An Update on Eales’ Disease

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Introduction
Since the initial description by Henry Eales of Eales’ disease in his patients with recurrent retinal hemorrhages, history of headache, variation in peripheral circulation and chronic constipation in 1880 and 1882, this disease still remains a clinical enigma with an undetermined precise etiology. The disease is now considered a clinical syndrome which possesses a specific clinical picture and natural course.

History
It was first described by Dr. Henry Eales (Fig 1), a British ophthalmologist in 1880 and 1882. Elliot was the first to recognize the inflammation of retinal veins and described it as periphlebitis retinæ. Subsequently many investigators documented both arteriolar and venular inflammation in Eales’ disease.

Definition
Eales’ disease is an idiopathic retinal periphlebitis characterized by capillary non-perfusion, neovascularization and recurrent vitreous hemorrhages, mainly involving the peripheral fundus, and occurring predominantly in young, healthy adult males (Fig 2).

Epidemiology
Initially having been reported in United Kingdom, it was subsequently reported in series from Canada, Germany, Greece, Korea, and Turkey. Presently it is more commonly seen in the Indian subcontinent with a frequency of 1 in 135-200 ophthalmic patients in a referral eye hospital in India. Male predominance of up to 97.6% has been found in most series. Mean age of onset is 26 years, although the disease has been seen to occur as early as 10 years of age.

Clinical features
Often Eales’ disease is asymptomatic in the initial stages of retinal perivasculitis. Some patients may develop symptoms such as floaters, blurring of vision or even
gross diminution of vision due to vitreous hemorrhage. In a series of Eales’ disease patients, 75 % had floaters and black spots, 60 % had painless dimness of vision. Bilaterality is common with the incidence being 50-90 %. Anterior uveitis is uncommon in Eales’ disease. However in severe active periphlebitis stage, spillover anterior uveitis may occur which is always non-granulomatous. The presence of granulomatous anterior uveitis points towards sarcoidosis. Eales’ disease shows patches of active and healed perivasculitis and vessel alteration in all quadrants unlike branch retinal vein occlusion, which generally remains confined to the affected quadrant.

Hypopyon is not seen in Eales’ disease and is a differentiating feature between it and Behcet’s disease. It also mimics sarcoidosis, and the presence of granulomatous anterior uveitis points towards sarcoidosis.

Healed perivasculitis is often seen as sheathing of veins. Other vascular changes include sclerosed cord of vessels, irregularity of vein caliber, and pigmentation along venules, kinky venules, abnormal vascular anastomosis and veins pulled into the vitreous cavity. Presence of active and healed choroiditis in Eales’ disease should make one suspect the presence of simulating disease such as sarcoidosis, tuberculosis or syphilis.

Central retinal periphlebitis involving the posterior pole, especially the macula, is markedly uncommon compared to peripheral periphlebitis. It is termed as central Eales’ disease which is a variant of classical Eales disease (Fig 3,4).

Macular changes are relatively uncommon. A recent series showed macular changes in 18 % of eyes, which included exudates over the macula, epimacular membrane and rarely subhyaloid hemorrhage. Peripheral retinal neovascularization was a frequent finding and was reported in 36-84 % cases. However optic disc neovascularization was a rare occurrence observed in only 9 % of cases. Dense vitritis is uncommon. Recurrent vitreous hemorrhage is the hallmark of this disease.

Surface neovascularization was seen in 50 % of eyes in one series. Fibrovascular proliferation also occurs in Eales’ disease (Fig 1,2). Differential diagnosis of Eales’ disease is presented in Tables 1 and 2.

<table>
<thead>
<tr>
<th>Table 1. Proliferative Vascular Retinopathy Mimicking Eales’ Disease</th>
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<tr>
<td><strong>Systemic</strong></td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Sarcoidosis</td>
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<td>Sickle cell disease</td>
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<td>Parsplanitis</td>
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<th>Table 2. Retinal Vasculitis Mimicking Eales’ Disease</th>
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<tr>
<td><strong>Systemic</strong></td>
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<tr>
<td>Behcet’s disease</td>
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<tr>
<td>Leukemia</td>
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<tr>
<td>Chronic myelogenous leukemia</td>
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<tr>
<td>Lyme Borreliosis</td>
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<tr>
<td>Multiple sclerosis</td>
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<tr>
<td>Sarcoidosis</td>
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<td><strong>Syphilis</strong></td>
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Fig. 3. Fundus picture (montage) left eye of a patient with Eales’ disease showing aggressive vasculitis, with sheathing of vessels in all the quadrants, hemorrhages in superior and temporal quadrants, and posterior pole involvement.

