INTRODUCTION

The white dot syndromes are a group of inflammatory chorioretinopathies of unknown aetiology which have in common a unique and characteristic appearance of multiple yellow-white lesions affecting several layers of the retina such as, retinal pigment epithelium (RPE), choriocapillaris, and the choroid. They also have overlapping clinical features\(^1\). Serpiginous choroiditis (SC) is one such entity. The word “serpiginous” is an adjective which means “with a wavy or indented margin”. It shows similar wavy or amoeboid like lesions in the choroid as a result of inflammation of unknown aetiology. This disease was first reported by Junius in 1932 who termed it as “peripapillaryretinochoroiditis”. Thereafter this clinical entity has passed through various nomenclatures by different authors (Table 1). The term “serpiginous choroidopathy” was coined by Gass in 1987.

Table 1: Different nomenclatures of serpiginous choroiditis by various authors\(^2\)

1. Peripapillary choroidal sclerosis by Sorsby, 1939
2. Helicoid peripapillarychorioretinal degeneration by Franceschetti, 1962
3. Geographic helicoid peripapillarychoroidopathy by Schatz, 1974
4. Geographic choroiditis by Baarsma, 1976

5. Serpiginous choroidopathy by Gass, 1987

Serpiginous choroiditis (SC) is a rare cause of posterior uveitis, usually less than 5% in most of the studies from the world. However, the incidence of SC is higher in India. The disease affects healthy, young to middle aged adults with higher male predominance. There is no familial predisposition, but the clinical entity was found to be associated with HLA-B7. Serpiginous choroiditis has varied clinical presentations in different geographical regions.

Table 2: Reported prevalence of serpiginous choroiditis in various Indian studies

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<tr>
<th>Study</th>
<th>Percentage of SC in patients</th>
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<td>Biswas et al [1997]⁶</td>
<td>19%</td>
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<td>Gupta et al [2001]⁷</td>
<td>25.1%</td>
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The typical form and more frequently its variants are increasingly noted in the Indian population and found to occur in younger age groups. In a country like India which is endemic for tuberculosis and abounds with both pulmonary and extrapulmonary forms a possible association with SC needs to be ruled out as existing management with corticosteroids and immunosuppressive agents has to be supplemented with antitubercular treatment (ATT).

Serpiginous choroiditis (SC) continues to remain a descriptive term for intraocular inflammatory disease characterised by a geographic pattern of choroiditis that typically extends from the peripapillary area and affects the overlying retinal pigment epithelium and the outer retina. This recurrent and progressive choroidal inflammation usually involves both eyes and can cause irreversible loss of vision during both the active stage due to involvement of the macula and due to complications such as choroidal neovascular membranes and cystoid macular oedema. In 1900, Jonathan Hutchison, an English surgeon, dermatologist and ophthalmologist, first described SC as a unique pattern of

<table>
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<th>Das et al [2005]$^8$</th>
<th>15.2%</th>
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<td>Rathinam et al [2011]$^9$</td>
<td>9%</td>
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choroidal inflammation characterized by creeping choroiditis which had the appearance of “the borders of a continent in a map”\textsuperscript{12}. Although there is a likely underlying autoimmune pathogenesis, the specific trigger for this immune response remains unknown. Active lesions are ill-defined, grey-white and jigsaw puzzle shaped and typically extends from the peripapillary area, affect the overlying retinal pigment epithelium (RPE) and the outer retina at the level of the choriocapillaries and are commonly located adjacent to atrophic scars. This recurrent and progressive choroidal inflammation usually can cause irreversible damage to the photoreceptors with permanent vision loss if the process involves the fovea\textsuperscript{13}. Healed lesions are more clearly defined than the active lesions, they subtly elevate the retina and appear to have hyperpigmented margins.

