of the retina in patients with CSC. Improvement of BCVA and central retinal thickness following therapy with the aid of PDT was in correlation with response to mfERG; although after absorption of the subretinal fluid there was a significant improvement in the recording on mfERG, the original values are not generally attained [119,120].

Laboratory examination

In the majority of cases, the results of laboratory examinations are not of any benefit for determination of the diagnosis. Nevertheless, in recent years a correlation has been stated with increased serum levels of plasminogen activator inhibitor 1 in patients with CSC [35]. Higher values of endogenous cortisol may also be identified, which is considered one of the main risk factors of the onset of CSC, or abnormal values of blood coagulation parameters (e.g. lower level of platelet derived growth factor) [79,121]. However, no laboratory test exists which is specific for the diagnosis of this pathology.

THERAPY OF CSC

Even despite all the advances in diagnostics, examination and therapeutic options, the optimal approach and choice of adequate treatment of CSC remains contentious. This controversy is due to the fact that although the pathology has a substantial tendency towards spontaneous recovery, with an excellent prognosis of resulting VA, on the other hand long-term retinal detachment may lead to pronounced irreversible anatomical and functional changes (Fig. 5). The principle of treatment is to induce reattachment of the neuroretina, to improve or preserve VA and to minimize the risk of recurrence. Upon selection of a suitable method of treatment it is always necessary to take into consideration the potential temporary course of the disease, the localization of the pathological leakage and the condition of the RPE.

Conservative approach – observation and modification of risk factors

In the case of the acute phase of the pathology, especially if serous detachment of the neuroretina is caused by a specific source of leakage, spontaneous resorption of the SRF occurs in the majority of cases (80–90%) within 3 months of the onset of the disease [47,122]. As a result, in the acute phase (first 3 months of the pathology), the recommendation is rather to observe the condition and attempt to reduce risk factors. It is appropriate to reduce or completely discontinue corticoid therapy if the patient uses this therapy chronically, and to adjust the patient's lifestyle, minimizing stress stimuli, and if applicable also to administer conservative therapy. However, situations exist in which therapy should be applied earlier. These are for example when the patient has high demands for improvement of vision (drivers by occupation, graphic artists etc.), recurrent form of the disease or in the case that untreated CSC in the contralateral eye has led to a significant deterioration of vision.

Medicamentous therapy

Although a range of studies have been conducted to examine the effect of orally administered pharmaceuticals, no causal medication exists at the present time. No positive influence has been demonstrated in the case of beta-blockers, anxiolytics, antidepressants, non-steroid antiphlogistic drugs, resorptive drugs, vasoprotectives or vitamin therapy [123]. Corticosteroids previously used as standard for the conservative treatment of CSC are no longer recommended whatsoever, since in the literature there are a whole range of studies indicating that general and parabulbar administration of corticoids may provoke the onset of CSC [35,66]. Long-term corticoid therapy is linked to prolonged presence of SRF and diffuse changes of the RPE, and in patients who for whatever reason are unable to reduce their dose of corticoids, we frequently struggle with a protracted, chronic pathology that responds to treatment only with difficulty. Care for these patients requires interdisciplinary cooperation, and the recommendation of an ophthalmologist for patients with CSC whose condition of health so permits is to discontinue long-term corticoid therapy or replace it with alternative treatment (e.g. biological therapy). Alkin et al. present the case of a positive effect of nepafenac 0.1% in the treatment of acute forms of CSC [124]. New observations have appeared in the literature attesting to the positive effect of mineralocorticoid receptor antagonists, especially eplerenone. According to recent results of clinical trials, eplerenone influences a number of pathophysiological pathways, thereby supporting the more rapid absorption of

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fluid, and is more effective in chronic states [125,126]. In the case of extensive RPE atrophies, however, its effectiveness is limited [127]. Further prospective clinical trials are essential in order to confirm its safety and efficacy, and to determine which clinical forms of CSC would profit from treatment with eplerenone.