Fig. 4. Fundus photograph of right eye in a case of central Eales’ disease showing active retinal vasculitis and hard exudates in macular star configuration.
Investigations

Fundus Fluorescein Angiography

It is often helpful to distinguish Eales’ disease from other retinal vascular disease and is particularly beneficial in the ischemic stages to delineate areas of capillary non-perfusion, retinal and optic disc neovascularization and questionable macular edema.

In cases of active retinal vasculitis, staining of the veins can be seen in the early venous phase with extravasation of the dye in the late phase. This is highly characteristic of active local inflammation in the retinal vessels. Extent and location of the neovascularization can be precisely delineated by Fundus Fluorescein angiography.

Neovascularization if present can be characteristic with sea fan appearance (Fig 5) with intense hyperfluorescence in the early arteriovenous phase of FFA. These new vessels leak in the late venous phase. Venous obstruction and venous stasis are seen well on FFA. Engorged and tortuous capillaries and veno-venous shunts can also be seen in the ischemic stage.

FFA is used to delineate the location and extent of retinal ischemia (Fig 5) while performing laser photocoagulation. It helps to assess the adequacy of photocoagulation and the need for additional laser photocoagulation, when FFA is repeated in the follow up visits.

Ultrasoundography

Ultrasound (combined A scan and B scan) is needed to rule out any associated retinal detachment, either tractional, rhegmatogenous or combined in an eye with opaque media. Ultrasound usually reveals echoes of variable density depending on the compaction of the vitreous hemorrhage.

Other findings in ultrasound are as follows
1. Subhyaloid echoes.
2. Posterior vitreous detachment complete or incomplete.
3. Membranes in the vitreous cavity.
4. Fibrovascular proliferation.

Natural Course

Clinical manifestations are due to 3 basic pathological changes:
1. Inflammation (peripheral retinal perivasculitis)
2. Ischemic changes; peripheral retinal capillary non-perfusion
3. Neovascularisation of the disc and retina which often leads to vitreous hemorrhage.

Loss of vision in Eales’ disease is due to the recurrent vitreous hemorrhage (Fig 6), macular changes (ischemia, edema, and hemorrhage), tractional and combined retinal detachment involving the macula. Vascular occlusions may also complicate the picture (Fig 7).
Blindness due to Eales’ disease is rare. In case series of 800 cases only 4 eyes had < 20/200 and 8% had visual acuity between 20/100 to 20/200.

**Classification**

Charmis in 1965, classified Eales’ disease into 4 stages

Stage 1: Very early in evolution and characterized by mild periphlebitis of small peripheral retinal capillaries arterioles and venules.

Stage 2: Perivasculitis of the venous capillary system is widespread. Vitreous haze is present.

Stage 3: New vessel formation with abundant hemorrhage in the retina and the vitreous is found.

Stage 4: End stage of massive and recurrent vitreous hemorrhages with retinitis proliferans and tractional retinal detachment.

Due to the overlap of the stages in the clinical setting the four stage classification is not very popular. Other investigators have proposed different system of grading depending on the extent of microangiopathy, proliferative retinopathy, and vitreous hemmorhage. These classification systems are useful for monitoring and assessment of the effect of the treatment.

More recently, Saxena and Kumar proposed a new classification system:

Stage 1: periphlebitis of small (1a) and large caliber vessels (1b) with superficial retinal hemorrhages.

Stage 2a: denotes capillary nonperfusion.

Stage 2b: neovascularization elsewhere /of the disc.

Stage 3a: fibrovascular proliferation.

Stage 3b: vitreous hemorrhage.

Stage 4a: tractional/combined rhegmatogenous retinal detachment.