The intraocular inflammation is treated with corticosteroids and immunosuppressive agents without the use of anti-microbial agents on the assumption that the choroidal inflammation is driven by an autoimmune process. This condition was believed to be more prevalent in Caucasians who were affected in their fourth to sixth decades. Three subtypes of serpiginous choroiditis exist and are as follows:

\textbf{a. Peripapillary type}
The classic or peripapillary (figure 1) geographic variety accounts for 80% cases of serpiginous choroiditis. Classic SC is a chronic inflammation of the choroid that is recurrent, and is believed to be immunogenic. Patients typically complain of blurred vision in association with metamorphopsia and central or paracentral scotomas\textsuperscript{14}. Clinical examination during the acute phase reveals a decrease in visual acuity. In the typical form a single focus of inflammation extends from the peripapillary area and radiates centrifugally in a jig saw puzzle or serpentine centrifugal manner. The lesion begins with ill-defined patches of greyish or creamy yellow subretinal infiltrates with a fluffy appearance which is typical of active choroiditis and may involve the macula by spread\textsuperscript{15}. 
The overlying retina is secondarily involved and becomes oedematous. Though rare, sometimes serous exudative detachment can occur. Typically multiple lesions in different stages of resolutions are seen in fundus\textsuperscript{16}. Many a time, the disease remains asymptomatic until the fovea is affected. It has been seen that about two third of patients with serpiginous choroiditis may present with scars or healed lesions at the time of initial presentation.

b. Macular serpiginous choroiditis
This differs from the typical form in that the lesions arise initially or only in the macula. Because of its location, the macular variant of serpiginous choroiditis differs from the typical form in many respects. Since it starts at the macular area it causes sudden loss of vision and hence the patient reports early in the course of the disease\textsuperscript{17} (figure 2). It causes early symptoms due to foveal involvement and presents with floaters, flashing lights, scotomas and blurred vision. Macular involvement is also associated with a destructive course and recurrences. This form can resemble infective lesions at the macula. The lesions in the macular form are often subtle and resemble many other macular pathological conditions whereas lesions of the typical type are classical and rarely pose any difficulty in

\textbf{Figure 2: Macular serpiginous choroiditis}
establishing the diagnosis. The macular type amounts to about 6% of cases seen\textsuperscript{18}. The visual prognosis in the macular form is less favourable than in the typical form because of early involvement of the fovea. The features shared by both the forms of the disease are the age at onset; absence of gender or familial predilection, laterality, progression, recurrences, and extensive RPE degeneration and scarring on resolution of the disease\textsuperscript{19}. Recurrences are frequent and new lesions are seen at the inactive borders of old lesions or within the lesion itself. The choroiditis begins in the macular area and is characterized by worse visual prognosis due to foveal involvement and higher risk of secondary choroidal neovascular membranes\textsuperscript{20}. This variety of serpiginous choroiditis often remains under-diagnosed or misdiagnosed and treatment delayed as it resembles other macular degenerations like age related macular degeneration or infections like toxoplasma retinochoroiditis and is associated with the worst visual prognosis.

c. **Ampiginous choroiditis**
Figure 3: Ampiginous choroiditis

In this condition, multifocal lesions occur in the posterior pole and periphery (figure 3). It can serve as a differential diagnosis for multifocal choroiditis due to infectious posterior uveitis. Recurrent acute posterior multifocal placoid pigment epitheliopathy (APMPPE) resembles SC in its angiographic features, its resultant pigmentary disturbances, and its recurrent course but tends to involve the peripheral retina and choroid. Visual loss here is a consequence of direct macular involvement due to oedema, scar or choroidal neovascular membranes. Ampiginous choroiditis was first reported by Lyness and Bird in 1984, who described a recurrent form APMPPE. Occasionally APMPPE may show lesions like serpiginous choroiditis which indicates that the two diseases may represent different parts of a clinical spectrum of the same condition. Nussenblatt designated
these cases “ampiginous choroiditis” to indicate that their clinical features were similar to both APMPPE and SC. Also, the lesions involve both the posterior pole and the periphery. Given the similar clinical features and courses of ampiginous choroiditis and SC, Nussenblatt considers ampiginous choroiditis as a variant of SC. Jones and colleagues reported six patients with clinical, fluorescein and indocyanine green angiography findings of both APMPPE and serpiginous choroidopathy and called them “relentless placoidchorioretinitis; The lesions appeared at the level of RPE and deep retina and tended to recur and to involve large areas. The patients, however, maintained good central vision in this type as long as macula was spared.22

