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INTERMEDIATE UVEITIS – A REVIEW

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Abstract

Intermediate Uveitis (IU) is an inflammatory disease, primarily involving the vitreous and peripheral retina. It accounts for around 8% of cases of uveitis and affects primarily children and young adults. The etiology is unknown but, found as an isolated and idiopathic condition or in association with systemic disorders such as multiple sclerosis and sarcoidosis and infectious diseases. Symptoms include painless blurring of vision, floaters and deterioration of vision. Clinical features seen are anterior segment affection with keratic precipitates and anterior chamber cells, vitritis, vasculitis in the peripheral retina, vitreal snow banks and cystoid macular edema (CME). CME was the major threat for deterioration of vision; other complications include vitreous haemorrhage, periphlebitis, cataract and glaucoma. Treatment of intermediate uveitis is based on periocular and oral corticosteroids. Cryotherapy or laser photocoagulations of the peripheral retina are options in patients when there is an insufficient response to periocular or systemic corticosteroids. Immunomodulatory therapy is used when other therapies fail. Pars plana vitrectomy (PPV) is indicated in patients with chronic significant inflammation, non-responsive cystoid macular edema, non-clearing vitreous haemorrhage, tractional retinal detachment and epiretinal membranes. IU is an intraocular inflammation involving the anterior vitreous, peripheral retina and pars plana. It usually affects patients from 5 to 30 years old, without gender or racial preferences. The etiology is unknown but there are several associated diseases. The long-term prognosis of intermediate uveitis is usually good, particularly with strict control of inflammation and with proper management of complications.

Key words- Intermediate Uveitis, Vitritis, Snow banks.

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INTRODUCTION

Intermediate uveitis is a diagnosis based on the anatomic location of ocular inflammation and is made when ocular inflammation primarily involves the vitreous and peripheral retina. Intermediate uveitis was first described as chronic cyclitis by Fuchs in 1908 [1] .The clinical description of intermediate uveitis was further elucidated by Schepens in 1950, when he described patients with a peripheral uveitis characterized by inflammation centered around the vasculature and exudative changes in the retinal periphery. In 1960, Brockhurst and colleagues [2] described additional patients with peripheral vascular abnormalities and an exudate along the ora serrata and pars plana, and later Welch and colleagues[3] used the term pars planitis to describe an inflammation characterized by the white accumulation on the pars plana. According to the Standardization of Uveitis Nomenclature working group, the primary site of inflammation is vitreous. Specific diseases such as Sarcoidosis and Multiple sclerosis (MS) are known to cause an intermediate uveitis like picture, and we will often classify patients as having an Intermediate uveitis associated with Sarcoidosis or Multiple sclerosis.

The term Pars planitis (PP) is used to describe a subset of patients with intermediate uveitis when a white exudates (Snow banks) occurs over the pars plana and ora serrata or as aggregates of inflammatory cells in the vitreous i.e. snow balls in the absence of an infectious etiology or a systemic diseases-Idiopathic Intermediate Uveitis.

EPIDEMIOLOGY - In Western literature IU has been reported in 1.4-22% of uveitis patients. In India the percentage of IU varies from 9.5-17.4% [4].The prevalence is estimated to be 5.9/100,000 and incidence 1.4/100,000 [5]. Primarily affects children and young adults. There is a bimodal distribution with one peak in the second decade and another peak in the third or fourth decade. No gender or race predilection. It's not hereditary though it has been observed in families.HLA associations have been identified in patients with multiple sclerosis and intermediate uveitis & also possible association of intermediate uveitis with HLA-A28, HLA-DR15, HLA-B8, HLA-DR51, and HLA-DR17 haplotypes.[6]

AETIOPATHOGENESIS - The cause of intermediate uveitis or pars planitis has not been elucidated. Known associations with systemic disorders such as MS, Sarcoidosis, Inflammatory bowel disease (IBD). Infectious disease associations include Epstein-Barr virus (EBV) infection, Lyme disease, Human T-cell lymphotrophic virus type1 (HTLV-1) infection, Cat scratch disease and Hepatitis C.

