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Eales disease

Elisa Ferrer, Mª Àngels Moral
Prous Science, P.O. Box 540, 08080 Barcelona, Spain

CONTENTS

Abstract 463
Introduction 463
Natural course and etiopathogenesis 463
Treatment 463
Conclusions 466
References 466

Abstract

Eales disease is an idiopathic vasculopathy of the peripheral retina predominantly affecting healthy young adults in the Indian subcontinent. The natural course of the disease may be variable and can lead to total blindness in the most severe cases. Treatment approaches consist mainly of oral corticosteroids and laser or vitreoretinal surgery. However, new therapeutic strategies have been shown to improve vision outcomes in this rare ocular disorder.

Introduction

Eales disease is an idiopathic retinal vasculopathy, first described by Henry Eales in 1880. It courses with initial inflammatory perivasculitis in the peripheral retina, followed by an ischemic stage involving retinal vein sclerosis, which ultimately develops into retinal neovascularization associated with recurrent vitreous hemorrhage (1). While rare in Western countries, Eales disease is especially prevalent in the Indian subcontinent. It is common among young adults, who may refer blurred vision, floaters and decreased visual acuity frequently due to vitreous hemorrhage. Although symptoms may appear only in one eye, retinal findings (periphlebitis, etc.) are generally bilateral. The natural course of Eales disease may vary from temporary or permanent disease regression to, more rarely, blindness (2).

Treatments for Eales disease may vary depending on clinical manifestations, but classically comprise oral corticosteroids to reduce inflammation and laser photocoagulation or vitreoretinal surgery to control neovascularization and vitreous hemorrhage. Newer treatment options such as intravitreal steroids, immunomodulatory agents or vascular endothelial growth factor (VEGF)-targeted strategies have also been investigated (1, 2).

Natural course and etiopathogenesis

Four different stages can be identified in Eales disease: stage I, intraocular inflammation featuring retinal periphlebitis; stage II, peripheral retinal nonperfusion due to venous occlusion (ischemic phase); III, neovascularization and vitreous hemorrhage; and stage IV, complications such as traction retinal detachment. During the inflammatory phase, perivascular exudates along the peripheral veins can be seen with fluorescein angiography, sometimes with superficial retinal hemorrhages. Later, peripheral nonperfusion develops with areas of obliterated, tortuous capillaries, and the appearance of veno-venous shunts among other vascular abnormalities. Retinal ischemia promotes the formation of newer blood vessels or neovascularization, typical of Eales disease, usually close to the site of venous occlusion. Neovascularization can affect the optic disk or elsewhere in the retina, and may cause recurrent bleeding. With time, neovascular lesions may become fibrotic and pull away the retina, hence causing traction retinal detachment. In the late proliferative phase, neovascular glaucoma can also be found (1-3).

The etiology of Eales disease is still unknown. It has been associated with systemic diseases of different origin, such as tuberculosis, neurological disease or parasitic infestations. However, these correlations have not been proven in large studies (1).

Eales disease has also been associated with immunological causes. In fact, lymphocytic infiltrates with predominance of CD4-positive T-cells have been identified in the epiretinal and subretinal membrane of Eales disease patients, indicating a potential role for T-cells in the proliferative phase of the disease, which makes them a target for therapeutic intervention (2, 4).

Recently, an 88-kDa protein has been identified in serum from patients with Eales disease, uveitis, tuberculosis, leprosy and rheumatoid arthritis, thus suggesting that it is an acute-phase reactant expressed during inflammatory conditions (5). However, its role in the pathogenesis of these disorders still needs to be defined.

Treatment

The management of Eales disease has involved pharmacological and surgical approaches. Oral cortico-

steroids and surgery have been the mainstay therapies to control inflammation and neovascularization and to prevent further complications. However, intravitreal corticosteroids or newer anti-VEGF therapies appear as alternatives with success reported in other ocular disorders. The following is a summary of current and potential new strategies for the treatment of Eales disease (see also Table I).

Intravitreal corticosteroids

Oral corticosteroids have been the first-line therapy for the inflammatory phase of Eales disease. Usually, oral prednisolone treatment starts at 1 mg/kg and is tapered to 10 mg per week over 6-8 weeks. However, if inflammation persists, more prolonged treatment may be required, hence increasing the risk for developing adverse events. In some cases, periocular (peribulbar) injection of triamcinolone acetonide has also been beneficial (1). However, symptoms may relapse when the effects of triamcinolone injection diminish over time (6). Recently, positive results with intravitreal administration of triamcinolone acetonide have also been reported. Intravitreal triamcinolone acetonide resolved intraocular inflammation with regression of periphlebitis and improved visual acuity in Eales disease patients refractory to oral corticosteroids and periocular triamcinolone (6), and also in 1 patient in whom oral corticosteroids were contraindicated (7). A prospective interventional case series demonstrated a significant reduction in perivascular inflammation in 83.3% of Eales disease eyes treated with intravitreal triamcinolone (8). Although long-term follow-up was not performed, these results indicate that intravitreal steroids may be an alternative to prolonged oral corticosteroid therapy and may decrease the need for further interventions.