Stage 4b: rubeosis iridis, neovascular glaucoma, complicated cataract and optic atrophy.

The same authors also published a new classification system-based on visual outcomes in Eales’ disease, characterizing the visual outcomes based on the severity of the disease.

Yet to date there is no standard classification system which is accepted and practiced.

**Etiopathogenesis**

It still remains unclear what the cause of the disease is, in spite of the several clinical and basic studies; however the following have been noted to probably have an association with Eales’ disease.

**Tuberculosis**

Pathological demonstration of tubercle bacillus was reported by Gilbert in 1935 and Stock in 1937. However Finoff in 1924 injected tubercle bacilli in 46 experimental animals and demonstrate vasculitis in only 1 eye. It appears that Eales’ disease may not carry viable organisms, but harbor nonviable organism or DNA of mycobacterium tuberculosis in significant number of cases. In a study, 11 out of 23 epiretinal membranes removed from eyes with Eales’ disease showed mycobacterium tuberculosis genome106 by nested PCR technique. However, culture of vitreous specimen did not show any growth of mycobacterium tuberculosis. It appears that Eales’ disease patients may not carry viable organisms, but may probably harbor nonviable organisms or DNA of mycobacterium tuberculosis in a significant number of cases.

**Hypersensitivity to tuberculoprotein**

Mantoux positivity has been reported in 42-98 % of Eales’ disease. Moreover, Mantoux is commonly positive in healthy adults in India and Eales’ disease was found in Mantoux negative patients too.

**Parasitic infestation**

Wania et al proposed possible association of Ascaris lumbricoides with Eales’ disease. There was no difference between the levels of IgM and IgG antibodies to Toxocara canis and Ascaris between Eales’ disease patients and controls in a study done at Sankara Nethralaya.

**Neurological involvement**

Various neurological lesions, such as multiple sclerosis, acute myelopathy, multifocal white matter abnormality, cerebral stroke, internuclear ophthalmoplegia, spastic paraparesis and hemiplegia have been reported. Other systemic diseases may be associated and are listed in Table 3.
Table 3. Systemic Diseases Associated with Eales’ Disease

Tuberculosis
Hypersensitivity to tuberculoprotein
Thromboangitis obliterans
Neurological disease
  Multiple sclerosis
  Acute or subacute myelopathy
  Multifocal white matter abnormality
  Cerebral stroke
  Others
Focal sepsis
Hematological abnormalities
  Acanthocytosis
  Increased plasma viscosity, erythrocyte rigidity and erythrocyte aggregation
  Hypereosinophilia
  Blood coagulation disorder
  Impaired oxygen release from blood
  Raised fibrinolytic activity
Vestibuloauditory dysfunction
Parasitic infection (Amoebiasis, Ascariasis)
Others

Immunology and immunopathology

Class I and class II HLA have been associated with Eales’ disease. HLA DQ2, DR52 and Bw6 were found in higher frequency in Eales patients and thus strongly associated with it 6. Experimental evidence also suggests autoimmune mechanism in the etiopathogenesis of Eales’ disease.

Recently Saxena and coworkers studied lymphocyte proliferative response against retinal S antigen, its uveito pathogenic fragments, yeast histone H3peptide, interphotoreceptor retinoid binding protein (IRBP).

Biochemical studies

Prathap et al has found raised α-globulin and decreased albumin levels in the serum of patients with Eales’ disease. Rangarajan et al has identified a distinct protein with molecular weight around 23 kda in serum of Eales’ disease. Sen et al found a raised α-1 acid glycoprotein levels in serum of the Eales disease.

A close relationship between the prominent neovascular proliferation in Eales’ disease and the intense expression of VEGF has been studied 6. The increased expression of VEGF, when compared to other conditions inducing neovascularisation, might explain the severity of neovascular growth and the propensity of repeated vitreous hemorrhages in Eales’ disease.

Rao et al has reported that the damage inflicted on the ocular tissue is due to reactive oxygen in uveitis. Lowered levels of antioxidant vitamins E and C and consequent accumulation of oxygen and lipid free radicals have been studied and could be the cause of the inflammation, neovascularization and retinal pathology in patients with Eales’ disease.