IMMUNOGENIC EVIDENCES - IU seems to be a T-cell-mediated disease, as it can be reproduced in experimental models using retinal S antigen/ Interphotoreceptor retinoid binding protein (IRBP), hyaluronic acid. Th1 cells produce the cytokines such as interleukin- (IL-) 2, IL-12, and IL-18, while cell-mediated immunity is mainly associated with tumour necrosis factor (TNF)-α [7]. Increased levels of interleukin (IL)-2 receptors and intercellular adhesion molecule-1 (ICAM-1) have been found in the serum of patients with intermediate uveitis. Elevated levels of IL-6 in the vitreous humor of patients with pars planitis confirm the local immune activation association with the disease [8] . T-cells are the predominant cell type in the vitreous in IU- up to 95% of all cells, of which CD4+ cells are 35-90% [9].

CLINICAL FEATURES-

SYMPTOMS

1. Most common symptom is unilateral Painless blurring of vision, accompanied by floaters.
2. Pain, photophobia, and redness of the eye are uncommon, occur most often during the initial episode, and are usually mild.

SIGNS

Anterior segment signs-

a) Mild conjunctival hyperaemia.

b) Children may have more severe external inflammation. Anterior segment inflammation is more common in children with uveitis, when there may be a moderate degree of anterior chamber cells with posterior synechiae. Band keratopathy may be seen in children [10].

c) Adults with intermediate uveitis have minimal anterior segment inflammation; except in intermediate uveitis associated with multiple sclerosis, which shows granulomatous anterior uveitis with formation of mutton-fat keratic precipitates.

d) Cataract due to ocular inflammatory disease and corticosteroid therapy. Posterior subcapsular cataract is the most commonly seen in IU.

e) Intraocular pressure is usually normal. Anterior and posterior synechiae may lead to Secondary angle-closure glaucoma or pupillary block glaucoma [11]

f) Patchy areas of iris depigmentation atrophy and heterochromia can occur, but unusual [12].

Posterior segment Signs-

a) Vitritis is a characteristic feature of IU, described as vitreous haze graded from trace to 4+.

b) Focal vitreous opacities (Snowballs) are present in almost all cases [13] . Large aggregates of gray-white or yellow material in the inferior vitreous base (Fig 1) overlying the pars plana and anterior retina are classic findings.

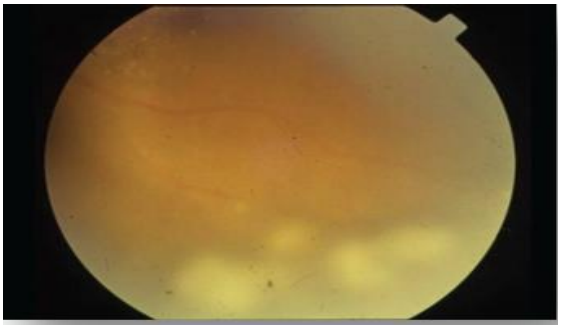


Fig 1- Vitreous opacities (Snowbanks)

c) Partial or complete posterior vitreous separation is common. Increase in floaters at the time of posterior vitreous detachments (PVD) sometimes leads to the first ophthalmologic examination and diagnosis of IU.

d) Contraction of anterior membranes can lead to tractional retinal detachment [14]. Epiretinal membrane, sometimes producing macular ectopia, may occur in the presence or absence of CME [15]. Retinal detachments, when they occur, tend to develop later in the disease process, due to persistent vitreal inflammation which then leads to vitreal contraction and retinal traction.

e) CME is the leading cause of visual loss in IU. Long-standing macular edema leads to retinal pigment epithelial stippling in the macula and may be a subtle sign of previous edema in patients with chronic intermediate uveitis.

f) Large, thin-walled cysts rarely progresses to inner lamellar or full-thickness macular holes.

g) Sheathing or obliteration of the small peripheral venules can be seen [16-19]. Perivasculitis is often associated with whitish infiltrates of the peripheral retina.

h) Retinal ischemia leads to peripheral retinal neovascularization and occasionally neovascularization of the optic nerve.[20] Peripheral retinal neovascularization may lead to vitreous haemorrhage, mostly seen in those with childhood onset of disease [21].

CLINICAL COURSE AND PROGNOSIS- Relatively good prognosis if well treated. IU associated with systemic diseases with multiple exacerbations tends to have a variable course depending on the disease and its severity. Disease may last as long as 15 years and preservation of vision will depend on control of macular disease. In follow up of upto 4 yrs, 75% of patients have a visual acuity of 6/12 or better [22].

