A CLINICAL STUDY ON EALES DISEASE

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CERTIFICATE

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This dissertation is submitted to the TamilNadu Dr.MGR Medical University, Chennai for the fulfillment of award of M.S. Degree in Ophthalmology.

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SECTION - I

EALES DISEASE

INTRODUCTION

Eales Disease can be defined as primary idiopathic perivasculitis unaccompanied by other ocular inflammatory disorders or obvious systemic disease. The most striking feature of the inflammatory disease is the occurrence of hemorrhage in the retina or in the vitreous or the recurrence of hemorrhage in the later and arising there from, the complications. The most feared are retinitis proliferance detachment of retina, complicated cataract and secondary glaucoma in the order of frequency.

HISTORICAL ASPECTS

Eales disease was first described by Henry Eales a British ophthalmologist in 1880 and 1882. He found it in seven young, male patients ranging in age from 14 - 29 yrs. with recurrent retinal hemorrhages.

In addition these patients had histories of headache, variation in peripheral circulation, chronic constipation and epistaxis.

He concluded that the repeated hemorrhages occurred as a “neurosis” in the absence of obvious constitutional disease and retinal inflammation but, were associated with constipation and epistaxis the former being due to vasomotor contraction and subsequent muscular inhibition and the latter to a compensatory

capillary dilatation. In the century that has followed he has been honoured with the eponym for the disease (Eales disease)

Duke - elder felt that Eales disease was not a distinct clinical entity but instead represented the clinical manifestation of many diseases.

Elliot first recognized the inflammation of retinal vein and described it as periphlebitis retinae. Subsequently several investigators documented both venular and arteriolar inflammation.

The researches of Axenfeld and Stock (1909 -11) drew attention to the aetiological significants of tuberculosis a relation histologically proved by Fleisher (1913-14) Cords suggested the grouping together of recurrent vitreous hemorrhage, perivasculitis, retinitis proliferans and the exudative retinitis of coats into one group.

After the observation there was a tendency especially among German writers to ascribe all cases of recurrent hemorrhages to tuberculous retinal periphlebitis. On the other hand, many other causes were suggested particularly endocrine disturbances by French and focal infection by British and American writers, and blood dyscrasias were implicated by various authors. Even today the aetilogy still remains idiopathic.

RETINAL ANGIOGENESIS

The terminal portion of the primitive ophthalmic artery invade the embryonic fissure of the human eye at about 5 mm stage. The fissure close between the fifth and seventh week. The vessel remain in the optic cup and becomes the hyaloid artery. It probably functions, at least initially to supply the lens and retina. At the fourth month of gestation, spindle shaped mesenchymal cells arise from the hyaloid artery where it enter the optic disc. The formation of the primitive vessels occur, behind the advancing edge of the invading mesenchymal cells. Endothelial cells differentiate first and adjacent cells form junctional complexes, which invade both zonulae occludentes and gap junctions.

As the vessel matures, the lumina enlarge and become patent. Pericytes are present from an early stage. A prominent feature of the developing vasculature is the association of mononuclear phagocytic cells which are thought to have a role in angiogenesis. Retinal Vascularisation proceeds from the centre to the periphery. Between 24-26 weeks of gestation, small blood vessels develop in the ganglion cell layer at the foveal slope. By a process of remodeling and retraction of the primitive capillary network, the adult pattern of arterioles, veins and capillaries is established.

DUKE ELDER'S CLASSIFICATION

1. Vasuculitis secondary to uveitis.
2. Vasculitis secondary to systemic diseases.
3. Apparently primary vasculitis.

COGAN DIVIDED VASUCULITIS INTO THREE GROUPS

(1969, William Mckenzie centerary symposium on the circulation in health and diseases, kimpton London)

1. Mild papillophlebitis
2. Moderate vasculitis - Bilateral - Arteriole/veins affected
3. Severe vasculitis - Arterioles involved more than veins.

RECENT CLASSIFICATION

1. Primary vasculitis
2. Vasculitis secondary to ocular disease
3. Vasculitis secondary to systemic disease

FEATURES OF VASCULITIS

SIGNS OF VASCULITIS

- Sheathing of vessels
- Narrowing of vessles
- Obliteration
- Peri-vascular oedema

EFFECTS OF VASCULITIS

As a result Of inflammation	- Oedema - Haemorrhage - Vitreous haze - Anterior uveitis - Complicated cataract
As a result of Occlusion	- Hypoxia - Neo-vascularization - Retinitis proliferans - Retinal detachment - Secondary glaucoma

EPIDEMIOLOGY

Eales disease was initially reported in the United Kingdom but subsequently several series have been reported from USA, Canada, Germany, Greece, Korea and Turkey. In addition several isolated case reports from other countries are available. The disease is now seen more commonly in the Indian subcontinent. At a tertiary referal eye institute in India, the disease was seen in 1 in 150-200 ochthalmic patients.

Eales disease usually affects healthy young adult. Male predominance has been reported in a majority of the series. The predominant age of onset of symptom is between 20 and 30 years.

AETIOLOGY

Till date Eale's disease remains an "Idiopathic Disease" however a number of aetiologies have been suggested.

1. Retinal circulation bears an analogy to the cerebral in which a similar perivasculitis may occur, the origin of which remains an enigma.
2. Most authors agree that tuberculosis figures predominantly. The freedom of the anterior uvea from inflammation in the majority of cases, the widespread peripheral distribution of the lesions in the terminal circulation of the retina in many of them, as well as the demonstration of active tuberculosis else where in the body, provide some evidence of its

haematogenous origin. The fact however that most cases show no sign of active infection but evidence of old lesion has inclined most author to consider that it is usually a tuberculo allergic process certainly the number of patients who have positive dermal test to tuberculoses lend support to the view. Tuberculin has been noted to cause a perivasculitis in the eye after Therapeutic injections or even dermal diagnostic test. Periphlebitis was first reported following B.C.G. vaccination by Franke / 1944 and further cases were recorded by Haar (1951) Miettinin (1958) and Frandsen (1959)

3. Focal infection and dental infection particularly used to be frequently quoted in the literature. A typical case, claimed to be due to metastasis from an abscess in the skin was reported by spicer (1907) and others in which infected tonsils seem to have aetiological significance by Looper (1926) Finnoff (1921-22) Swab (1935) knapp (1935) and Neubauer and Radan Hauser (1962)
4. Endocrine factors have for many years been cited as aetiological agents, usually in a vague way, but particularly stress has been placed on such factors as menstruation (power 1881) the sexual glands (Hutchionson 1881, Clegg 1961, Mawas & Hershberg 1953 and others) and hyperthyroidism (Arloing and Rainaud 1930; Godde Jolly 1961) There is little substantial evidence to prove these.