Laser therapy

Conventional argon laser therapy has been used for several years in order to manage both the acute and chronic phase of CSC [16]. With regard to the large percentage of spontaneous resorption of SRF, the recommendation is to wait 3 months from the onset of the pathology before intervention [128]. If spontaneous reattachment of the neuroretina does not take place and the point of leakage is sufficiently distant from the center of the fovea (more than 500 µm), direct laser photocoagulation of the leaking point is indicated (hyperfluorescence according to FAG). If the hot-spot is less than 500 µm from the center of the fovea, or if diffuse affliction of the RPE is already expressed, the recommendation is to select an alternative therapeutic approach [128]. Following laser coagulation of the hot-spot, in uncomplicated cases anatomical reattachment of the neuroretina usually takes place within 2 weeks of the performance of the procedure. Adjustment of central VA as a rule requires twice that amount of time. Photocoagulation usually reduces the period of duration of the pathology and accelerates resorption of the SRF, but has no influence on resulting VA [129].

The aim of laser photocoagulation is the scarring of the defective RPE through which fluid is penetrating into the subretinal space. Targeted point laser coagulation of the hot-spot is performed on the basis of prior fluorescein (or indocyanine green) angiography. The principle of the dual healing effect of the photocoagulation laser is a direct thermic effect, as well as secondary expansion of the RPE cells from the surrounding healthy tissue and healing of the RPE defect [130]. In the place of application of the laser beam, the thermal destruction of tissue and the adjacent neurosensory retina takes place, and absolute scotoma may appear in the place of treatment. Potential adverse effects of laser photocoagulation should be taken into consideration, especially if it is necessary to use a laser in close proximity to the fovea or in the papillomacular bundle. Further potential complications include accidental shot of the fovea, hemorrhage, fibrosis, secondarily occurring CNV, slow progressive enlargement of RPE atrophy of the original laser spot (enlargement of the laser spot may in time affect the fovea and cause irreversible loss of VA) [16].

A modality to a conventional laser is a subthreshold or micropulse laser. The principle of a micropulse laser is the division of the continual laser beam of a wavelength of 810 nm (or 577 nm) into individual micropulses separated by a pause, thus minimizing the generation of thermal energy that has a mutilating effect on the tissue in the treated and surrounding area. It supports the biological response of the tissue, which leads to a restoration of the integrity and physiological function of the RPE cells, with resorption of the SRF. Subthreshold diode micropulse laser therapy may be a safe and effective therapeutic modality for cCSC in future [118].

Photodynamic therapy – PDT

In addition to laser therapy, photodynamic therapy has also been used successfully in recent years. It was introduced into practice based on the idea that CSC primarily affects the choroid. PDT was originally used in the treatment of solid tumors, and later in the treatment of wet form ARMD [131]. Positive results of treatment of chronic form of CSC by photodynamic therapy with the use of the photosensitizing substance verteporfin were first published by Yannuzzi and Piccolino in 2003 [77,132]. Since that time, the safety and effectiveness of ICG-navigated PDT in the treatment of CSC has been confirmed by a series of clinical trials [11,13,135–136].

The principle of PDT consists in the intravenous administration of the photosensitizing substance verteporfin (Visudyne, Novartis AG, Bülach, Switzerland), and its activation through the use of laser light in red wavelengths. Because the induction of the photochemical reaction takes place intravenously, there is no thermal damage to the tissue during PDT. In the place of irradiation, PDT induces constriction of the choroidal vessels, leading to their modification, reduces choroidal perfusion, and as a consequence of these changes reduces choroidal exudation [137,138]. According to the conclusions of clinical trials, PDT enables more rapid resorption of the SRF in comparison with the group of patients who are treated with laser photocoagulation [132,139]. In order to determine the precise localization and extent of the lesion, the results of ICG (medium venous phase) are used, according to which the laser spot is targeted precisely at the zone(s) of hyperfluorescence during the treatment [94,140]. PDT may be applied in the standard dose and length of irradiation of the lesion, which is used in the treatment of wet form ARMD (parameters according to TAP study: laser beam with a wavelength of 689 nm applied for a period of 83 seconds in exposure of 600 mW/cm^2, within 5 minutes of the end of intravenous infusion of verteporfin – in a dose of 6 mg/m^2, energy 50 J/cm^2) [137]. With regard to the potential danger posed by standard PDT treatment (deterioration of VA, wider destruction of normal or already breached RPE with atrophic changes, potential choroidal ischemia, risk of development of secondary CNV), in recent years priority has been given to alternative dosing regimens of verteporfin and the used laser beam, known as "safety-enhanced" PDT. Either a reduced dose of radiation is used in "reduced (half)-fluence" (HF-PDT – 42 seconds, or half energy– 25 J/cm2), or a reduced dose of verteporfin in "reduced (half)-dose" (HD-PDT, i.e. 3 mg/m^2 of Visudyne) [12,28,128,133,141].