DIFFERENTIAL DIAGNOSIS-

1) Infectious conditions- Lyme's disease, Toxoplasmosis, T Tuberculosis, Syphilis, Human T-cell Lymphotrophic virus-1(HTLV-1), Epstein Barr virus Infection and Cat scratch disease

2) Non-Infectious conditions

a. Multiple sclerosis (Most common ocular findings in patients with multiple sclerosis include intermediate uveitis, anterior uveitis, and periphlebitis, and the uveitis may precede or follow the development of multiple sclerosis. IU characterized by pars plana snowbanks, retinal periphlebitis and pan uveitis.)

b. Sarcoidosis (Features that distinguish Sarcoid uveitis from idiopathic uveitis include peripheral multifocal choroiditis, choroidal granulomas, and retinal microangiopathy, periphlebitis, or retinal arterial ectasia ,pronounced anterior segment inflammation[23])

c. Intraocular Lymphoma (Retinal or vitreous infiltrates mimicking uveitis)

d. Amyloidosis (produce vitreous mostly in older patients opacities without vasculitis or Cystoid macular oedema)

e. Whipple's disease(assoc: with vitritis without Snow banks)

f. Retinal vasculitis with vitritis [24] resembling IU seen in- Behcet's disease, Eales disease, Collagen Vascular disease and Necrotizing systemic Vasculatides

3) Post surgical and Trauma – Irvine gass syndrome (Mild vitreous inflammation after cataract extraction is common in the Irvine–Gass syndrome, associated with CME and optic nerve edema [25].)

4) Endogenous Candida endophthalmitis (associated with snow ball exudates)

5) Uveitic entities like Fuch's heterochromic cyclitis with vitreous haze, Vogt-Koyanagi-Harada disease with vitritis and retinal detachments and Juvenile Idiopathic Arthritis (JIA)

6) Diffuse large B-cell lymphoma can present as a vitreous infiltrate prior to the development of central nervous system lymphoma. Breast carcinoma can metastasize to the vitreous; cytokeratin stains of biopsied vitreous cells are

useful in diagnosis [26].

COMPLICATIONS-

1.Cystoid macular oedema

2.Macular Epiretinal formation

Cataract and glaucoma may occur in eyes with prolonged inflammation, those particularly if requiring long term steroid therapy.

1.Retinal detachments occur in advanced cases. Can be tractional, rhegmatogenous, occasionally exudative.

2.Vitreous haemorrhage may occur from snow bank or disc new vessels particularly in children with pars planitis

WORK UP-

1.Routine baseline workup comprised of complete blood count, erythrocyte sedimentation rate, purified protein derivative skin test (PPD) and chest X-ray are mandatory. Serum ACE level, VDRL test, FTA-ABS test, Lyme antibody testing, serology for Cat scratch disease, toxocara antibody testing, and HTLV-1 antibody.

2.Seek consultation with a gastroenterologist in patients with symptoms suggestive of inflammatory bowel disease or Whipple disease.

3.Diagnostic vitrectomy, in cases when tumours are suspected, in patients with severe vitreous inflammation where retinitis, endophthalmitis cannot definitely be excluded and in cases where responses to medical therapy is refractory. Cytological evaluation of cerebrospinal fluid and neuro imaging (MRI Brain, CT Chest) may be necessary for ruling out the possibility of Intraocular Lymphoma, MS, and sarcoidosis.

IMAGING STUDIES- Fundus Fluorescein angiography, B-scan ultrasonography, Optical coherence tomography (OCT), MRI Brain- The presence of neurologic symptoms or a history of optic neuritis should prompt the clinician to obtain an MRI of the brain and subsequent consultation with a neurologist to rule out Multiple Sclerosis. If there is a high clinical suspicion of Sarcoidosis as the cause of intermediate uveitis, a chest X-ray (CXR) or a Gallium scan should be obtained. Subclinical Pulmonary Sarcoidosis, undetectable by CXR, may be detected via CT Chest.

DIAGNOSIS- Diagnosis is based on clinical findings. Patient's complaints of defective vision and or floaters in the absence of pain, redness, photophobia should alert the ophthalmologist. Presence of vitreous cells that outnumber anterior chamber cell infiltration, vitreous snowballs, and the presence of pars plana exudation, suggest IU. A careful history, ocular and systemic examination together with laboratory studies, is needed to exclude associated disorders.