5. Constipation was originally cited as a primary cause by Eales (1880) and although others agreed no importance is now attached to the association.
6. A dietary deficiency of vitamin C has been suggested (Ciotola & Bosoni 1941, Zwiasses etal 1948)
7. Parasitic infestation is prevalent in the Indian subcontinent possible association of ascaris lumbricoides with eales disease was proposed. The authors have done humoral antibody levels against toxocara canis and ascaris antigens in 18 serum samples from eales patient and 18 from healthy control by Elisa. There was no difference between the level of IgM and IgG antibodies to toxocaracanis and ascaris between eales patients and controls.
8. Neurological involvement-various neurological lesions such as multiple sclerosis, acute or subacute myelopathy, multifocal white matter abnormality, cerebral stroke, intra nuclear ophthalmoplegia, spastic paraparesis, chronic progressive non-compressive myelopathy and hemiplegia, have been reported in isolated case reports in eales disease.

RETINAL VASCULITIS MIMICKING EALES' DISEASE

SYSTEMIC	OCULAR
Behcet's disease	Bird shot Retinochoroidpathy
Leukaemia	Coats' disease
Lyme borreliosis	Pars Planitis
Multiple sclerosis	Viral retinitis
Sarcoidosis	
Syphilis	
Systemic Lupus erythematosis	
Toxocariasis	
Toxoplasmosis	
Tuberculosis	
Wegner's granulomatosis	

9. Other systemic disease association

Several systemic infectious disease have been claimed to be associated with eales disease. These include focal sepsis hematological disorders like acanthocytosis and abnormal red cell morphology.

Recently Elles and coworkers have reported a case of eales disease with evidence of factors V leiden mutation. The authors felt such an abnormality could be responsible for thrombosis of retinal vessels and

closure of capillary beds in the retinal periphery. Such abnormality could also probably be responsible for some cases of eales disease with cerebral stroke. In a study in North America vestibuloauditory disturbances have been reported in a group of patients with eales disease, however in a case control study of eales disease patients in India no vestibuloauditory disturbances were found.

SYSTEMIC DISORDER ASSOCIATED WITH EALES' DISEASE

Tuberculosis	Abraham, Ashton, Bonnet, Finoff, Gupta, wagner, Verhoeff & Simpson.
Hypersensitivity to tuberculoprotein	Elliot, Donders.
Thromboangitis obliterans	Marchesani, Benedict & Wagner, Wagner, Schmid.
Neurological disease	
▪ Multiple sclerosis	Fielo & Foster, Opala et al
▪ Acute or subacute myelopathy	Singhal & Dastur
▪ Multifocal white matter abnormality	Masson et al
▪ Cerebral stroke	Gardon et al
Focal sepsis Haematological abnormalities	Putanna
▪ Acanthocytosis	Kahan et al, Rahi et al, Jain et al.
▪ Increased plasma viscosity, erythrocyte rigidity and erythrocyte aggregation	Bertrams et al
▪ Hypereosinonhilia	Bryselhout et al

10. Immunology and immunopathology-several investigators have proposed immunogenic mechanism in eales disease. Apart from hypersensitivty to tuberculoproteins systemic immunological or autolmmune reactions to retinal autoantigens have been proposed. Recent studies indicated class I and class II HLA association in this disease. Light microscopic and immunohistochemical studies of epiretinal membrane and subretinal membrane in eales disease have demonstrated lymphocytic infiltration predominantly with T cells. This study indicated that a cell mediated immune mechanism might be playing a role in the proliferative phase of disease with membrane formation on the surface of the retina.

IMMUNOLOGICAL STUDIES IN EALES'S DISEASE

IMMUNOGLOBULIN LEVELS	
a. Normal immunoglobulin level	Muthukaruppan et al, Koliopoulos et al
b. Leukaemia	Johnson et al
Normal T Lymphocyte subsets, antibody response to BCG and retinal S-antigen	Muthukaruppan et al
Increased level of circulating immune complexes	Andrews et al
Normal level of class I Histocompatibility antigen (HLA)	Bertrams et al

11. Recently saxena and co-workers studied lymphocyte proliferative response against retinal s-antigen. Its uveito pathogenic peptides, yeast histone H3 peptide and uveito pathogenic fragments of inter photoreceptor retinoid binding protein (IRBP). Six out of 24 eales disease patients showed significant proliferative response against retinal s-antigen, its uvietogenic fragments and IRBP. None of the controls showed any response to retinal antigen or IRBP.

    However such, cellular immune response to retinal antigen and their fragments have been seen in patients having Behcets disease. Bird-short retino choroidopathy, parsplanitis, ocular sarcoid, sympathetic ophthalmia and vogt-koyanagi-Harada disease. This was probably non-specific and occurred due to breakdown of blood retinal barrier thereby exposing the immune system to these retinal auto antigen.

PATHOLOGY

Despite the heterogeneous etiology of eales disease. It has a common pathogenic mechanism. In this mechanism the essential factors is a chronic and incomplete vascular occlusion with resultant tissue hypoxia. This is thought to stimulate the irregular enlargement of existing capillaries, development of capillary aneurysm and retinal neovascularisation.

Donders has shown that the predominant features of eales disease is patchy, perivascular or intramural infiltration of lymphocytes or a granulation tissue. Occasionally with but usually without giant cells. Vasculitis usually starts in the retinal periphery and extends posteriorly. The eales lesion passes through inflammatory, obliterative and proliferative phases. The obliterative phases is not due to a single process. But is the result of endothelial proliferation thrombosis and / or terminal fibrous occlusion. The later process produces the sheathing of the involved segment of veins seen ophthalmo scopically.

The proliferative phase is the response of the uninvolved segment of the neighbouring vessel. The changes include dilatation, tortuosity, micro aneurysm and / or new vessel formation.