One of the major effects of oxidative stress on cellular membranes in patients with Eales’ disease is a decrease in platelet membrane fluidity. The decreased membrane fluidity suggests alterations in the physiological events, which may result in alterations in the functioning of retinal photoreceptors 7.

Investigation in Eales’ Disease

Investigations are done to differentiate Eales’ disease from sarcoidosis, syphilis, tuberculosis and sickle cell retinopathy. The list of investigations in a case of Eales’ disease are enumerated in Table 4.

Table 4. Investigations for Eales Disease

<table>
<thead>
<tr>
<th>To rule out leukemia and hematological disease:</th>
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<tr>
<td>Hemoglobin (Hb) and Hemacrit (PCV)</td>
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<tr>
<td>Total RBC count</td>
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<tr>
<td>Total WBC count and differential count</td>
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<td>Other tests:</td>
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<tr>
<td>Platelet count</td>
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<tr>
<td>Erythrocyte sedimentation rate</td>
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<td>Reticulocyte count</td>
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<tr>
<td>Postprandial blood sugar</td>
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<td>Lysozyme (sarcoidosis)</td>
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<td>Mantoux test</td>
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<td>Basic coagulation test</td>
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<tr>
<td>Bleeding time</td>
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<td>Clotting time</td>
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<tr>
<td>Clot retraction</td>
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<tr>
<td>Plasma clotting time</td>
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<tr>
<td>Sickle cell preparation</td>
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<tr>
<td>Hemoglobin electrophoresis (sickle cell retinopathy)</td>
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<td>Immunoglobin profile VDRL and Treponema</td>
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<tr>
<td>Pallidum Hemagglutination Test (TPHA)</td>
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<td>Anti-nuclear antibody (SLE &amp; other collagen diseases)</td>
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<tr>
<td>Serum angiotensin converting enzyme (sarcoidosis)</td>
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<tr>
<td>Radiological tests:</td>
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<tr>
<td>X-ray chest (tuberculosis and sarcoidosis)</td>
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Management

It depends on the stage of the disease which includes:

1. No-treatment with periodic evaluation in the regressed stage of perivasculitis or fresh vitreous hemorrhage.
2. Treatment with oral or peri-ocular steroid in active peri-vascularitis stage.
3. Laser photocoagulation in case of the neovascularization of retina or optic disc, or gross capillary non-perfusion.
4. Vitreous surgery is indicated in non-resolving vitreous hemorrhage (usually > 3 months).
5. Any associated retinal detachment warrants a vitreoretinal surgery.
6. The roles of anticoagulant hyperbaric oxygen and anti-tubercular treatment remain controversial.

A particular patient may require one or more of the above modalities to treat Eales’ disease. Early and aggressive treatment of Eales’ disease have been shown to be beneficial in terms of anatomical and visual outcomes.

Observation

Patients with inactive vasculitis can be observed periodically at 6 months intervals. Patients with fresh vitreous hemorrhage are observed at an interval of 4-6 weeks, if the underlying retina is attached by ultrasound or indirect ophthalmoscopy. Such vitreous hemorrhage often clears by 6-8 weeks.

Medical therapy

Corticosteroids remain the mainstay of the treatment. There is no definitive dosage in active retinal perivasculitis stage. Dosage is tailored for each patient based on the severity of the inflammation. Some require a maintenance dose of 15-20 mg/day for 1-2 months. In case of associated macular edema one may add depot steroid injection. There are reports of intravitreal steroids being used for cases of Eales’ disease with favorable outcomes.

In general, the response to corticosteroid was found to be extremely good in several studies. Therefore the need for cyclosporine and other immunosuppressive agents is limited in Eales’ disease. As many investigators believe that hypersensitivity to tuberculoproteins play a role in the etiology of Eales’ disease, anti tubercular therapy has been given in Eales’ disease empirically which includes rifampicin 450 mg and isoniazid 300 mg once daily for a period of 9 months. In patients with positive Mantoux and active perivasculitis, oral corticosteroids and antitubercular therapy has been recommended. However the role of ATT in Eales’ disease treatment remains controversial.

