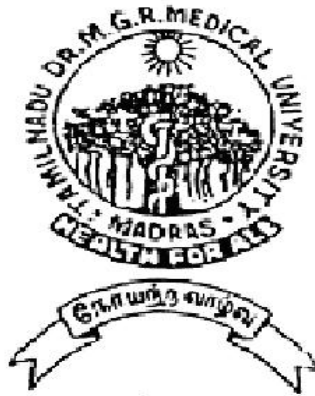


**CLINICAL MANIFESTATIONS, DIAGNOSTIC  
INDICATORS AND PROGNOSTIC INDICATORS  
OF OCULAR SARCOIDOSIS**

*Dissertation Submitted for*

**MS Degree (Branch III) Ophthalmology**

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**Chennai – 600 032.**

## ***CERTIFICATE***

**Certified that this dissertation entitled “CLINICAL MANIFESTATIONS, DIAGNOSTIC INDICATORS AND PROGNOSTIC INDICATORS OF OCULAR SARCOIDOSIS” submitted to the Tamilnadu Dr M.G.R Medical university, Chennai is the Bonafide work done by DR.S.SUSHMITHA under our supervision and guidance in the Uvea Department of Aravind Eye Hospital and Post graduate Institute of Ophthalmology , Madurai during her residency programme from May 2009 to April 2012 .**

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## ***Introduction***

Sarcoidosis is a chronic multisystemic granulomatous disorder with protean ocular and systemic manifestations due to exaggerated immune response to variety of self and non self antigens<sup>1</sup>. Manifestations of sarcoidosis are predominantly intra thorasic with pulmonary infiltration and hilar lymphadenopathy , but other sites such as eyes, skin , bones & joints are also affected<sup>6</sup>. The clinical course of sarcoidosis varies from acute , self limited process to a chronic progressive one , leading to severe functional impairment .

Ocular sarcoidosis can be considered as an example of *chronic granulomatous non infectious pan uveitis*.

The word sarcoidosis was first coined by **Jonathan Hutchinson** in the year 1878. In the following years ,further developments were encountered in the subject of systemic and ocular sarcoidosis and thereby its clinical manifestations, pathogenesis and other associations were described by **Caesar Boeck<sup>3</sup>, Heerfordt and Schaumann<sup>3</sup>** in detail.

## ***Literature review***

### ***Epidemiology***

Sarcoidosis presents with a bimodal curve <sup>3</sup>peaking at 20 to 30 years and then at 50 to 60 years. Ocular involvement is seen in all age groups but the severity and type of presentation may vary. Female preponderance<sup>3</sup> has been noted with increased disease severity in females. Sarcoidosis is common in african americans and blacks<sup>3</sup> than caucasians, disease severity is increased in them and also associated with a poor prognosis. The disease is world wide in distribution with incidence of ocular involvement varying among different countries.

### ***Etiology(Associations)***

No specific etiology has been cited so far, but many associations have been suggested, they are:

- <sup>1</sup>HLA related: HLA B8 and HLA DRB1 have a proven association with sarcoidosis

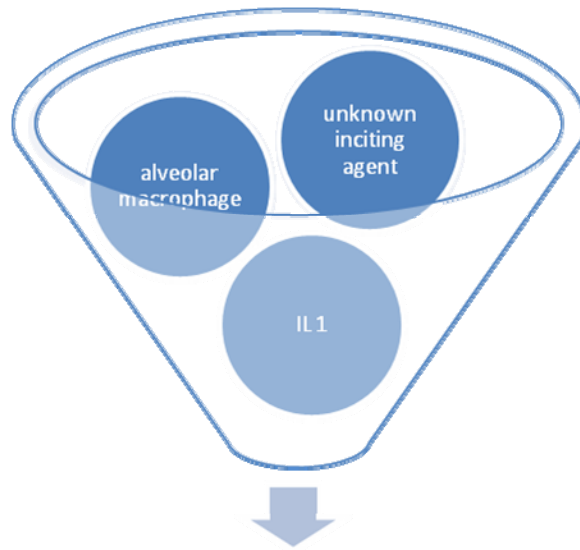
- <sup>1</sup>Controversial association with mycobacterium tuberculosis with demonstration of mycobacterial DNA in almost 50% of sarcoidosis patients, while at the same time nested PCR failed to detect sequences specific for mycobacterium tuberculosis in lymph nodes and lung biopsies of sarcoidosis patients
- <sup>1</sup>There is also an association stating that sarcoidosis favours non smokers

