REVIEW OF LITERATURE

Studies on serpiginous choroiditis

Biswas et al studied the clinical profile, treatment and visual outcome of ampiginous choroiditis\textsuperscript{36}. In 2012, they reported on the clinical profile and management of patients diagnosed to have ampiginous choroiditis in a tertiary care referral centre in India. It was concluded that ampiginous choroiditis is a separate disease entity due to its distinct clinical features. It is a disease with multiple relapses, which can be effectively controlled with a combination of immunosuppressive therapy and a good visual acuity can be maintained on long-term follow-up.

Sahu et al reported a variant form of serpiginous choroiditis called macular serpiginous choroiditis\textsuperscript{37}. Nine eyes of 6 patients with the macular form of serpiginous choroiditis were evaluated clinically and by angiography in a longitudinal fashion for a period of 12-36 months. The active stage and the recurrences were treated with oral or periocular corticosteroids and two patients were supplemented with oral azathioprine. Angiographic findings were characterised by early hypofluorescence followed by leakage and staining of the borders and the lesion itself had no any evidence of choroidal ischaemia or retinal
vascular abnormalities. It was concluded that the macular variant of serpiginous choroiditis can mimic many other macular pathologic lesions, thus posing a diagnostic dilemma. Because of its relentless destructive course, early diagnosis and prompt treatment is required to prevent sight-threatening complications. Mahendradas et al, in 2007, reported on serpiginous choroiditis-like picture due to ocular toxoplasmosis. They found an atypical presentation of ocular toxoplasmosis in the form of serpiginous choroiditis-like picture in an immunocompetent 32-year-old man with blurred vision in one eye. Fundus fluorescein angiography and relevant laboratory tests including anti-toxoplasma serology and polymerase chain reaction (PCR) in aqueous humour were performed. The serology in the blood and PCR in aqueous humour were positive for toxoplasma gondii infection. The patient was treated with anti-toxoplasma antimicrobials and systemic steroids. At the end of six weeks of treatment the fundus lesions had healed well with good visual recovery. Hence it was concluded that serpiginous choroiditis like picture can be an atypical manifestation of ocular toxoplasma gondii infection. Serpiginous choroiditis in a herpes-positive patient was reported in 2011 by Rodman et al. Viruses are one of the most common causes of infections involving the posterior segment of the eye. Viral infections can be congenital or acquired and can affect the retina, choroid, or optic nerve. Herpes simplex virus has been
implicated in a number of posterior segment conditions, including serpiginous choroiditis (SC), which has generally been described as idiopathic.

A 57-year-old black female presented with decreased and distorted vision in both eyes of 10 months duration. Fundoscopy revealed radial, deep grayish lesions emanating off the optic disc in a peripapillary fashion. Serologic testing was positive for herpes simplex virus and thus may suggest a causative link between the virus and the choroiditis. SC has been historically cited as an idiopathic process. There have been only rare reports linking this process with a viral aetiology. Laboratory testing and clinical work-up needs to be obtained in any patient suspected of having SC, to detect a viral aetiology. Treatment of an underlying condition may lead to optimum resolution in these patients.

Serpiginous choroiditis was described by Lim et al in 2005 in a review article. Serpiginous choroiditis is a rare, usually bilateral, chronic, progressive, recurrent inflammation of the choroid, retinal pigment epithelium, and choriocapillaris of unknown aetiology. Based on clinical presentation, it can be classified into peripapillary, macular, and ampiginous types. The clinical course, regardless of the presentation, is progressive with multiple recurrences leading to potentially significant visual loss. Visual outcome is directly related to the
involvement of the para-fovea and fovea by the lesions or secondary choroidal neovascularization. The histological findings of the lesions are atrophy of the choriocapillaris, retinal pigment epithelium and photoreceptor cells, and moderate diffuse lymphocytic infiltrates throughout the choroid. Multiple aetiologies including autoimmunity, infection, vasculopathy, and degeneration were proposed but none is well supported by clinical and laboratory evidence. Fluorescein and indocyanine green angiography have been useful in the assessment of the extent and the activity of lesions. Due to the insidious and progressive clinical course, an assessment of treatment outcomes needs long term follow-up. Currently, treatment with immunosuppressive and alkylating agents have shown possible efficacy in small case series. Larger clinical studies and interventional trials are required to further our understanding of the pathogenesis, aetiology, and for the evaluation of treatment strategies.

**Studies on tubercular choroiditis**

Diagnosis of tubercular uveitis by quantitative polymerase chain reaction was described by Sharma et al in 2011 to report the use of real-time or quantitative polymerase chain reaction (qPCR) in confirming the diagnosis of tubercular uveitis. A qPCR assay using primers targeting the MPB64 gene of
Mycobacterium tuberculosis (MTB) was developed. Vitreous fluid samples from patients presumed to have tubercular uveitis were assayed to identify and quantify the mycobacterial load. The amount of the test sample product was interpolated from the standard curve of cycle threshold values generated from known starting copy numbers of standard MTB DNA. Quantitative PCR detected and quantified MTB genome from the vitreous fluid of eyes clinically suspected with tubercular uveitis.