The results of studies comparing "safety-enhanced" PDT and conventional PDT are comparable. While achieving a similar anatomical and functional effect, "safety-enhanced" PDT minimizes the harmful effect on the perfusion of the choriocapillaris and its atrophying influence on the RPE and thickness of the retina [12,133]. The authors Nicoló and Kim in their publications compared the functional and anatomical results in patients with cCSC treated using HF-PDT and HD-

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-PDT. Both authors present findings that no statistically significant differences exist in the anatomical or functional results between these therapeutic modalities, Nicoló merely states more rapid absorption of SRF in the case of HD-PDT [10,141].

Thanks to its positive results and satisfactory safety profile as demonstrated by the clinical trials conducted to date, reduced PDT is considered the treatment of first choice, although it remains off-label in indication for CSC [142,143].

Anti-VEGF therapy

With regard to the pathophysiology of the disease, the use of anti-VEGF agents is contentious in the treatment of CSC. A series of clinical trials have provided ambiguous results of the effect of anti-VEGF agents in the treatment of CSC [18,144,145]. The pathology itself is not associated with a higher level of VEGF in the vitreous, and the effect of anti-VEGF treatment for CSC without the presence of CNV has not been demonstrated overall [146]. However, a different situation applies in complicated cases of secondary CNV upon a background of CSC. In the last 5 years especially, when thanks to advances in multimodal imaging (OCT-A) it has become possible to demonstrate CNV associated with CSC pathology with far greater sensitivity and specificity, the use of anti-VEGF agents in these cases has gained ever-increasing significance, and in the most severe conditions in combination with PDT [147]. Previous clinical trials have demonstrated an anatomical and functional effect of bevacizumab, ranibizumab and aflibercept in the treatment of CNV associated with CSC [146,148,149]. However, only limited data exists documenting the safety and efficacy of combined PDT and anti-VEGF treatment. Asahi demonstrated positive results of combined therapy with HD-PDT + aflibercept in patients who were unresponsive to conventional treatment (laser photocoagulation, monotherapy with PDT, monotherapy with anti-VEGF), and recorded greater success above all in eyes complicated by CNV [150].

Ranibizumab is the only registered pharmaceutical in the Czech Republic that may be used in the treatment of rare forms of CNV, thus also those upon a background of CSC.

Other therapeutic alternatives

Despite the fact that no causal medicamentous therapy exists in the treatment of CSC, a series of smaller clinical trials have demonstrated positive results in the treatment of CSC upon the use of finasteride (dihydrotestosterone synthesis inhibitor) in a dose of 5mg per day or acetylsalicylic acid acting against choroidal vascular congestion, ischemia and inflammatory changes accompanying CSC [28]. Good results may also be attained by eradicating infection of Helicobacter pylori in indicated cases and treatment of obstructive sleep apnea as potential risk factors triggering this disease [28,35].

CONCLUSION

Today's technical advances in the diagnosis and treatment of CSC in combination with our own clinical experiences represent a substantial improvement in the prognosis for our patients with CSC, for whom it is necessary to ensure not only correct diagnosis of the pathology based upon multimodal imaging, but above all correct setting and timing of adequate treatment. From our results to date it also ensues that treatment of chronic forms of CSC should be commenced in the early stages in order for us to attain the best possible anatomical and functional results, before irreversible changes are expressed such as DRPE or complicating CNV.