Microscopic study of vitreous aspirate in eales vitreous hemorrhage, showed organized vitreous hemorrhage with an evidence of membrane formation and peri vascular round cells. The later finding suggest, chronic inflammatory process around the vessel wall.

CLINICAL FEATURES

Eales disease with a characteristic clinical picture, flourescein angio graphic finding and natural course is considered a specific disease entity. Patients are often 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 massive vitreous haemorrhage. In a series of eales disease cases 75% patients were found to have black spots or floaters and 60% suffered pain free dimness of vision.

Vision in these patients can be normal to hand movements or light perception only. Bilaterality is quite common (50-90% of the patients)

Clinical manifestations of this disease is due to three basic pathological changes.

1. Inflammation (Peripheral retinal perivasculitis)
2. Ischemic changes (Peripheral retinal capillary non-perfusion
3. Neovascularisation which often leads to vitreous haemorrhage.

Anterior uveitis is uncommon is eales disease. However in the severe active periphlebitis stage spillover anterior uveitis may occur. Such anterior uveitis is always non-granulomatous. The presence of granulomatous anterior uveitis should lead one to suspect existence of sarcoid uveites which mimics eales disease. Hypopyon is not seen in eales disease and may indicate behcet's disease.

INFLAMMATION

It is a common manifestation of eales disease. Signs and symptoms of eales disease occur at varying times in the course of the disease but are less common in the late stages.

Vascular sheathing in found in upto 80% of patients with involvement ranging from thin white line limiting the blood column on both sides to heavy exudative sheathing. The thin white line tend to be continuous and the heavy exudative sheathing is usually segmental.

Areas of vascular sheathing frequently leak dye on flourescein anglography. However the sheathing does not always correspond to the staining. Additionally the intensity of dye leakage seen with flourescein anglography is not always proportional to the activity of the inflammatory process. Superficial flame shaped haemorrhages are often located in the area of sheathed vessels.

Patients frequently have cells and debris in vitreous. Macular edema also occurs in the eye with sheathing and is more common when epi-retinal membrane are present.

NON-PERFUSION

All patients with eales disease have varying degree of peripheal retinal perfusion. The non-perfusion is essentially confluent, with temporal quadrant most commonly affected. Intra retinal haemorrhages often first appear in the affected area followed by vascular tortuosity with frequent collateral formation around occluded vessels. Fine solid white lines representing the remains of obliterated large vessels are commonly seen in the area of non-perfusion. The fine lines retain the configuration of the normal retinal vasculature.

The junction between the antero-peripheral non-perfusion and the posterior perfused retina is usually sharply demarcated. Elliot and spitnaz have carefully documented the vascular abnormalities at the junction between perfused and non-perfused area. These include microanerysm, arterio-venous shunt, venous beading and occasionally hard exuate and cotton wool spots.

Despite extensive peripheral non-perfusion the macula is usually spared, preserving central vision. However in some patients the non-perfusion extends to the macula.

Patient with eales disease can also develop branch vein occlusion. The branch vein occlusion is either solitary or multiple. One can distinguish BRVO in eales from primary BRVO as the latter remains confined to the affected where eales disease usually shows some patches of active or healed perivasculitis or alteration in other quadrants.

NEO-VASCULARISATION

It is observed in 80% of patients with eales disease. New vessele can be from either on the disc (NVD) or else where (NVE) within the retina. NVE is usually located at the junction between the perfused an non-persued area of retina. These patients can develop rubeosis iridis. Haemorrhage from the neo-vascularisation is common and is one of the major cause of visual loss. Retinal neo-vascularisation is frequently associated with a prominent fibrous component. They may have extensive retinal and vitreal proliferation of relatively avascular interlocking strands and sheets of fibrous scar tissue. These eyes have associated antero-posterior vitreo-retinal traction and are at a risk of developing retinal detachment.

Ophthalmoscopic findings in eales disease often vary and depend on the stage of the disease. Arterioles are some times affected along with veins.

Active retinal perivasculitis was seen in only 5% of cases. Healed perivasculitis was often seen as the sheathing of the veins. Other vascular changes include sclerosed cord of venules, irregularity of vein caliber, pigmentation along venules, kinky venules, abnormal vascular anastomosis and veins pulled into the vitreous cavity. Active or healed choroiditis was not seen in eales disease. It present it should have led us to suspect the presence of simulating disease such as sarcoidosis, tuberculosis orsyphils. However a few small chorioretinal atrophic patches close to the retinal vessels were seen. Central retinal periphlebitis is markedly uncommon compared to peripheral retinal periphlebitis. Such central involvement is often limited to one or more venous trunks. It was classified as central eales, a variant of classical eales disease.

Macular changes were relatively uncommon. The most common macular change seen was macular edema. Other changes included exudates in the macula and epimacular membrane. Rarely was subhyaloid haemorrhage. Macular hole and submacular fibrosis observed. Peripheral retinal neovascularisation of the retina was quite frequently seen in eales disease and

was reported in 36-81% of cases. Optic disc neovascularisation was significantly uncommon observed in 9% of cases in one series.

Dense vitritis is uncommon in eales disease, however mild overlying vitreous haze can be seen in the area of active retinal vaculitis. Recurrent vitreous haemorrhage is often the hallmark of this disease the cause of vitreous haemorrhage is such eyes is often bleeding from retinal or disc neovascularisation, but it can also occur due to rupture of capillaries or large venules during the active inflammatory stage. In such case, following resolution of vitreous haemorrhage no neovascularisation is detectable clinically or by flourescein anglography.

Surface neovascularisation or neovascular vitreous fronds were seen in 50% of eyes. In the patients who underwent vitreous surgery tractional and rhegmatogenous retinal detachment were observed in combined traction – rhegmatogenous retinal detachment a break was observed at the base of vascular proliferation.

FUNDUS FLUORESCEIN ANGIOGRAPHY (FFA)

Though FFA is not routinely needed to distinguish all cases of eales disease, FFA is beneficial in the ischaemic stage to delineate area of capillary nonperfusion retinal and/or optic disk neovascularіation and questionable macular edema.