Methotrexate

As discussed earlier, T-cells may play a role in the pathogenesis of Eales disease and therapies targeting activated T-lymphocytes may be beneficial. In this sense, the efficacy of oral methotrexate, known to cause B- and

Table I: Summary of experimental strategies in Eales disease (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions/Objectives	Ref.
Triamcinolone acetonide	Case report	Triamcinolone acetonide, 4 mg i.vitr.	2	Intravitreal administration of triamcinolone acetonide improved the persistent retinal periphlebitis in 3 treated eyes of 2 patients with Eales disease who had not responded to treatment with oral corticosteroids and peribulbar injection of triamcinolone acetonide	6
	Case report	Triamcinolone acetonide, 4 mg i.vitr.	1	Intravitreal triamcinolone acetonide treatment caused regression of periphlebitis, neovascularization and macular edema in the affected eye of a patient with Eales disease in whom oral corticosteroids were contraindicated	7
	Open	Triamcinolone acetonide, 4 mg i.vitr.	12	Ten of 12 eyes treated with intravitreal triamcinolone acetonide showed significant reduction in leakage from retinal vessels in patients with Eales disease	8
Methotrexate	Open	Methotrexate, 12.5 mg p.o. 1x/wk x 12 wks	21	Methotrexate therapy resolved periphlebitis and improved or maintained visual acuity in all treated eyes (n=21) of patients with Eales disease. Side effects were mild or moderate in severity and reversible upon dose reduction or discontinuation	9
Azathioprine	Retrospective	Azathioprine, 50 mg p.o. o.d. x 1 wk → 50 mg p.o. b.i.d. x 1 wk → 50 mg p.o. t.i.d. [max. 2 mg/kg/d] x 9 [max.] y	34	Azathioprine in combination with systemic steroids effectively reduced relapse rate in treated eyes (n=67) of patients with retinal vasculitis. A decreased inflammatory score was found in 56% of eyes, and visual acuity maintenance or improvement in 65% of eyes	10
Bevacizumab	Case report	Bevacizumab, 1.25 mg i.vitr.	1	Bevacizumab treatment resulted in the regression of both disc and retinal neovascularization in the affected eye of a patient with Eales disease	17
Ranibizumab	Open	Ranibizumab, i.vitr. 1x/mo x 3 mo	5	This study will assess the safety and efficacy of ranibizumab in patients with macular edema due to Eales disease	18

T-cell suppression, was evaluated in an open study that enrolled 21 patients with Eales disease (9). At the end of the treatment period, all eyes maintained or improved visual acuity after methotrexate therapy, with 71% of eyes displaying excellent visual acuity outcomes (6/6 or better). Complete periphlebitis remission was seen in 85.7% of treated eyes. In general, methotrexate did not cause any hematological abnormalities (only 1 patient experienced mild leukopenia) and the most common adverse events reported were mild gastrointestinal symptoms. Thus, weekly pulsed therapy appeared as an effective and safe option, although careful patient monitoring must be undertaken when prescribing methotrexate.

Azathioprine

Immunosuppressive agents have been used as second-line treatment in the management of Eales disease (1). A retrospective study found azathioprine (50 mg/day for 1 week, increasing up to 50 mg t.i.d. in the absence of side effects) useful for improving intraocular inflammation and reducing the rate of retinal vasculitis relapse when used in combination with oral corticosteroids in patients with retinal vasculitis of different origin, including 15 patients with idiopathic retinal vasculitis. However, azathioprine did not allow for corticosteroid dose reduction in all patients. Regarding the safety profile, lymphopenia was common but did not require treatment discontinuation in any of the cases (10).

Surgery: laser photocoagulation/vitrectomy

Laser photocoagulation is a technique that has been extensively used to treat eye diseases involving neovascularization, such as age-related macular degeneration (AMD) or diabetic retinopathy. Laser treatment cauterizes leaky vessels and prevents further loss of vision, but it does not improve vision loss that has already occurred. Panretinal photocoagulation refers to the application of laser in a scatter pattern to reach large areas of the peripheral retina and it has provided successful outcomes in the proliferative phase of Eales disease. Vitrectomy has been also used in Eales disease to treat cases of recurrent vitreous hemorrhage, tractional retinal detachment or just to clear vitreous opacities (1).

A retrospective study evaluating 46 eyes of patients with Eales disease concluded that combined panretinal photocoagulation and vitrectomy may be a promising approach to treat eyes with active fibrovascularization and persistent vitreous hemorrhage. In this study, 93.3% of eyes treated with both procedures due to nonresolving vitreous hemorrhage and vitreous hemorrhage associated with retinal detachment achieved visual acuity values of 20/200 or better (11). Another retrospective study in patients with complicated Eales disease reported similar results and suggested that vitrectomy may be required in those cases where repeated laser photocoagulation is not sufficient to control recurrent neovascularization (12).