1. Fever, fatigue, or night sweats are typical signs of sarcoidosis and tuberculosis, whereas loss of sensitivity or paresthesias of the hands, arms, or legs are suggestive of possible MS.
2. Signs of dermatitis may point to Lyme disease, tuberculosis, or syphilis, whereas arthritis of the knee may suggest the possibility of Lyme's, disease, and contact with cats may raise the possibility of Bartonella infection.

TREATMENT-

1) Corticosteroids- Corticosteroids are the mainstay of therapy. Most of patients will require either systemic therapy or periocular injections. Periocular corticosteroids are very effective in treating many patients with intermediate uveitis. Usually, local injection of depot preparation of long acting methylprednisalone 40 mg or triamcinolone acetonide 20 mg is given retro septally through the lower lid or into the sub-Tenon space supertemporally. Two or three injections given over a 6–8-week period should be tried before the technique is deemed ineffective. Complications of Periocular injections are increased IOP, cataract, aponeurotic ptosis and allergic reactions with conjunctival breakdown. Repeated injections may cause enophthalmos and orbital scarring. If local therapy is not effective or bilateral severe disease is seen at presentation Oral corticosteroids are indicated. Started at 1 mg/kg/day with gradual tapering after two weeks. The disease should be controlled with 5 mg or less daily.

2) Intravitreal triamcinolone (IVTA) may be an alternative to periocular injections in refractory cases though they carry the risk of RD, vitreous haemorrhage, IOP elevation and endophthalmitis. IVTA was associated with an improvement in vision of more than two lines in 50% of the eyes within 12 weeks after injection [27]. Cataract and glaucoma were the common side-effects.

3) Systemic corticosteroid therapy is used for most patients with bilateral intermediate uveitis or uniocular disease resistant to periocular

corticosteroid treatment. 0.5– 1 mg/kg/day of prednisolone is administered and then slowly tapered depending upon the clinical response. Patients should have a purified protein derivative (PPD) test before systemic corticosteroid treatment, to determine whether antituberculous medications are needed.

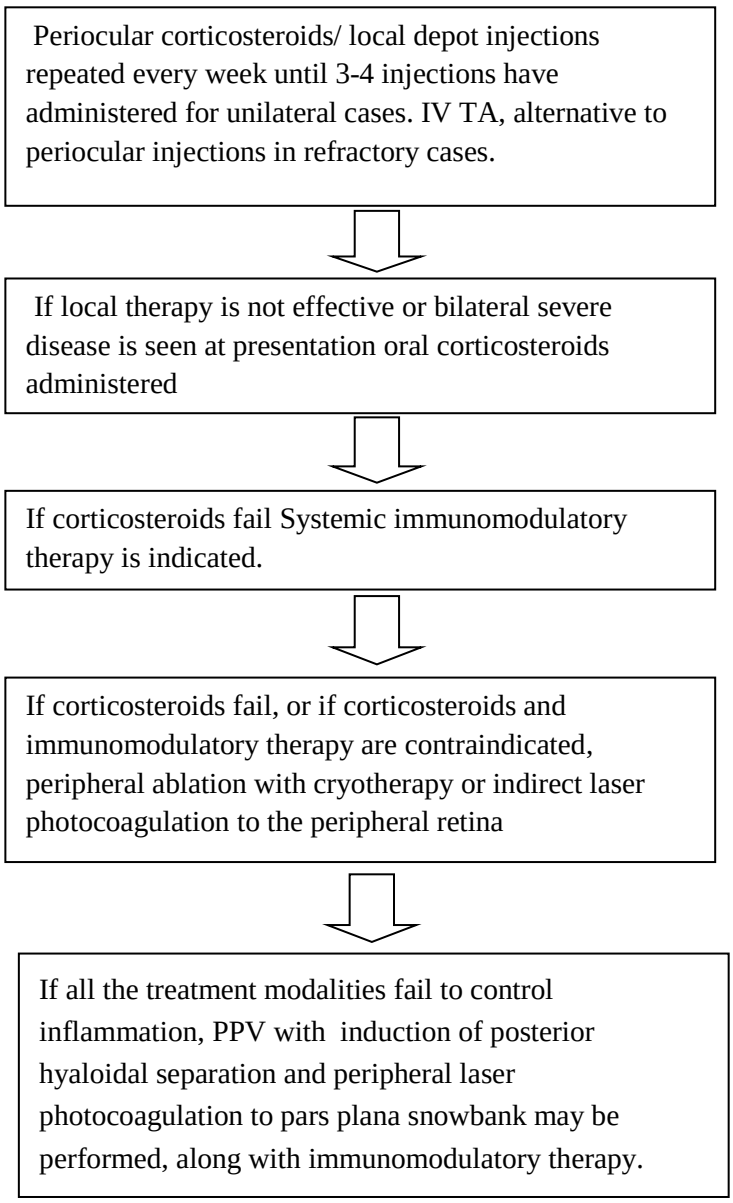
4)Immunosuppressive agents- Immunomodulatory therapy may be considered when Corticosteroids fail or used as a part of steroid sparing treatment and thereby reducing steroid induced systemic side effects. Methotrexate, Azathioprine, Cyclosporine, Mycophenolate mofetil, Tacrolimus have been used in treating IU. Cyclophosphamide and Chlorambucil have been used in refractory uveitis.