**Tubercular choroiditis**
Diagnosis and treatment of TB remains a challenge especially in the developing world, which bears the majority of the global disease burden. Posterior uveitis most often indicates choroidal involvement of tuberculosis. Choroiditis in tuberculosis can present in a serpiginous-like fashion\textsuperscript{23} (figure 4).

An extensive overlap with serpiginous choroiditis has been noted in the Indian population due to the resemblance of lesions to the ampiginous form. In a country endemic for tuberculosis a possible association between the two diseases needs to be considered. Treatment of typical serpiginous choroiditis is with steroids, immunosuppressive agents and specific antimicrobials. The lesions heal with significant scarring but, despite macular involvement, the fovea tends to be
spared in the majority of eyes, leading to final good visual acuity. The main types of choroidal involvement in tuberculosis include choroiditis, subretinal abscess, military tubercles, and tuberculomas. Yellowish subretinal abscesses can occur from liquefaction necrosis within a tubercular granuloma. Overlying vitritis and retinal haemorrhages are often found associated with the abscess.

ANCILLARY TESTS

**Fundus Fluorescein Angiography (FFA)**

Intravenous fluorescein angiography is a technique for examining the circulation of the retina and choroid using a fluorescent dye and a specialized camera. It involves injection of sodium fluorescein into the systemic circulation, and then an angiogram is obtained by photographing the fluorescence emitted after illumination of the retina with blue light at a wavelength of 490 nanometers. The test uses the dye tracing method. The dye used is 5ml of 10% solution or 10ml of 5% solution. Fluorescein angiography does not involve the use of ionizing radiation. FFA shows hyperfluorescence or hypofluorescence of the lesions. Based on the phase of the study the location of the lesion and the presence of leaking,
staining or blocked fluorescence one can identify the activity of the lesion and the presence of complications\textsuperscript{27}.

**Indocyanine green angiography (ICGA)**

ICGA represents a major advance in imaging of the choroidal circulation. Recent technical innovations have permitted this diagnostic technique to find clinical application in many chorioretinal conditions\textsuperscript{28}. ICG is a tricarbocyanine dye (molecular weight 775) which is highly protein bound and does not readily escape from the choriocapillaries. The main advantage of ICGA is that it allows specific analysis of choroidal circulation and its interactions with the retina. Indocyanine green absorbs and reflects in the near infrared portion of the spectrum (805 nm and 835 nm, respectively). In this fashion, the retinal pigment epithelium (RPE) is essentially rendered invisible. These characteristics also facilitate visualisation of the choroid\textsuperscript{29}. Identification of neovascular membranes and scars due to posterior uveitis and inflammations can be done using ICG\textsuperscript{30}.

**Fundus autofluorescence (FAF) principles**

Lipofuscin accumulation is actually a hallmark of normal aging in many cells, including the RPE. The autofluorescence signal from RPE cells is very much
correlated with lipofuscin content and accumulation. FAF is increased with RPE dysfunction due to impaired processing and clearing of lipofuscin. Conversely, the FAF signal may be decreased in the setting of RPE or photoreceptor loss. Because of its diverse composition, lipofuscin has a broad spectrum of excitation (300-600 nm) and emission (480-800). Thus it can be excited by many wavelengths of visible light in the blue and green portion of spectrum. The amount of AF is determined by the amount of fluorophores, which varies during the acute and resolution phases of inflammation. Hypertrophy and reactive hyperplasia of retinal pigment epithelium (RPE) is associated with increase in AF, due to accumulation of fluorophores. A transmission defect during fundus fluorescein angiography (FFA), because of RPE atrophy, appears to be hypo-autofluorescent. It has been found to have an application in APMPPE, MEWDS, MCP, SC, AZOOR, BSRC, AZOOR, and in acute syphilitic posterior placoidchorioretinitis\(^\text{31}\).