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THERAPY FOR VITREOUS SEEDING CAUSED BY RETINOBLASTOMA. A REVIEW

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SUMMARY

Retinoblastoma is the most common primary malignant intraocular tumor in children. Seeding, specifically the dispersion of the tumor into the adjacent compartments, represents a major parameter determining the degree of retinoblastoma according to the International Classification of Retinoblastoma. In this article we focused on vitreous seeding, one of the main limiting factors in the successful "eye preservation treatment" of retinoblastoma. This article presents an overview of the history of vitreous seeding of retinoblastoma, established treatment procedures and new-research modalities. The introduction of systemic chemotherapy in the treatment of retinoblastoma at the end of the 1990s represented a significant breakthrough, which enabled the progressive abandonment of radiotherapy with its attendant side effects. However, the attained concentrations of chemotherapeutics in the vitreous space during systemic chemotherapy are not sufficient for the treatment of vitreous seeding, and the toxic effects of systemic chemotherapy are not negligible. A significant change came with the advent of chemotherapy in situ, with the targeted administration of chemotherapeutic drugs, namely intra-arterial and intravitreal injections, contributing to the definitive eradication of external radiotherapy and a reduction of systemic chemotherapy. Although vitreous seeding remains the most common reason for the failure of intra-arterial chemotherapy, this technique has significantly influenced the original treatment regimen of children with retinoblastoma. However, intravitreal chemotherapy has made the greatest contribution to increasing the probability of preservation of the eyeball and visual functions in patients with advanced findings. Novel local drug delivery modalities, gene therapy, oncolytic viruses and immunotherapy from several ongoing preclinical and clinical trials may represent promising approaches in the treatment of vitreous retinoblastoma seeding, though no clinical trials have yet been completed for routine use.

Key words: retinoblastoma, vitreous seeding, eye preservation treatment, intravitreal chemotherapy

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INTRODUCTION

Retinoblastoma (Rb) is the most common malignant intraocular tumor in childhood age, with an incidence of 1 in 13844 born children in European countries [1], while in the Czech Republic it is diagnosed on average in 6 to 7 children annually [2]. According to heredity, the pathology is divided into two forms. Hereditary Rb (approximately 40% of cases), characterized by embryonic mutation of the retinoblastoma (Rb1) gene, is usually diagnosed in children at around the age of one year, and the finding may be either bilateral or multifocal, though in 10–15% of cases is only unilateral. The non-hereditary form of Rb mostly afflicts only one eyeball, forms one lesion, and appears more frequently in older children between 1 and 3 years of age. These patients have a mutated Rb1 gene only in the tumor tissue [3]. The growth of Rb begins with a small, semi-transparent lesion in the sensory part of the retina, after which it progressively takes on a whitish coloring, and a dilated afferent and efferent vessel appears. Upon further growth the tumor leaves the retina, and an exophytic or endophytic image of growth may occur. A very rare form of Rb is diffuse growth of Rb [4,5]. Localized intraocular Rb is divided into groups A to E based on the advanced stage of the pathology according to the ICRB (International Classification of Retinoblastoma), which helps determine the probability of preserving the eyeball, as well as of preserving visual functions [2,6], Table 1. Rb seeding constitutes the dispersion of tumor particles into the adjacent compartments, and is the main parameter for determining

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the degree of Rb according to the ICRB (groups C, D and E). Seeding of intraocular Rb may occur into 4 different anatomical localities (Table 2) [7].

In this article we have focused on vitreous seeding. On the basis of morphology, vitreous seeding is divided into 3 groups: dust (Fig. 1), spheres (Fig. 2) and clouds (Fig. 3) [7,8]. These three types differ not only in their morphology, but also in their response to treatment [8]. Vitreous seeding is one of the main limiting factors in the successful "eye-preservation treatment" of retinoblastoma.