Rao et al in 2013 reported on serpiginous choroiditis and infectious multifocal serpiginoid choroiditis. They inferred that serpiginous choroiditis is a posterior uveitis displaying a geographic pattern of choroiditis, extending from the juxtapapillary choroid and intermittently spreading centrifugally. The choroiditis involves the overlying retinal pigment epithelium and the outer retina. This intraocular inflammation typically involves both eyes in otherwise healthy, middle-aged individuals with no familial or ethnic predilection. Pathogenesis is unclear; based on limited histopathologic studies, however, favourable response to immunosuppressive agents, the absence of association with systemic or local infectious or non-infectious diseases and an organ-specific autoimmune inflammation seems likely to be the underlying process.
Tubercular serpiginous like choroiditis presenting as multifocal serpiginous like choroiditis was reported by Bansal et al in 2012. Clinical characteristics and evolution of choroiditis lesions from the acute to healed stage with regard to recurrence, visual outcome, and complications was studied on 105 patients. It was concluded that tubercular serpiginous-like choroiditis can present as multifocal choroiditis affecting predominantly middle-aged men. It was frequently bilateral with vitreous inflammation and is characterized by multifocal lesions that are non-contiguous to the optic disc. Lesions responded to combined antitubercular and steroid therapy, usually spared the fovea and had a good final visual acuity.

It was a retrospective, nonrandomized, comparative interventional case study performed on three hundred eighty-six patients with active uveitis who were treated at a tertiary care single centre uveitis practice. Uveitis was presumed to be tubercular in patients who showed evidence of latent or manifest tuberculosis without any other known cause and who did not show recurrence of uveitis after 12 months of antitubercular treatment. Statistical analysis was carried out at a 5% level of significance. The main outcome measures were clinical signs significantly associated with tubercular uveitis. Broad-based posterior synechiae, retinal vasculitis with or without choroiditis and serpiginous-like choroiditis were seen
significantly more commonly in patients with latent or manifest tuberculosis in tuberculosis-endemic areas are suggestive of a tubercular cause of uveitis and merit specific treatment.

Presumed tubercular serpiginous like choroiditis clinical presentations and management was studied in 2003. The series aimed to report the occurrence of serpiginous like choroiditis of presumed tubercular origin. This was a retrospective, non-comparative, interventional case series. Eleven eyes in seven consecutive patients with a diagnosis of choroidal tuberculosis simulating serpiginous choroiditis were studied between 1997 and 2000. All patients had their fundus photographs taken at the time of initial presentation as well as during follow-up. All patients underwent a Mantoux skin test and chest radiography. In addition, five patients had their aqueous or vitreous humour subjected to polymerase chain reaction (PCR) for *mycobacterium tuberculosis*. Sputum examination, biopsy or both were carried out whenever recommended by the pulmonologist. Systemic antituberculosis chemotherapy was instituted in combination with treatment for ocular inflammation. Clinical presentations included three morphologic variants; multifocal progressive choroiditis showing wavelike progression to confluent, diffuse lesions resembling serpiginous
choroiditis (three eyes); diffuse choroiditis characterized by diffuse plaque like choroiditis with an amoeboid pattern suggestive of serpiginous choroiditis at initial presentation (four eyes); and mixed variety where opposite eyes had mixed features (four eyes). All patients had strongly positive Mantoux skin test results and positive chest radiograph results. The PCR results from aqueous and vitreous humour in four samples was positive for mycobacterium tuberculosis; one had sputum positive for acid-fast bacilli, whereas two had histopathologic evidence of tuberculosis from cervical or parahilar lymph nodes. Treatment was associated with resolution of choroidal lesions and visual improvement. Final visual acuity of 20/30 or better was achieved in five eyes. Choroidal tuberculosis may present as multifocal progressive or diffuse choroiditis resembling serpiginous choroiditis. It is important to recognize these presentations because these eyes show good response to systemic antituberculosis chemotherapy.

**Studies on multifocal choroiditis**

Gan et al described serpiginous like choroiditis as a possible marker for tuberculosis in a non-endemic area in 2013 on a retrospective case series 44.

Multifocal outer retinal and inner choroidal inflammation is a marker for intraocular tuberculosis of increasing importance, even in a non-endemic area.
Originally described as 'serpiginous-like choroiditis', the lesions are multifocal, irregular in shape, numerous, widespread, often asymmetrical and often demonstrating both active and resolved lesions simultaneously. Active lesions show contiguous extension. However further studies to confirm investigations needed in these patients were recommended.