### ***Pathogenesis***

Primary mechanism proposed is increased inflammatory cell compartmentalisation at the sites of infection<sup>7</sup>, the result is generalised immunological dysregulation resulting in hyperglobulinemia, autoantibody production, impairment of T cell mediated responses (anergy), increase in number of CD cells at the sites of infection and decrease in their relative proportion in blood (compartmentalisation),



*Pathogenesis of sarcoidosis*



## TWO ROLES



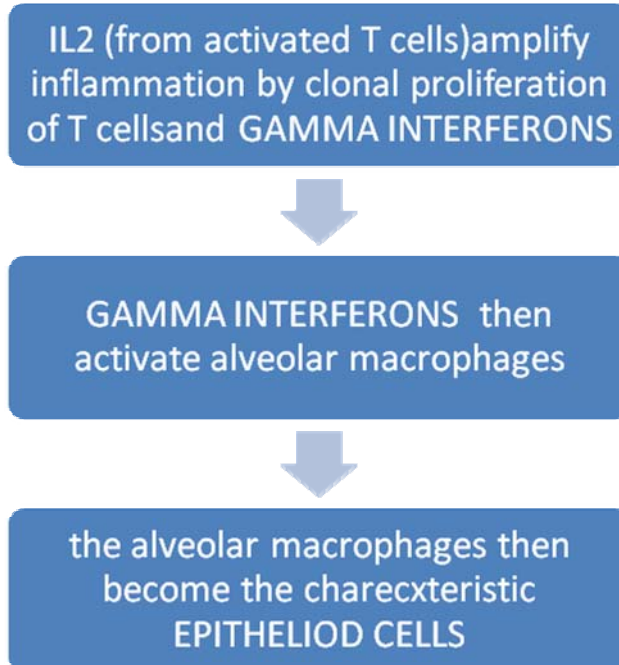
recruitment of CD4 lymphocytes to the local site which become **ACTIVATED T CELLS**

they produce IL2, TNF & IL6  
they also increase Ig production



secretes fibronectin and other growth factors

thereby increasing **FIBROBLAST PROLIFERATION AND CHEMOTAXIS**



***Histology***

Primarily a non caseating granulomatous inflammation consisting of the following structures<sup>3,7</sup>

Epithelioid Cell: polyhedral mononuclear histiocyte that is derived from monocytes of peripheral blood or macrophages of tissue which have marked secretory functions. They secrete cytokines and other mediators like ACE, lysozyme, glucuronidase, collagenase and calcitriol multinucleated giant cells of langhans type, with nuclei in the periphery of the cell or arranged in an arc or incomplete circle

Thin rim of lymphocytes are seen in the periphery Central areas of the granuloma undergo fibrinoid degeneration

Many inclusion bodies have been noted in the cytoplasm of giant cells, they are: Schaumann or lamellar bodies, asteroid bodies and Wesenberg Hamazaki bodies

### ***Clinical Manifestations :***

#### ***Systemic features***

Commonest site of involvement is the lung, where lesions are primarily seen along the bronchi and blood vessels, manifesting as alveolar lesions with bilateral hilar lymphadenopathy. It usually has an asymptomatic course, sometimes presents with features of chronic cough and dyspnoea. Other features noticed are splenomegaly, altered liver function tests, renal insufficiency and radiological abnormalities in the phalangeal bones of hands and feet as small circumscribed areas of bone resorption in the marrow cavity, skin lesions in the form of lupus pernio, erythema nodosum and inflammatory plaques. Lesions have also been noticed in the mucous membranes of the oral cavity, pharynx and larynx. Serious cardiac abnormalities such as conduction defects, myocardopathy, pericarditis, pericardial effusion and cor pulmonale have been reported by some. Branson et al<sup>51</sup> have described the frequency of systemic features in sarcoidosis as follows,