In case 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. Adjacent retina can also show increased permeability and diffuse leakage. In the healed stage of vasculitis only the staining of the vessel wall occurs without only leak in the late venous phase. Venous obstruction and venous stasis can well be visualized by FFA, which will show complete nonperfusion (BRVO) or relative dilatation and tortuosity of veins distal to the stasis. Areas of capillary closure, engorged and tortuous capillaries and veno-venous shunts can also be seen in the ischaemic stage of the disease.

The extent and location of neo-vascularisation can be precisely delineated by fundes flourescein angiogram. Neovascularsation, if present can be quite characteristic with sea fan appearance with intense hyperflourescense in the early arterio-venous phase of the fundus flourescein anglogram. Such neovascularisation usually leak in the late venous phase. Neovascuslarsation when located in the far periphery can be missed on routine FFA. FFA often helps to delineate the location and extent of retinal ischemia and can be of guidance while performing laser photocoagulation. It also helps to evaluate the adequacy of photocoagulation and the need for additional laser photocoagulation, when FFA is repeated on a follow up visit.

FFA is used to identify subtle changes in the macula for example macular edema, epimacular membrane and so forth.

ULTRA SONOGRAPHY

Ultra sonography is needed to rule out any associated retinal detachment, either tractional, rhegmatogenous or combined, in an eye with opaque media. Early vitreous surgery is indicated if such association is demonstrated. Ultrasonography usually reveals echoes of variable density depending on the compaction of vitreous haemorrhage. Both incomplete and complete posterior vitreous detachment with or without tractional retinal detachment can be seen. Membrane in the vitreous cavity vitreous schisis and fibrovascular proliferation may be demonstrated.

BIOCHEMICAL STUDIES

Several biochemical studies have been done on the serum and vitreous samples of patients with eales disease. Pratap etal have found raised alpha globulins and decreased albumin levels in the serum samples of patients with eales disease.

BIOCHEMICAL ABNORMALITIES IN EALES' DISEASE

Rise in alpha-globulins & reduced albumin level	Pratab et al
Abnormal protein band of pI 5.9 and molecular weight of 23KD	Rengarajan et al
Raised Serum alpha-1 acid glycoprotein level	Sen et al

Oxidative stress has been implicated in the pathogenesis of various diseases. In uveitis the damage inflicted on the ocular tissues due to reactive oxygen species has been reported by Rao etal. Armstrong etal have demonstrated elevated lipid peroxides in retinal neovascularisation incase of diabetic retinopathy where there was no inflammation. They have proposed a mechanism whereby the lipid peroxides induced the syntheses of cytokines and growth factors in the retina during neovascularisation. From the above observation it was predicted that in eales disease with inflammation and neovascularisation, free radicals and lipid peroxide products might accumulate due to oxidant insult over powering anti oxidant defense.

Accumulation of thiobarbituric acid reacting substance (TBARS) was an index of the production of excessive oxidant. Where as a deficiency of vitamin c and E was an indication of the weekened anti oxidant defense. VIT E deficiency could cause deficiency of VIT A needed for retinal physiology. The estimation of TBARS and vitamin C, E and A in erythrocytes of eales disease patients revealed decreased level of anti oxidants.

Sulochana and coworkers have identified purified and characterized an 88 KDa protein from the serum and vitreous of eales disease patients the partial N terminal sequence (28amino Acids) revealed this protein to be unique. This protein is a glycoprotein and exhibits anti TBARS activity in vitro.

Polyclonal antibody has been produced against this purified protein and using this antibody it has been demonstrated that the 88KDA protein variously present in the vitreous and serum of eales disease patients was immunologically identical.

Since patients have profound oxidative stress characterized by decreased antioxident vitamin E and C and increased accumulation of lipid peroxides supplementation of antioxidants might be beneficial.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of eales disease depends on the stage of presentation of disease.

Clinical presentation can be

1. Peripheral retinal perivasculitis in one or both eyes.
2. Neovascular proliferation of retina or optic disc with peripheral retinal perivasculitis in the same or other eye.
3. Vitreous haemorrhage with peripheral retinal pervasculitis in the same or the other eye.

In the last two situations in young healthy adults in the Indian subcontinent a strong clinical suspicion of eales disease in quite justified. The diagnosis of eales disease in active perivasculitis stage can sometimes be challenging. A set of laboratory test in retinal vasculitis in the absence of medical history suggestive of underlying systemic disease has been found to be non-contributory. Sarcoidosis can often mimic eales disease in the active inflammatory stage.

Parsplantis patients can have retinal periphlebitis close to parsplana exudate, however retinal haemorrhages, vascular alteration and retinal neovascularsiation are absent in pars planitis.

FFA is an important ancillary test in eales disease and is required in the ischemia or proliferative stage of eales disease.

Retinal vasculitis with features suggestive of ischemia has been noted to have a high incidence of development of systemic disease.

NATURAL COURSE

The natural course is quite variable with temporary or even permanent remission in some cases and relentless progression to total blindness. Retinal ischaemia stimulate neovascular growth from the surrounding normal vasculature the common site is just proximal to the site of obstruction. The retinal and disc new vessels are the most important cause of repeated vitreous hemorrhage. The regressed new vessels get replaced by glial tissue. The glial tissue on contraction causes several retinal complication. The macula may get distorted or detached the regressing new vessel often get pulled into the vitreous usually a tear develops at the point were the venule draining the neo vascular lesion joins the retina. This leads to rhegmatogenous retinal detachment.

DAS AND NAMPERUMALSAMY GRADING OF EALES RETINOPATHY

GRADING OF EALES RETINOPATHY

Grades Description of Lesion	I Mild	II Moderate	III Advanced	IV Very Advanced
Angiopathy Venous changes (Tortuousity, Periphlebitis)	< 1/12	< 2/12	< 3/12	< 3/12
Microaneurysms Retinal Heme	< 1/12	< 2/12	< 3/12	< 3/12
Proliferative Retinopathy				
New Vessels	-	< 1/12	< 2/12	< 2/12
Fibrous tissue proliferation	< 1/12	< 2/12	< 3/12	< 3/12
Vitreous hemorrhage	< 2/12 obscured	< 4/12 obscured	< 8/12 obscured	< 8/12 obscured
1/12 = 30^{o} of an arc				

This classification was useful in assessing and monitoring the effect of treatment in eales disease.