Results from a larger retrospective case series evaluating 71 eyes of 63 patients showing Eales disease complications reported improved visual acuity in 76% of cases after vitrectomy with or without adjuvant procedures (scleral buckling, gas/oil tamponade). Eyes operated for vitreous hemorrhage showed slightly better outcomes than those operated for retinal detachment (13). Vitrectomy was also found useful when administered to the asymptomatic fellow eye in Eales disease patients as add-on therapy to laser photocoagulation to prevent further complications (14).

All these studies highlighted the importance of performing early vitrectomy. Actually, a comparative study showed that early vitrectomy (*i.e.*, performed when the duration of vitreous hemorrhage was inferior to 6 months) resulted in better visual acuity outcomes than deferred vitrectomy, which was associated with complications such as macular edema and macular degeneration (15). Thus, early vitrectomy reduces the time that hemorrhagic toxic products are in contact with the macula (*i.e.*, cone photoreceptor cells), which likely prevents complications.

Anti-VEGF therapies

Retinal neovascularization during the proliferative phase in Eales disease is the cause of vitreous hemorrhage and other associated complications, ultimately leading to loss of vision in the affected eyes. Interestingly, Eales disease has been associated with extensive VEGF expression in one isolated report (16). In that case, enucleation had to be performed due to terminal neovascular glaucoma, hence allowing posterior immunohistochemistry of enucleated eye sections, which showed intense VEGF staining in the preretinal neovascular membrane. VEGF is a major angiogenic factor that has been shown to play a role in other neovascular ocular disorders, such as AMD or diabetic macular edema. Therefore it seems plausible that anti-VEGF therapies may be an alternative approach for the treatment of Eales disease. To date, an isolated case of a young male patient with Eales disease has reported regression of both optic disc and retinal neovascularization 1 month after intravitreal bevacizumab (Avastin™; Genentech) treatment, which did not recur for up to 4 months (17).

In this context, a short, open, nonrandomized clinical study sponsored by Genentech and the Oregon Health and Science University will evaluate the safety and efficacy of ranibizumab in patients with Eales disease, in particular its ability to manage macular edema present in those patients (18). Ranibizumab (Lucentis®; Genentech) is a recombinant humanized monoclonal antibody fragment that recognizes and inhibits VEGF-A, which promotes angiogenesis in response to hypoxia. It has been approved in the United States and in Europe for intravitreal use in the treatment of neovascular AMD and is in early clinical development for macular edema and other ocular conditions (17, 19).

Antioxidants

Oxygen-derived free radicals are known to be involved in the pathogenesis of inflammatory disorders. Reactive oxygen species (ROS) trigger a cascade of toxic events, such as lipid peroxidation or inhibition of mitochondrial respiratory chain enzymes, among other oxidative protein modifications, which contribute to inflammation in the eye and other tissues. In Eales disease, chronic inflammatory infiltrates consisting of lymphocytes and monocytes have been found in the epiretinal membrane. Furthermore, several studies have found evidence of increased oxidative activity in Eales disease. Levels of thiobarbituric acid-reactive substances (TBARS), an index of lipid peroxidation and oxidative stress, were found to be elevated in the vitreous of Eales disease patients compared to vitreous samples from diabetic vitreous hemorrhage patients, while superoxide dismutase (SOD) activity and glutathione (GSH) levels were significantly diminished (20). Another study further identified increased expression of inducible nitric oxide synthase (iNOS) and elevated 3-nitrotyrosine in monocytes isolated from Eales disease patients, which correlated with decreased SOD activity and increased lipid peroxidation. These results indicate that reactive nitrogen species, together with oxidative stress, may mediate the development of retinal vasculitis (21).

Two further studies showed a significant reduction in SOD activity and elevated levels of malondialdehyde, indicative of increased lipid peroxidation, in platelets from patients with Eales disease, compared to matched healthy controls (22, 23). In addition, alterations in platelet membrane fluidity have been described in Eales disease patients as a result of increased oxidative stress (24). Moreover, accumulation of 8-hydroxydeoxyguanosine (8-OHdG), indicative of oxidative DNA damage, has been detected in leukocytes of Eales disease patients with active and healed retinal vasculitis. Levels of 8-OHdG positively correlated with decreased antioxidant SOD activity, GSH content and disease severity (25). Hydroxyl radical generation has also been found in monocytes of patients with Eales disease (26). Interestingly, the toxic effects of hydroxyl radicals could be attenuated by iron chelation with diethylenetriaminepentaacetic acid (DTPA) and deferoxamine, as iron catalyzes the production of hydroxyl radicals via the Fenton reaction.

Conclusions

The mechanisms underlying Eales disease have yet to be fully identified, although immune-mediated processes may be involved in the pathogenesis of this disorder. Treatment options are still limited, but the introduction of intravitreal corticosteroids holds promise for the management of the inflammatory phase and to prevent further complications. Also, experimental VEGF-targeted therapies are emerging as potential candidates to control neovascularization in Eales disease. As oxidative stress may be a component in disease pathogenesis, the potential therapeutic efficacy of antioxidants should be investigated.

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