*Table 1 : frequency of systemic involvement in sarcoidosis*

<b>System affected</b>	<b>Frequency(%)</b>
Lymph nodes	78
Lungs	77
Liver	67
Heart	20
Skin	16
Brain	8
Kidney	7
Eye	6
Spleen	50

***Ocular features:***

Can be classified under three headings:

- Ocular adnexa
- Anterior segment
- Posterior segment

**Ocular adnexa:**

periocular region<sup>1</sup>: granulomatous involvement of skin with millet shaped nodules on the eyelids

Lacrimal Apparatus<sup>1</sup>: commonest presentation is with infiltration of the lacrimal gland presenting with keratoconjunctivitis sicca. Dacrocystitis and bilateral dacryoadenitis have been observed

Orbit<sup>21,1</sup>: orbital involvement is a rare feature with proptosis as the presenting sign, mostly unilateral sometimes presents bilaterally mimicing pseudotumour and other inflammatory syndromes in the orbit

Extraocular muscle involvement<sup>16</sup>: Sarcoid induced inflammatory myositis can resemble grave's ophthalmopathy

**Anterior segment:**

Conjunctiva<sup>1,3</sup>: commonest manifestation is that of conjunctival granulomas that appear typically as golden fleshy yellow nodules located on the upper and lower palpebral and forniceal conjunctivae where chronic inflammation leads to cicatrisation and symblepharon. Extensive granulomas can lead to diplopia and keratoconjunctivitis sicca (from devitalisation of conjunctival epithelium)

Sclera<sup>2,31</sup>: rarely presents as scleritis and episcleritis<sup>15</sup>, scleral plaques composed of sarcoid nodules have been reported. Limbal nodules<sup>20</sup> can occur which present as severe sclerokeratitis

Cornea<sup>3</sup>: four common patterns of corneal involvement have been noted

1. Inferior corneal thickening
2. Band shaped keratopathy( secondary to chronic uveitis or hypercalcemia)
3. Stromal thinning
4. Interstitial keratitis

Uveitis: presents usually as panuveitis, which includes both acute and chronic forms,

Acute Anterior Uveitis<sup>2,3,7</sup>: typically affects women of reproductive age group. They present with symptoms of pain, photophobia, blurred vision and red eyes with ciliary congestion, keratic precipitates, aqueous flare and slightly miotic pupil. Associated with systemic manifestations like erythema nodosum and hilar lymphadenopathy, usually has an indolent self limiting course.

Chronic anterior uveitis<sup>2,3</sup>: commonest mode of presentation of ocular sarcoidosis. It can present as silent uveitis with permanent ocular

damage before the intraocular infection is diagnosed. Also presents as typical granulomatous uveitis with large, greasy, mutton fat keratic precipitates and granulomatous nodules on the iris namely, Koeppe's, Busacca's and true iris nodules that are typically pink vascular, larger than other nodules and are typical of sarcoidosis. Interestingly there is no inflammatory reaction and the nodules heal without scarring.

### **Posterior Segment**

Intermediate Uveitis: vitritis<sup>3</sup> is a major manifestation of posterior segment involvement. Other characteristic findings are snow balls and snow banking. Vitreous snow balls<sup>7</sup> are greyish white globoid bodies, seen in the dependant portion of the vitreous (inferior vitreous) ranging in size from small particles to one third disc diameter in size, they may be associated with pars plana exudates<sup>7</sup>. Presence of only anterior vitreous cells usually signifies a spill over uveitis from anterior segment. Snow balls can frequently occur in chains giving rise to string of pearls appearance. Vitreous hemorrhage can result from optic nerve or retinal neovascularisation.