THERAPY FOR VITREOUS SEEDING

History

Historically the first recorded treatment of Rb was enucleation of the eyeball. This therapy was proposed a life-preserving procedure by James Wardrop in 1809 [9]. Almost one hundred years later this was followed by external radiotherapy, which represented the first possibility of eye-preservation treatment, thanks to Hilgartner's demonstration of the radiosensitivity of Rb in 1903 [10]. However, in addition to ocular complications (cataract, irradiation retinopathy, vitreous hemorrhage, glaucoma), external radiotherapy also increases the later effects of the pathology, which are local effects in connection with orbital growth defect, endocrinopathy, secondary brain tumors, post-radiation sarcomas, and in the case of hereditary retinoblastoma the procedure above all increases the risk of secondary malignancies [9]. In recent decades, conservative therapy of retinoblastoma has experienced rapid development. The introduction of systemic chemotherapy (the currently used protocol of six cycles of VEC – Vincristine, Etoposide, Carboplatin) and focal therapy (cryotherapy, transpupillary thermotherapy and brachytherapy) at the end of the 1990s enabled the progressive abandonment of external radiotherapy. The risks of systemic chemotherapy include the onset of secondary leukemias and myelodysplastic syndrome potentiated by eto-

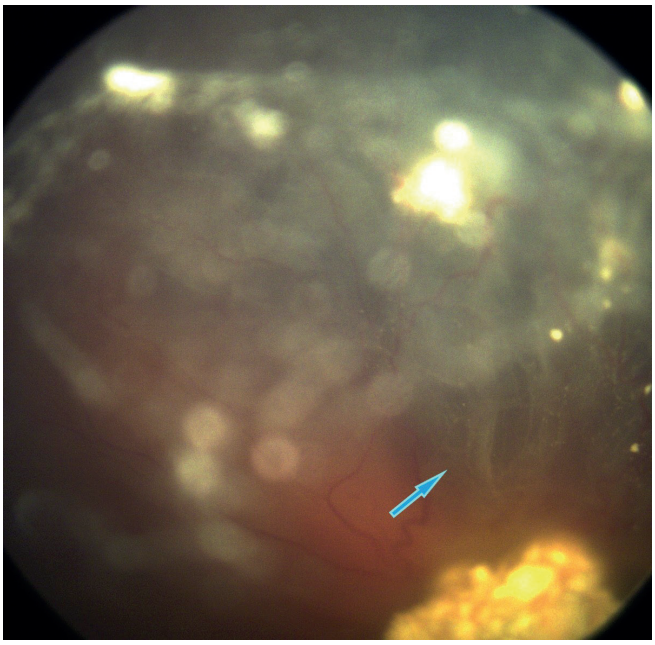


Figure 1. Classification of vitreous seeds: **dust**

Table 2. Four distinct anatomic sites of intra-ocular retinoblastoma [7]

1.	tumor dispersion into the vitreous gel following endophytic disruption of ILM and hyaloid at tumor apex
2.	tumor suspension spreading into the retro-hyaloidal space secondary to endophytic disruption of the ILM at tumor base alone, and partial or complete posterior vitreous detachment
3.	tumor suspension into the subretinal space created by exophytic growth
4.	tumor suspension into the aqueous fluid of the posterior and anterior chambers secondary to disruption of the anterior hyaloid

ILM – internal limiting membrane

Table 1. International Classification of Retinoblastoma (ICRB) [6]

Group	Quick reference	Specific features
A	Small tumor	Rb ≤ 3 mm in size
B	Large tumor Macula Juxtapapillary Subretinal fluid	Rb > 3mm in size or Macular Rb location (≤ 3 mm to foveola) Juxtapapillary Rb location (≤ 1.5 mm to disc) Clear subretinal fluid (≤ 3 mm from margin)
C	Focal seeds	Subretinal seeds ≤ 3 mm from Rb Vitreous seeds ≤ 3 mm from Rb Both subretinal and vitreous seeds ≤ 3 mm from Rb
D	Diffuse seeds	Subretinal seeds > 3 mm from Rb Vitreous seeds > 3 mm from Rb Both subretinal and vitreous seeds > 3 mm from Rb
E	Extensive Rb	Extensive Rb occupying > 50% of globe or Neovascular glaucoma Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space Invasion of postlaminar optic nerve, choroid (> 2 mm), sclera, orbit, anterior chamber

Rb - Retinoblastoma