Recently, low dose oral methotrexate pulse therapy (at a dose of 12.5 mg/week) has been described to be clinically effective in Eales’ disease, and was found to be associated with an acceptable safety profile.

Photocoagulation

It is the mainstay of therapy in proliferative stage of Eales’ disease. In case of gross capillary non-perfusion, photocoagulation is suggested. Currently laser photocoagulation is mostly used due to obvious advantage of reaching the periphery where retinal neovascularization and ischemia is mostly observed. Argon green laser is used usually. In case of significant cataract or mild vitreous hemorrhage red krypton laser can effectively be used. This is delivered by slit lamp or indirect ophthalmoscopy. Following vitrectomy, an endolaser probe or indirect ophthalmoscope laser can be used for laser delivery on the operating table.

Aim of photocoagulation in Eales’ disease is to regulate the circulation by diverting blood from hypoxic areas to healthy retina, (thereby reducing the formation of vasoproliferative factors), to obliterate surface neovascularization and close leaking intraretinal microvascular abnormalities. In patients with retinal neovascularization direct treatment with moderately overlapping burns is suggested. In case of elevated neovascularization photocoagulation of the feeder vessels beneath the frond is done.

Aneurysms and arteriovenous shunts are also treated in a similar fashion. Pan retinal photocoagulation is necessary when there is optic disc neovascularization. There are few minor complications associated with laser photocoagulation. Retinal hemorrhages are possible in a few cases but major bleeding is uncommon with proper selection of intensity and other parameters of photocoagulation. Occasionally retinal gliosis laid down by the regressing new vessels undergoes further contraction and cause a variety of retinal complications.
such as macular distortion due to epiretinal membrane and retinal tear resulting in retinal detachment. Laser photocoagulation can be done once the inflammation has subsided reasonably with anti-inflammatory medications like steroids as it is not advised in the active inflammatory stage which can worsen the neovascularization due to the angiogenic factors liberated.

**Vitreoretinal Surgery**  
Vitrectomy alone or combined with other vitreoretinal surgeries is often required in Eales’ disease (Please refer to the flowchart for treatment plan of vitrectomy). The aim of vitreous surgery is to clear vitreous opacities and evaluate the fundus for neovascularization. Along with vitrectomy, laser photocoagulation can also be performed by endophotocoagulation or indirect laser ophthalmoscopy. A standard 3 port pars plana vitrectomy is the method of choice. Patients with fewer episodes of vitreous hemorrhage and preoperative laser photocoagulation have a better visual prognosis. Early vitrectomy has been found to yield significantly better results as compared to deferred vitrectomy 13.

**Anterior retinal cryoablation (ARC)**
ARC is considered in small undilating pupil, hazy media due to cataract, after-cataract, or residual hazy vitreous, where it is usually reserved as adjunct to photocoagulation.

**Anti VEGF Agents**
Kumar A et al recently reported a successful and rapid regression of disc and retinal neovascularization in a case of Eales’ disease after intravitreal bevacizumab 14. These agents may prove as important adjunctive agents in the management of Eales’ disease in future, especially in patients who experience recurrent hemorrhages due to aggressive posterior segment neovascularization.

**Summary and Conclusions**
Eales’ disease, with its characteristic clinical features and fluorescein angiography findings is a specific vitreoretinal disease. The disease can mimic several other ocular and systemic diseases presenting as retinal vasculitis or proliferative vascular retinopathies. Since its original description, many investigators have considered an association with tuberculosis to be the prime cause of this disease. Recent immunological, molecular biological, and biochemical studies indicate a probable multifactorial etiology. Human leucocyte antigen, retinal autoimmunity, mycobacterial tuberculosis genome, and free radical mediated damage play their role in etiopathogenesis of the disease.

Although its etiopathogenesis remains unclear, the management options are quite well established. Systemic corticosteroids have been found to be beneficial in active perivasculitis stage. Photocoagulation
is indicated in cases with gross capillary nonperfusion or retinal neovascularisation. Results of vitrectomy in non resolving vitreous hemorrhage with or without retinal detachment are satisfactory.

References