MANAGEMENT OF EALES DISEASE

Management of eales disease depends on the stage of the disease. It includes non-treatment with periodic evaluation in the regressed stage of periphlebitis or fresh vitreous haemorrhage. Treatment with oral or periocualr steroid in the active perivasculitis stage and laser photocoagulation in case of neovascularisation of retina or optic disc, or gross capillary non perfusion vitreous surgery is indicated in non-resolving vitreous haemorrahage (more than 3 months) any associated retinal detachment will however warrant early vitreo retinal surgery.

The role of anti coagulant hyperbaric oxygen and anti-tubercular therapy remains contro versial.

Management Options Include:

a. Observation
b. Medical
c. Photocoagulation
d. Vitreoretinal surgery

A. OBSERVATION :

Patients with inactive retinal vaculitis can be observed periodically at 6 month to 1-year interval. Patient with fresh vitreous hemorrhage also are asked for observation at intervals of 4-6 weeks if under lying retina is found to be attached by IDO or by ultra sound such vitreous hemorrhage often clears by 6-8 weeks.

B. MEDICAL THERAPY :

Corticosteroid remain the main stay of therapy in the active perivaculitis stage of eales disease. The efficiency of corticosteroids has been proven in idiopathic retinal perivasculitis. Dosage must be tailored for each patient on the basic of severity of inflammation.

In the majority of cases oral prednisolane 1mg/kg of body weight is needed this is tapered to 10 mg per week over 6-8 weeks. Some patients may require a maintenance dose of oral prednisolone 15-20 mg/day for 1-2 months. In case of associated macular edema one may add periocular depot steroid injection.

Efficiency of systemic or periocular corticosteriod in the inflammatory stage of eales disease was studied in a nonrandomized clinical trial where systemic steroid and post subtenon injection of steroid were found beneficial if there was involvement of three quadrants with CME

Systemic corticosteroids alone were helpful when there was two-quadrant involvement. In the case of 1 quadrant involvement periocular corticosteriods were administered. The natural course of eales disease remained unaltered inspite of steroid therapy. There was no difference in response to treatment in mantoux – positive and mantoux – negative groups of patients.

As many investigators believe that hypersensitivity to tuberculoproteins play a role in the etiology of eales disease, anti-tubercular treatment has been given in eales disease empirically.

In patients with a positive mantoux test and active perivasculitis some investigators have recommended treatment with a combination of oral corticosteriods and anti tubercular therapy.

The role of ATT drugs in the treatment of their disease remains controversial. The disease having a variable course and known to be self-limiting.

C.PHOTOCOAGULATION:

Photocoagulation is the mainstay of therapy in the proliferative stage of eales disease. In case of gross capillary non-perfusion photocoagulation is suggested.

Historically meyer schweckerath first used xenon arc photocoagulation for eales disease. Subsequently others have reported the efficiency of photocoagulation in the proliferative stage of eales disease. Combined xenon arc photocoagulation in the paracentral zone and anterior retinal cryopexy in the periphery have been used successfully. Currently laser photocoagulation is mostly used due to the obvious advantage of reaching the retinal periphery where retinal ischemia and neovascularisation are mostly observed. Although argon green laser is most commonly used, in case of significant cataract or mild vitreous haemorrhage red krypton laser can be effectively used. Such a laser can now be delivered through a slit-lamp delivery system or an indirect ophthalmoscope.

Following vitrectomy an endolaser probe or indirect ophthalmoscope laser can be used for laser delivery on the operating table. The aim of photocoagulation in eales disease to regulate the circulation by diverting blood from hypoxic areas to healthy retina thereby decreasing the formation of vasoproliferative factors to obliterate surface neo-vascularisation and close leaking intraretinal microvascular abnormalities.

In patients with retinal neovascularisation direct treatment with moderately strong overlapping burns is suggested. In case of elevated neovascularisation photocoagulation of the feeder vessel beneath the frond is done. Aneurysm and arteriovenous shunt vessels are also treated in a similar way.

For gross capillary non-perfusion sectoral scatter photocoagulation is suggested. Panretinal photocoagulation is necessary when there is optic dice neovascularisation. There could be minor complications associated with laser photocoagulation. Retinal haemorrhages are possible in a few cases but major bleeding is uncommon with proper selection of the intensity and other parameters of photocoagulation. Occasionally following photocoagulation retinal gliosis laid down by regressing new vessel undergone further contraction and causes a variety of retinal complication such as macular distortion due to epiretinal membrane formation and retinal tear resulting in retinal detachment.

Laser photocoagulation is not advised in active inflammatory stage as there is chance of worsening of neovascularisation due to several angiogenic factors liberated. Once the inflammation is subsided with the anti inflammatory medications such as corticosteroids, laser photocoagulation can be done.

D. VITREORETINAL SURGERY

Vitrectomy alone or combined with other vitreoretinal surgical procedures is often required in eales disease, vitrectomy is often not needed in the first episode of vitreous haemorrhage such patients should be advised to

keep their head elevated while sleeping. This permits the haemorrhage to settle down.

The vitreous haemorrhage usually clears between 6 and 8 weeks. Ultrasonography should always be performed to exclude the presence of associated retinal detachment. Cases of non-resolving vitreous haemorrahage with obscurration of central vision of 3 months duration may be subjected to vitrectomy. Vitrectomy done between 3 to 6 months has better visual outcome than done after 6 months. In the presence of tractional retinal detachment extensive vitreous membrance or epimacular membrane early vitrectomy can be considered. If preoperative ultrasonography reveals a complete posterior vitreous detachment vitreous surgery can be easy and less complicated.

The aim of vitreous surgery is to clear the vitreous opacities and also to evaluate the fundus for any retinal neovascularisation. Along with vitrectomy laser photocoagulation can be performed by endophotocoagulation or indirect laser delivery system. A standard three-port pars plana vitrectomy is the method of choice. Excision of the posterior hyaloid face and clearing of sub hyaloid blood are needed. Epimacular membranes can be peeled following vitrectomy. Visual results following vitrectomy in eales disease were generally good. Visual improvement was seen in 77-88.6% patients following vitrectomy in eales disease. Intraoperative complications following vitreous surgery included recurrence of vitreous hemorrhage, cataract, rubeosis iridis and neo vascular

glaucoma. Patients with fewer episodes of vitreous haemorrahage and preoperative laser photocoagulation had better visual prognosis.