Posterior Uveitis: The most characteristic feature is retinal vasculitis<sup>7</sup> which presents as periphlebitis along with perivenous



exudates. Periphlebitis is associated with segmental cuffing or more extensive sheathing referred to as candle wax drippings or en taches de bougies<sup>3</sup>, which were originally described by Franceschetti<sup>3</sup> as yellow, waxy and discrete choroidal infiltrates situated around retinal veins. Arterial vasculitis is almost never seen. Other features include choroiditis,<sup>11,12</sup> multifocal choroiditis and choroidal granulomas<sup>18</sup> are commonly seen. Multifocal choroiditis typically presents as small, creamy or white lesions with little substance frequently involving the macula and postequatorial regions. Choroidal granulomas are yellowish grey lesions measuring more than 1 disc diameter in size, rarely massive choroidal granulomas may extend into the vitreous cavity mimicking a malignant melanoma or metastatic carcinoma. More extensive posterior pole choroiditis has been observed in sarcoid and may mimic the appearance of serpiginous choroiditis<sup>13</sup>. Residual chorioretinal scarring presents as round punched out lesions in the peripheral retina. Pigmentary changes in the retina are usually seen involving the posterior segment, they are focal discrete areas of pigment epithelial atrophy like cobblestone degeneration and are particularly seen in the inferior equatorial area, the changes varying from being

subtle to extensive. These pigmentary changes are believed to evolve primarily from choroidal granulomas<sup>11</sup>.

Optic nerve involvement<sup>9,11</sup> : presents as disc edema due to posterior uveitis, direct infiltration with granulomas and raised ICT, papillitis with blurred margins, optic nerve head granuloma<sup>9</sup> leading to a substantial nerve fibre bundle defect or vascular occlusion, retobulbar optic neuritis and optic atrophy

Neovascularisation<sup>10</sup> : Sarcoidosis can stimulate neovascularisation either anterior or posterior to the equator. Surface neovascularisation and so called sea fans<sup>3</sup> resembling sickle cell disease have been reported and can cause retinal or vitreous hemorrhage. The presentation of hemorrhagic retinopathy, along with branch and retinal vein occlusions, capillary non perfusions and subsequent neovascularisations have been reported. Optociliary shunts, dilated collateral veins on the optic nerve head, connecting central vein to the peripapillary choroidal venous plexus have also been reported. Arterial macroaneurysms<sup>32</sup> with multifocal chorioretinitis have been described in elderly females and were associated with severe cardiovascular abnormalities.

### Angiographic Findings

*FFA*: venule wall staining and leakage

Macular, peripapillary and diffuse edema

Ischemia and neovascularisation

*ICG*: additional choroidal features including early lobular hypofluorescence, choroidal vasculitis and both diffuse and late hypofluorescence can be made out.

### ***Complications***

- a. Secondary glaucoma<sup>19</sup>: both open angle and angle closure are encountered.

At the chamber angle, small, greyish white nodular exudates are seen on the trabecular meshwork<sup>7</sup>, along with them peripheral anterior synechiae and goniosynechiae are also frequently seen, these findings are collectively referred to as trabecular sarcoidosis. Secondary open angle glaucoma can result owing to raised aqueous production, decreased aqueous outflow, trabecular meshwork edema or infiltration from inflammatory cells. Secondary angle closure glaucoma can develop due to rapid development of posterior synechiae, leading to

iris bombe and pupillary block. The anterior synechiae can crowd the trabecular meshwork and lead to secondary angle closure glaucoma.

- b. Cataract<sup>3</sup>: chronic uveitis can lead to hyalinisation of anterior segment as well as pupillary membranes and secondary cataracts
- c. Corneal band keratopathy<sup>3</sup>: develops when sarcoidosis is associated with hypercalcemia
- d. Cystoid macular edema: most common sight threatening complication
- e. Retinal ischemia
- f. Neovascularisation<sup>17</sup>

Syndromes Associated With Sarcoidosis:

*Heerfordt's Syndrome (Uveoparotid Fever)*<sup>3</sup>

- Uveitis
- Parotitis
- Fever
- Facial and other cranial nerve involvement

*Lofgren's Syndrome*<sup>3</sup>

- Acute iritis
- Erythema nodosum
- Bilateral hilar lymphadenopathy

## ***Diagnosis Of Ocular Sarcoidosis***

The diagnosis of sarcoidosis has been considered so far as a diagnosis of exclusion, as it is an idiopathic systemic granulomatous disease, diagnosis usually remains contingent on a preponderance of evidence. In an event of suspicion of ocular sarcoidosis based on the clinical findings, the approach is usually directed at finding out the evidence for systemic associations of sarcoidosis.