**Principle of Optical Coherence Tomography (OCT)**
Optical coherence tomography (OCT) is a non-invasive optical medical diagnostic imaging modality which enables in vivo cross-sectional tomographic visualization of the internal microstructure in biological systems. OCT is analogous to ultrasound B mode imaging except that it uses light rather than sound, therefore achieving unprecedented image resolutions (1-10 µm), approximately 100 times higher than conventional ultrasound by using broad bandwidth light sources in combination with interferometric detection techniques (figure 5). The light source is
low-coherent in that it has a broad frequency bandwidth. All the light frequencies interfere with each other resulting in a self-modulated light source where the width of the individual peak in the time domain is proportional to the image axial resolution, measured by the coherence length \( (Lc) \) of the source \((\text{Eq. } (1))\) divided by the average tissue refractive index.

OCT can be used to both during the active and healed phase of posterior uveitis. It can be used to detect complications of uveitis. OCT is as effective at detecting CME as is FFA but is superior in demonstrating axial distribution of fluid 32.

**QuantiFERON - TB Gold test**

Tuberculosis complex infected individuals have lymphocytes that recognise mycobacterium antigens. This recognition process involves the generation and secretion of interferon–gamma, which is measured by enzyme linked immunosorbent assay (ELISA) 33. The advantage of this test is that it has a higher specificity than the tuberculin test and is unaffected by prior BCG vaccination34. QuantiFERON-TB Gold is a whole blood antigen specific, in vitro diagnostic test that utilises a cocktail of peptides. Interferon gamma release assays are in vitro assays, which measure the interferon-\(\gamma\) (IFN-\(\gamma\)) released by sensitized T cells after
stimulation by the mycobacterium tuberculosis antigen. The mycobacterium tuberculosis antigens used are early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). All mycobacterium tuberculosis and pathogenic mycobacterium bovis strains secrete these antigens. It is more specific for M. Tuberculosis than tests that use tuberculin PPD$^{35}$.

**Scope for the study**

This study is an attempt to identify with certainty the presence of serpiginous choroiditis, to distinguish the morphological features and to determine the utility of aqueous humour analysis in choroiditis due to autoimmune or non-tubercular disease from that due to tubercular aetiology. Knowledge in the variation of presentation could provide better management as antituberculosis treatment can be used to treat those patients with active or latent tuberculosis. Administration of steroids alone will not prevent disease progression in tubercular choroiditis which resembles serpiginous choroiditis and may in fact worsen the ocular status. Prevention of blinding complications such as choroidal neovascularisation will be possible as precise treatment with anti microbes will not only halt progression but also prevent recurrences.
Definitions

Cases were considered to be due to tubercular aetiology if posterior uveitis was seen as the presence of single or multiple active patches of choroiditis with or without vitritis and vasculitis and one or more of the following: a) positive HRCT; b) positive ESR; c) positive PPD test; d) extraocular sample with acid-fast bacilli on cultures; e) history of culture-proven tuberculosis from ocular sample; f) abnormal chest X-ray compatible with tuberculosis; g) positive results when aqueous humour was investigated by PCR, nested PCR or RT-PCR, and h) satisfactory response to antituberculous therapy. All patients in this group received four antituberculous drugs for three months and two drugs for six months, with addition of prednisone (1 mg/kg/day) after a few weeks. Biopsies were taken from extrapulmonary lesions if required. Controls were aqueous humour samples from normal patients with no evidence of tuberculosis or uveitis.