E. ANTERIOR RETINAL CRYOABLATION

Anteriors retinal cryoablation has been successfully tried in eyes with vitreous haemorrhage caused by PDR while primary ARC is considered in small undilating pupil, hazy ocular media due to cataract, after cataract or residual vitreous Hemorrhage in eales disease. It is usually reserved on an adjunct to photocoagulation in eales disease.

RECENT ADVANCES

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

Scatter photocoagulation can cause regression of retinal neo-vascularisation and reduce the risk of severe vision loss. However this anatomically destructive treatment may be associated with side effects during such treatment. Because VEGF has been showed to play a role in retinal neo-vascularisation anti VEGF treatment have been hypothesized, as an alternative adjunctive treatment for retinal neo vascularisation. Evaluation of anti VEGF drugs for diabetic retinopathy have concentrated upon their role in the management of diabetic macular edema.

VEGF inhibitors Lucentis (ranibizumab) in macular edema due to eales disease are under clinical trial.

SECTION - II

A CLINICAL STUDY ON EALES DISEASE

AIM OF THE STUDY

1. To determine various epidemiological factors
2. An attempt to find out the aetiology.
3. To describe the commonest presentation.
4. To look out for systemic involvement and association with tuberculosis.
5. To assess the effectiveness of various treatment modalities.
6. To assess the visual prognosis.

MATERIALS AND METHODS

72 cases of eales disease patients who attended the retina clinic of Regional Institute of Ophthalmology and Government Ophthalmic Hospital, Egmore, Madras - 600 008 between January 2005 to September 2006 were taken up for study.

CRITERIA FOR INCLUSION

All cases diagnosed as eales disease were taken up for study. Cases were diagnosed as eales on the basis of inflammation, not confined to 1 quadrant, neovascularisation with vitreous hemorrhage, when other causes of vitreous hemorrhage was rules out.

A standard proforma was used to collect and document all the details regarding the cases included in the study.

After collecting detailed information regarding history and complaints a thourough examination of the anterior segment was done with a slit lamp. Retinoscopy was done for all cases with a clear media to assess the refractive status. For the examination of the posterior segment all the cases were subjected to direct ophthalmoscopy indirect ophthalmoscopy and three-mirror examination.

Visual acuity and intra ocular pressure were recorded in both eyes of all cases.

Fundus flourescein angiogrpahy was done for all cases that had atleast one eye with a clear media. 5ml of 10% flourescein was used for all cases.

All the cases were subjected to the following laboratory investigations:

1. Haemogram - Hb% total WBC count, differential count, erythrocyte sedimentation rate.
2. Peripheral smear.
3. BP
4. Chest X-ray
5. Serum Cholesterol
6. Urine albumin / sugar.
7. Mantoux.

8. C reactive protein.
9. Blood VDRL
10. Blood Sugar
11. Bleeding time / clotting time
12. Elisa for HIV

All the cases were referred to the following departments attached to the Madras Medical College on need when there was evidence of involvement.

1. Chest Clinic
2. Dental Clinic
3. Rheumatology Clinic
4. Dermatology Clinic
5. ENT Clinic
6. Neurology Clinic

Based on the clinical features and the results of various investigations diagnosis was made and a standard treatment protocol was followed.

ANALYSIS AND DISCUSSION

AGE INCIDENCE

AGE GROUP	NO.OF PATIENTS
19-29	56
30-33	9
34-40	7

Among the 72 cases 56 cases were in the 19 - 29 years age group (77.8 %). The earliest age at which the disease has been seen was 19 years.

[Eales has reported the age of incidence between 19 - 21 years.]

[Elliot in 1954 reported the average age of incidence as 26.9 years.]

SEX INCIDENCE

All the cases diagnosed as eales were male patients. Eales was not diagnosed in females.

[Murphy and collegues in their study of 55 patients in USA found that men and women were equally affected].

Other studies show 90% of male preponderance.

OCCUPATION & SOCIO ECONOMIC STATUS

Of 72 patients 36 patients were manual labours, 17 patients were drivers, 7 patients were painters, 9 patients were carpenters and 3 patients job less. All the patients belonged to poor socio economic status.

OCCUPATIONS	NO OF PATIENTS
Manual Labours	36
Drivers	17
Painters	7
Carpenters	9
Job less	3

Commonest affectation seen among manual labours.