The diagnostic tests can be classified as follows:

1. Lab investigations
2. Radiological investigations
3. Histopathological investigations
4. Skin tests

The individual ones are described as follows,

Chest xray: it is a simple and useful screening and diagnostic test for sarcoidosis, especially as 90 to 93 % of patients exhibit pulmonary involvement the following classification is commonly used to grade the disease involvement on the basis of radiological findings<sup>33,7</sup>

Stage 0 – normal chest xray

Stage 1 - bilateral symmetrical hilar lymphadenopathy only

Stage 2 – bilateral hilar lymphadenopathy with bilateral symmetrical lung infiltration

Stage 3 – bilateral symmetrical lung infiltration only

Stage 4a- bilateral hilar lymphadenopathy with bilateral symmetrical lung fibrosis

Stage 4b- bilateral symmetrical lung fibrosis only

Typical of sarcoidosis on chest xray is bilateral adenopathy with right paratracheal involvement

CT scan<sup>1</sup>: useful when other investigations are inconclusive or there are no visible sites for biopsy. HRCT is of better value in such cases.

Gallium scan<sup>33</sup>: considered to be more sensitive than chest xray in detecting pulmonary disease, whole body gallium scan is also recommended as extrapulmonary uptake is very common. It also helps to localise the possible sites for biopsy and thereby decreases the risk of blind invasive diagnostic procedures. IV injection of 5 to 8 mcurie of gallium citrate is given and uptake is assessed after 48 to 72 hours. <sup>67</sup>Ga localises to sites of active inflammation with T cells and macrophages. Two distinct patterns of gallium uptake have been described, they are,

- panda image<sup>33</sup>- combined abnormal bilateral symmetrical uptake of gallium by lacrimal and parotid glands with or without submandibular gland uptake
  - lambda image<sup>33</sup>- gallium uptake by parahilar and infrahilar lymph nodes and right paratracheal lymph nodes. It was reported that only 4 out of 12 patients with ocular changes of sarcoidosis had increased gallium uptake over the orbits and therefore gallium scanning was of limited value in chronic sarcoidosis. Gallium scanning though sensitive has its own limitations, pulmonary uptake of gallium is not specific as it is seen in other chronic inflammatory conditions such as TB, silicosis and malignancies such as lymphomas and carcinomas. Abnormal gallium uptake in salivary and lacrimal; glands has been encountered in sjogren's syndrome, TB and following radiotherapy
- Serum ACE<sup>33</sup>: it is normally produced by the endothelial cells of lung and cells of proximal renal tubules, it converts angiotensin I to angiotensin II. It is also produced by macrophages and epithelioid cells, macrophage related ACE is responsible for its elevation in sarcoidosis, the level of serum ACE is a function of total body granuloma activity thereby reflecting the granuloma load. ACE levels are increased in upto 60 to 90% of patients with active sarcoidosis<sup>23</sup>. Serum ACE may not be

typically elevated if the disease is restricted to a small area such as the eye, in such cases it is better to rely on localised values as in aqueous, vitreous or tear levels of ACE. False positives and negatives are encountered as in any other serum marker, in spite of this granulomatous uveitis in the presence of elevated serum ACE is suggestive of sarcoidosis.

Lysozyme: secreted by monocytes, macrophages and giant cells and reflects their activities, increased serum lysozyme levels are associated with decreased activity<sup>33</sup>, they usually parallel ACE levels but may be elevated in their absence

Hypercalcemia: observed in 10 to 15 % of patients with sarcoidosis<sup>3</sup>, occurs due to increased concentrations of 1,25 dihydrocholecalciferol, is associated with normal serum phosphate, normal or slightly raised serum phosphatase and increased 24 hour urinary excretion. Hypercalciuria is more common than hypercalcemia and can be assessed by 24 hour urinary calcium determination<sup>33</sup>, persistent hypercalcemia can lead to nephrocalcinosis<sup>3</sup>.