5) Newer drugs like Infliximab, eternercept, interferon alpha are being increasingly used as first-line/ second-line drugs in the management of refractory uveitis.

Surgery -When drug therapy has failed or recurrent inflammation is seen despite corticosteroid use, cryotherapy or laser photocoagulation may be used to control the disease. Peripheral ablation of the pars plana snowbank with cryotherapy or indirect laser photocoagulation to the peripheral retina can be done.

1) Cryotherapy is performed by applying a double row, single freeze of transconjunctival cryopexy to the pars plana and posterior to it, extending to an area 1 o'clock-hour beyond all evidence of disease activity. Photocoagulation burns may be placed confluently in three or four rows just posterior to the snowbank. The rationale for these procedures is to treat the neovascularization associated with pars plana exudation and vitritis and to destroy the vascular component of the peripheral retinitis or vitritis, thus eliminating the entrance site for inflammatory mediators into the eye. The effect of cryotherapy is evident within several weeks and lasts for 3–6 months. A second treatment may be given if the first is effective. Complications include transient increased vitreal inflammation, reduced accommodation, cataract, and hyphema.

2) Pars plana Vitrectomy (PPV) is a useful tool for the management of chronic IU. Media opacity, vitreous membranes causing Tractional retinal detachment, macular puckers are indications. The major rationale for performing pars plana vitrectomy in uveitis is the removal of significant media opacities. PPV helps in decreasing inflammation in the anterior chamber and in the vitreous and in reduction of anti-inflammatory medication postoperatively and improvement of CME.



FOLLOW UP-

1. Observe patients every 1-4 weeks during the active phase of the disease, more frequently if CME or severe inflammation is present.
2. Since corticosteroids can cause glaucoma at anytime, it is imperative that patients return for intraocular pressure monitoring at 4-week intervals while using corticosteroids or after periocular

injections. Periocular triamcinolone can cause steroid responsive glaucoma many months after an injection.

3. Consider fluorescein angiography and/or OCT whenever CME is suspected.
4. Consider reordering any relevant laboratory tests if the clinical situation changes.
5. Smoking cessation should be strongly encouraged, as there is noted to have increased risk of uveitic CME in smokers with intermediate uveitis.

CONCLUSION

Intermediate uveitis is an idiopathic, insidious, inflammatory disease affecting the pars plana, peripheral retina and underlying choroid, commonly presents in young adults although it is relatively uncommon in children. Runs a chronic course and sometimes being misdiagnosed, as the presenting symptoms are minimal to begin with, can lead to permanent visual impairment. Gives rise to a number of complications like complicated cataract, cystoid macular oedema, vitreous haemorrhage, secondary glaucoma, vitreous membranes and neovascularisation. Those with decreased vision because of inflammation or CME may require periocular injections or systemic administration of corticosteroids and who develop recalcitrant disease and those who experience severe side effects from the steroid therapy requires immunosuppressive agents. Laser photocoagulation or cryotherapy of the peripheral retina is useful in patients who develop neovascularisation of the vitreous base, in those who are not responsive to periocular injections. PPV with or without cryotherapy or laser photocoagulation is indicated in patients with marked vitreous debris, CME, and in those who develop a vitreous haemorrhage. Early recognition and treatment are essential for preserving vision, and a multidisciplinary approach may be required.

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