PERSONAL HABITS

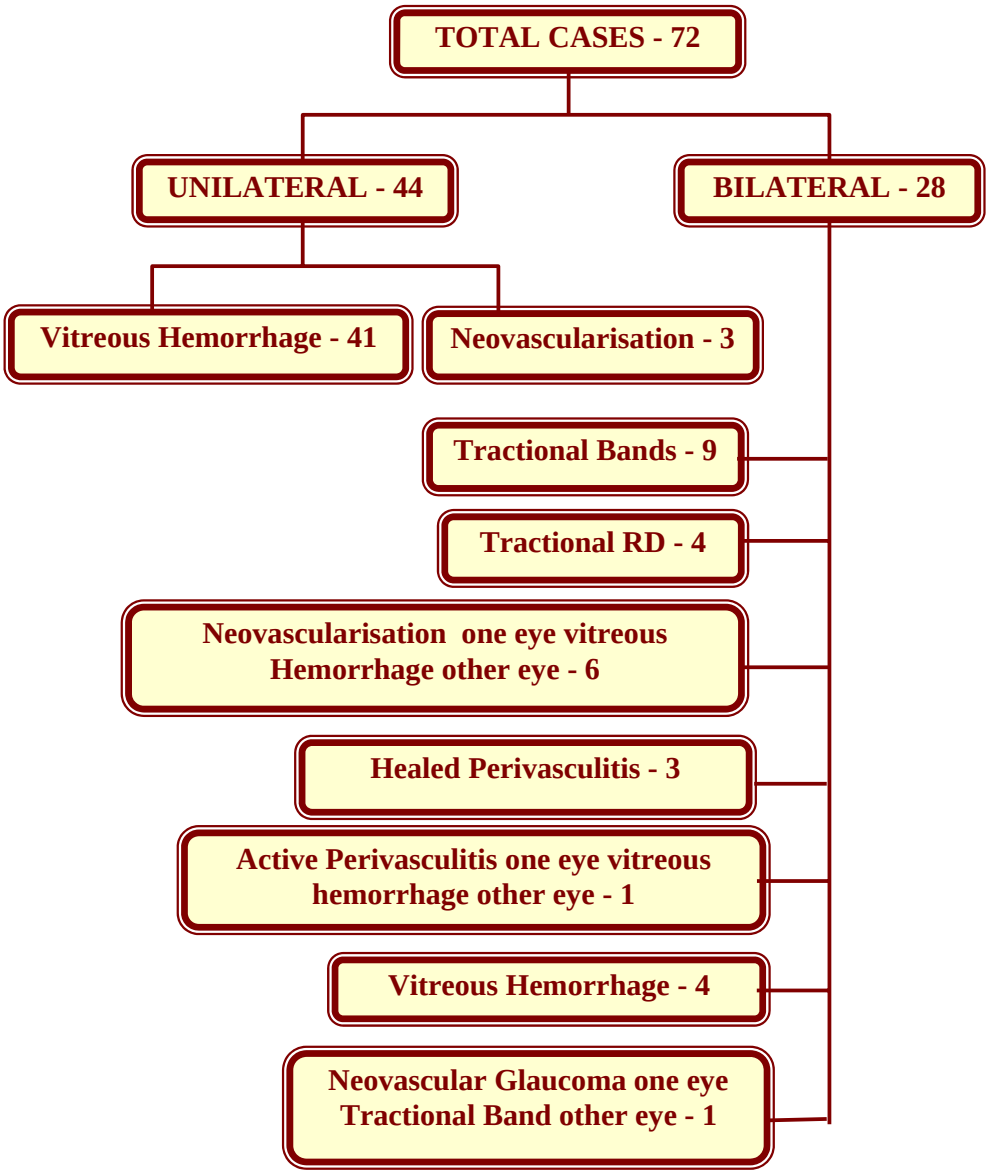
PERSONAL HABITS	NO. OF PATIENTS
Smokers	54
Non-Smokers	18

75% of the patients were found to be smokers. The smokers are advised to stop smoking as it is not known whether it has any relevance with the aetiology.

[Improvement of general health with change of habits, diet, physical and mental rest. (Schiff - Werthimes 1951, Choyce & Cross 1953].

LATERALITY

Of the 72 cases 44 cases were unilateral and 28 cases were bilateral. Of the 44 unilateral cases, 41 cases presented with vitreous hemorrhage and 3 patients presented with neovascularisation in the periphery.



Most of the cases presented unilaterally in our study.

[Bilaterality is the rule and is found in over 90% of cases if they are observed for a period such as 5 years - Duke elder.]

MODE OF PRESENTATION AND REFRACTIVE STATUS

ONSET OF SYMPTOMS	NO. OF PATIENTS	PERCENTAGE	REFRACTIVE STATUS	NO. OF PATIENTS
Acute	45	62.5%	Emmetropes	32
Insidious	27	37.5%	Hypermetropes	23
			Myopes	9

- 62.5% of patients presented with acute onset of symptoms.
- 37.5% of the patients presented with insidious onset.
- Of the 72 patients, 32 were emmetrope, 23 hypermetrope , 9 myopes.
- Refraction was not possible in 8 patients.
- The incidence of eales seems to be less among myopes.
- All the myopes were less then - 2D

INVESTIGATIONS

INVESTIGATION	POSITIVE	NEGATIVE
Mantoux test	9	63
ESR	12	60
C-reactive protein	-	72
Peripheral smear	-	72
HIV Status	-	72

- Of the 72 cases, 12.5% of the patients were mantoux positive.
- 87.5% of the patients were negative.
- [Elliot (1954) found that tuberculin skin test positive in all his 52 cases except one and Donder found 7 negative test in 100 cases.]
- ESR was raised in 16.6% of patients.
- C-reactive protein was negative in all patients.
- Peripheral smear examination was proved to be within normal limits in all patients.
- All patients were HIV negative.

SYSTEMIC ILLNESS & FOCAL SEPSIS

Of the 72 patients no associated systemic diseases were detected in any patients. Among all cases 4 patients had dental sepsis.

[Spicer 1907 showed that some of his cases of eales disease had dental sepsis. Loope 1920, Fillnoff 1921-22, Neubaur & Roden Bausses 1962 showed that some of them had ENT sepsis.]

TUBERCULOSIS

Of the 72 patients only one patient was on ATT for tuberculoma left parietal lobe. 3 patients were old cases of Pulmonary Tuberculosis treated with no evidence of active tuberculosis. None other patients had any evidence of tuberculosis.

All patients were investigated for active pulmonary and extra pulmonary tuberculosis. X-ray did not show any evidence of pulmonary tuberculosis in all 72 cases.

POSTERIOR SEGMENT MANIFESTATION

POSTERIOR SEGMENT MANIFESTATION	UNILATERAL	BILATERAL	NO. OF PATIENTS
Perivasculitis	-	4	4
Neovascularisation	3	6	9
Vitreous hemorrhage	41	4	45
Tractional band	-	9	9
Tractional retinal detachment	-	4	4
Neo vascular glaucoma	1	-	1

3 patients presented with healed perivasuclitis, 1 patient had active perivasculitis in one eye and vitreous hemorrhage in other eye.

3 patients had unilateral presentation of neovascularisation, 6 cases had neovascularisation in one eye with vitreous hemorrhage in other eye.

All cases underwent scatter argon green laser photocoagulation.

Of the 72 cases of eales 45 cases presented with vitreous hemorrhage. Of the 45 cases, 41 cases had unilateral and only 4 cases had bilateral vitreous hemorrhage. Of the 41 cases of unilateral vitreous hemorrhage 22 cases in the right 19 cases in the left.

[Some writers have found left eye was usually affected first - Eales 1880. Others the right, Donders 1958 and other have observed no significant difference.]

Of the 41 unilateral cases of vitreous hemorrhage 1 patients of tuberculoma left parietal lobe on ATT developed RD during observation period.

On the basis of the hypothesis that tuberculosis is the aetiology of eales disease anti-tuberculosis treatment has been the most common specific measure recommended so far (Von Hipper 1905, Igrersheimer 1910)

Some reports have claimed good results and some have shown disappointing results (Rudd 1950, Wagner & Zintz 1951, Solarski 1955)

Of the 72 cases, 9 cases had bilateral Tractional bands and one patient had Tractional band in one eye and Neovascular glaucoma in the other eye.