Changes observed amongst the routine investigations which usually reflect the chronic inflammatory responses are as follows<sup>33</sup>,



- Decreased total count
- Lymphopenia
- Thrombocytopenia
- Elevated ESR
- Abnormal liver enzymes
- Polyclonal gammopathy with A:G reversal

Conjunctival Biopsy: it is a simple procedure with low complication rates, tissue is easily accessible, lower fornix is the preferred site, lower lid is retracted and a strip of tissue of 1cm x 3mm is excised with wescott scissors and the specimen is then examined under the microscope for histopathological features<sup>29</sup>.

Lacrimal Gland Biopsy: done in patients with clinically enlarged lacrimal glands and with positive gallium uptake, conjunctival or skin route is usually preferred<sup>7</sup>. Minor salivary gland biopsy has been found to be very productive and is positive in 58% of sarcoid patients<sup>3</sup>

Skin Biopsy: quite specific to make a diagnosis of sarcoidosis, usually taken from lesions of lupus perino, maculopapular eruptions , sub cutaneous nodules and erythema nodosum.To make a positive diagnosis , the histopathological features must be suggestive of non caseating granulomas , described earlier.

Bronchioalveolar lavage: uveitis patients with normal chest x ray may show increased proportion of CD3 cells and elevated CD4/CD8 ratio<sup>7,3</sup>, which are consistent with active pulmonary sarcoidosis. Lymphocytes rosetting around macrophages is seen in BAL specimens and also in cells sloughed from in vitro cultured sarcoid granulomas. Sarcoid alveolar macrophages express increased ICAM 1 and LFA 1

Transbronchial Lung Biopsy: biopsy is done using a bronchoscope, and the material taken is usually bronchial mucosa and part of adjacent lung, non caseating granulomas were detected in 54 to 80% of sarcoid patients<sup>33</sup>, positivity rates were increased in x ray positive cases, the overall diagnostic yield was estimated to be around 90%

cutaneous anergy: The patient with sarcoidosis who has been previously exposed to bacille calmette guerin vaccination ,(even after previous TB exposure) may fail to show a response to intradermal tuberculo protein, this phenomenon is referred to as cutaneous anergy<sup>6</sup>. It demonstrates the reduced ability to acquire or express delayed hypersensitivity. This cutaneous anergy is found in approximately 95%. Commonly response is elicited with tuberculo protein, can be arrived with other agents also. It is likely that this response represents a relative depletion of CD4 lymphocytes in the

peripheral circulation, thereby reflecting the compartmentalisation of T cells that contributes to the pathogenesis.

*Kveim siltzbach reaction*: This test was introduced in 1941, suspension from spleen of sarcoid patients is injected intradermally and a cutaneous papule containing non caseating granuloma is detected. 4 to 6 weeks after sub cutaneous injection of the suspension, reddish brown papule varying from few mm to 1.5 cm is detected, which reveals typical non caseating granuloma on HPE examination. The test was found to be positive in almost 80% of patients<sup>6</sup>. False positive results in less than 1% of patients, seen in TB, Crohn's disease. However a negative result does not exclude the diagnosis, steroids produce false negative results, therefore it should not be performed in patients on long term steroids.

*Pulmonary Function Tests*: useful for initial diagnosis and follow up, common abnormality noticed is increased alveolar oxygen gradient with decreased diffusing lung capacity.

***International criteria for the diagnosis of ocular sarcoidosis (IOWS)<sup>34</sup>***

The diagnostic criteria were based on clinical signs, lab investigations, biopsy results;

Seven clinical signs and five investigations were included in the diagnostic criteria as shown in tables 2a and 2b

Table 2a *Criteria for diagnosis of ocular sarcoidosis:*

<b>CLINICAL SIGNS</b>	<b>INVESTIGATIONS</b>
Mutton fat keratic precipitates / small granulomatous keratic precipitates / iris nodules ( koeppe , busaca)	Negative TB skin test in a BCG vaccinated patient or in a patient having had a positive skin test previously
Trabeculr meshwork nodules and or tent shaped peripheral anterior synechiae	Elevated sr ACE levels or sr.lysozyme
Vitreous opacities displaying string or pearls	Chest xray revealing bilateral hilar lymphadenopathy
Multiple chorioretinal peripheral lesions	Abnormal liver enzyme tests
Nodular and or segmental periphlebitis +/- candlewax drippings & or retinal macroanurysm in an inflamed eye	Chest CT in patients with negative chest xray result
Optic disc nodule(s) / granuoma (s) solitary chornonical nodule	
Bilaterality	