**Studies on investigations**

Usefulness of aqueous humour analysis for the diagnosis of posterior uveitis was studied by Rothova et al in 2008 for the diagnosis and treatment of patients suspected of having infectious posterior uveitis. This was a case control study performed on 152 eyes from 152 patients with active posterior uveitis. They underwent diagnostic aqueous testing by real time polymerase chain reaction (PCR) and by pathogen specific analysis of intraocular antibody production (Goldmann-Witmer coefficient [GWC]) for herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and the parasite Toxoplasma gondii. Independent of the immune status of patients, positive PCR results were observed more frequently in viral infections than in toxoplasmosis (P<0.001). As a consequence of aqueous analysis, change of treatment was necessary in 36 patients (24%). None of the patients experienced complications during or after aqueous
sampling. It was concluded that despite the posterior location of inflammation, aqueous analyses with PCR and GWC for HSV, VZV, CMV, and T. gondii revealed an infectious cause in 29% of patients with posterior uveitis.

Nested PCR positive tubercular ampiginous choroiditis was reported in 2012 by Biswas et al. They reported that ocular tuberculosis forms the essential differential diagnosis of any chronic and recurrent choroiditis, especially in high endemic areas. The presumed tubercular aetiology can be substantiated using highly sensitive and specific tests such as nested PCR on intraocular fluid.

Fundus autofluorescence imaging to document evolution, progression and healing pattern of serpiginous choroiditis was evaluated by Gupta et al in 2014. They reported that fundus autofluorescence provides clinically useful information about several retinal diseases beyond that obtained by conventional imaging techniques. Fundus autofluorescence is of value in detecting active and healed choroiditis.

In the year 2012, Carreno et al studied the assessment of fundus autofluorescence in serpiginous and serpiginous-like choroidopathy to correlate the activity status disclosed in fluorescein angiography and fundus autofluorescence imaging.
The variations of fundus autofluorescence images in the evolution of serpiginous choroidopathy and serpiginous-like choroidopathy showed that fundus autofluorescence may be a useful tool for patients with serpiginous choroiditis. It is possible to reserve other invasive techniques, such as angiography for cases with suspicious activity disclosed by fundus autofluorescence imaging. Fundus autofluorescence can define serpiginous choroiditis during both the active inflammatory stage and during healing.

A study on fundus autofluorescence in serpiginous choroiditis was done by Gupta et al and published in 2012 to report the fundus autofluorescence characteristics in serpiginous choroiditis \(^49\). They found that fundus autofluorescence highlighted the areas of disease activity and was a quick imaging tool for monitoring the course of lesions in serpiginous like choroiditis and that the pattern of fundus autofluorescence changed as the lesions evolved from the acute to the healed stage. Both the centre of the lesion and the periphery showed distinct characteristics.

The role of indocyanine green angiography (ICGA) in posterior uveitis was studied by Agrawal RV et al and published in 2013 \(^50\). The most characteristic feature noted on ICGA was the presence of different patterns of hypofluorescent
dark spots which were present at different stages of the angiogram. ICGA provides the clinician with a powerful adjunctive tool in choroidal inflammatory disorders. It is not meant to replace already proven modalities such as the fluorescein angiography but it can provide additional information that is useful in establishing a more definitive diagnosis in inflammatory chorioretinal diseases associated with multiple spots. It still needs to be determined if ICGA can prove to be a follow up parameter to evaluate disease progression. This study was performed on patients with autoimmune and infectious form of posterior uveitis and provided an insight into importance of indocyanine green angiography.

The role of Real-time PCR was studied by Santos et al in 2011\textsuperscript{51}. In this work the authors analysed the sensitivity and specificity of real-time PCR to detect the etiological agent from blood, plasma, vitreous and aqueous humour and compared with the diagnostic hypothesis. Twenty-seven patients were studied and real-time PCR method was used for the detection of herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), mycobacterium tuberculosis (TB) and toxoplasma gondii (Toxo) in the aqueous humour as well as in the vitreous, blood and plasma. Their results showed the presence of toxoplasma, CMV, VZV or HSV-2 in 19.2% of aqueous humour samples, and in 30% of vitreous humour samples. In plasma and
blood samples, only CMV was detected (11.1% and 3.7%, respectively). It was concluded that real time PCR was able to detect and to confirm diagnostic hypothesis in uveitis. Their data also confirms that vitreous humour is the best source for molecular diagnosis of infectious uveitis.

Diagnostic efficacy of polymerase chain reaction in granulomatous uveitis was done in 1999 by Gupta et al. This was an evaluation of the role of polymerase chain reaction (PCR) for detection of Mycobacterium tuberculosis in the aqueous humour samples obtained from eyes with active uveitis. Aqueous humour samples from patients having inflammatory reaction in the anterior chamber or posterior uveitis along with any one or more of the following: 1) active vasculitis; 2) anterior vitreous cells; 3) choroiditis; 4) chorioretinitis; 5) retinochoroiditis were withdrawn by anterior chamber paracentesis and subjected to PCR. PCR was performed using primers capable of amplifying a 150 b.p. segment from a conserved repetitive sequence in the genome of M. tuberculosis. The study showed that PCR can be effectively used for the diagnosis of intraocular tuberculosis in the presence of uveitis.