4 cases presented with Tractional Retinal Detachment in both eyes and were referred for internal procedure.

VISUAL ACUITY

Visual acuity of 100 eyes of 72 patients.

Visual Acuity	Initial Vision	After 3 Months		
		Improvement	Static	Detorioration
6/6 - 6/9	17	-	17	-
6/12 - 6/36	18	-	18	-
6/60 - 1/60	16	14	2	-
CFCF - HM	44	40	3	1
PL+	4	-	4	-
NO PL	1	-	1	-

As shown in the tabular column it has been observed that majority of the patients with vitreous hemorrhage recovered well and regained good visual acuity.

For others the visual acuity was relatively stable. There was detorioration of vision in one case with development of RD.

2 cases of unilateral vitreous hemorrhage and 4 cases of bilateral vitreous hemorrhage had persistence of vitreous hemorrhage after 12 weeks and were taken up for vitrectomy. 5 patients had visual improvement and 1 patients vision remained static.

Although the visual acuity of patients with eales disease range from normal to NO PL most eyes retain good acuity – Murphy RP, Renie Wa Proctor Lr et al, Survey of patients with eales disease.

MANAGEMENT

41 cases of unilateral vitreous hemorrhages were kept under observation after doing B scan to rule out associated retinal detachment. Of the 41 cases, 38 cases of vitreous hemorrhage resolved within 8-12 weeks duration and reasonable visual acuity was regained. FFA was done in all cases after hemorrhage was resolved and 28 cases underwent scatter argon green laser photocoagulation, one patient of tuberculoma left parietal lobe on ATT develop RD during follow up and advised vitrectomy with endo laser and internal tamponade. 2 cases had persistence of vitreous hemorrhage after 12 weeks due to recurrence and were taken up for vitrectomy and vision remained static.

Of the 28 bilateral cases, 6 cases of neovascularisation in one eye were treated with scatter laser and vitreous hemorrhage in the other eyes were kept under observation.

9 cases of bilateral tractional bands not involving macula were kept under observation and initial vision was maintained after 3 months of observation.

Of the 4 cases of bilateral vitreous hemorrhage one eye with longer duration of defective vision was taken up for vitrectomy right eye in 3 patients and left eye in 1 patient. The other eyes were kept under observation.

3 cases of healed perivasculitis in both eyes were kept under observation. And vision remained the same after 3 months.

4 cases of tractional retinal detachment were advised vitrectomy with endo laser and internal tamponade.

1 case of neovascular glaucoma in one eye with NO PL was treated with cyclocryopexy.

1 case of active perivasculitis in one eye and vitreous hemorrhage in the other eye was started on steroids tapered after 3 weeks and kept under observation. Vitreous hemorrhage resolved in 10 weeks.

SUMMARY

1) 72 cases of eales disease were studied.

2) 56 cases (77%) were in the age group of 19-29 years of age. The earliest age at which the disease has been seen was 19 years of age.

3) Sex incidence : All the cases were only males.

4) Laterality : The disease was unilateral in 61.1% of the cases and bilateral in 38.8% of cases at the time of presentation.

5) 75% of patients had an acute onset of symptoms and 25% of patients had an insidious onset.

6) Defective vision was the commonest presentation.

   a. Of the 72 cases, 32 cases were emmetropes 44.4%

   b. 23 cases were hypermetropes 31.9%

   c. 9 cases were myope 12.5%

   d. Refraction could not be done for patients with bilateral vitreous hemorrhage and bilateral tractional retinal detachment.

7) Of 72 patients mantoux was positive in 9 patients 12.5%

8) Creactive protein was found to be negative in all patients.

9) ESR was raised in 12 patients 16.6%

10) All systemic disease like hypertension, diabetes, haemoglobinopathies were ruled out.

11) No systemic involvement was associated with any patients.

12) One patient was a known case of tuberculoma left parietal lobe on ATT, developed RD.

13) 2 patients were old cases of treated pulmonary tuberculosis with no active lesion.

14) 46 (63.8%) of patients presented with vitreous hemorrhage of which 41 patients had unilateral vitreous hemorrhage, 4 patients had bilateral vitreous hemorrhage and 1 patient had vitreous hemorrhage in one eye and active perivasculitis in other eye.

15) 9 patients (12.5%) presented with bilateral Tractional bands in the periphery not involving the macula.

16) 9 patients (12.5%) presented with neovascularisation elsewhere of which 3 patients had neovascularisation in one eye and other eye was normal. 6 cases had neovascularisation in one eye and vitreous hemorrhage in other eye.

17) 3 cases (4.16%) presented with healed perivasculitis in both eyes with sheathing.

18) 4 cases (5.5%) presented with long standing Tractional retinal detachment.

19) One case (1.38%) presented with neovascular glaucoma in one eye and Tractional band not involving macula in other eye.

20) One case presented with active perivasculitis in one eye and vitreous hemorrhage in other eye.

CONCLUSION

Eales disease with its characteristic clinical features and flourescein angiographic findings is a specific vitreoretinal disease. From this study, it is evident that the most common presentation is vitreous hemorrhage in young healthy males. It has been observed that the earlier the patient develop the disease, the more common the patient may go in for complications and visual prognosis was relatively better in patients who had a later onset of disease. If the cases are detected early and treated adequately with laser, based on the FFA as the hemorrhage resolves, and early intervention of non-resolving vitreous hemorrhage prevents visual deterioration. In this study, there was found to be no association with any systemic diseases. Eales disease has been delinked from systemic tuberculosis. Even in our study, one in 72 cases had active tuberculosis. This has statistically insignificant association. Although its aetio pathogenesis remains unclear the management options are quiet clear. Systemic steroid has been found to be beneficial in the active perivasculitis stage. Photocoagulation is indicated in cases with gross capillary non-perfusion or retinal neovascularisation. Early vitrectomy in non-resolving vitreous hemorrhage with or without endolaser depending on the retinal status should be the sheet anchor of managing these patients. The use of intravitreal VEGF inhibitors in preventing / regressing neo vascular retinal changes in eales disease should be studied and if effective will be a boon in treating these cases.

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