*Table 2b: Levels of certainty for the diagnosis of sarcoidosis :*

Biopsy supported diagnosis with a compatible uveitis – DEFENITIVE OCULAR SARCOIDOSIS
Biopsy was not done but chest x ray was positive showing bilateral hilar lymphadenopathy with compatible uveitis – PRESUMED OCULAR SARCOIDOSIS
Biopsy was not done, chest x ray did not show bilateral hilar lymphadenopathy, but there were 3 if the above intraocular signs , 2 postive lab tests – PROBABLE OCULAR SARCOIDOSIS
Lung biopsy was done and its results were negative , but atleast 4 of the above signs and 2 of the lab signs were positive – POSSIBLE OCULAR SARCODIOSIS

Thus the systemic association for suspected cases of ocular sarcoidosis can be proven with the help of battery of tests mentioned above. But the definitive diagnosis is only by histological confirmation. It is also to be noted that uveitis may still exist with sarcoidosis in the face of negative systemic tests.

### ***Prognostic Indicators of ocular sarcoidosis***

The prognosis and outcome of ocular sarcoidosis have been studied by many authors , concentrating on induvidual perspectives in their respective

studies. The main conclusions drawn at the end of their studies have been analysed and consolidated to view the major factors that determine the visual outcome and thereby the prognosis of sarcoidosis.

Main factors studied were:

1. Demographic variables
2. Relating the systemic manifestations of sarcoidosis to ocular sarcoidosis
3. Comparing the various manifestations of ocular sarcoidosis
4. Comparing the outcome amongst different types of uveitis
5. Relating the course of the disease( duration)

there are other factors such as duration of illness, compliance to treatment, delay in presentation to hospital, early treatment institution, presence of other comorbid conditions and surgery.

In majority of the studies the major determinant of prognosis considered was: *BCVA at the end of disease course both in better and worse eye.* This factor was analysed widely in all studies and conclusions were drawn based on the ultimate visual outcome of the patient. Considering the various factors studied individually;

*Demographic variables:*the three underlying factors were evaluated in detail,

1. age
2. sex
3. race

Age as a variable:The mean age at presentation was noted as 42 years, with a range of 13 to 79 years<sup>31</sup>.It was noted that younger patients had an increased incidence of vitreous hemorrhage in pars planitis , which was not seen in older patients. This was probably attributed to the tendency of young patients to develop exuberant inflammation.

But the overall visual acuity was worse among older patients, probably due to increased incidence of CME and visually significant cataracts in older patients<sup>31</sup>

Therefore knowing about the increased risk of vitreous hemorrhage in young patients would help us to detect it early and thereby controlling the significant visual damage caused

Sex as a variable: Females definitely had an increased frequency of presentation compared to males<sup>31</sup> ( adjusting for other two factors , age and race).Notably females also had decreased visual acuity compared to malesThe worst acuity was recorded amongst black females, probably due to increased incidence of CME.But the values remained the same even after adjusting for

CME, other reasons were vitreous and lens opacities, as vitreous opacities were commoner in males, cataracts were considered as major culprits

Race as a variable: White patients (males and females) had an increased rate of posterior segment inflammation<sup>31</sup>, compared to the black counterparts. It was also reported that, the European blacks had a higher rate of PSI than American blacks. Race relations of ocular sarcoidosis, including posterior segment inflammation, may be due to different etiologies of underlying systemic disease, in addition to genetic and environmental differences between the populations.

Comparing the outcome amongst different types of uveitis: After adjusting the various parameters for age, sex and other demographic variables, the visual outcome was analysed as follows, main ocular manifestations associated with worse prognosis of visual acuity of less than 20/40 were development of CME, secondary glaucoma, posterior uveitis and intermediate uveitis<sup>26</sup>. Apart from these, other factors were also suggested such as, delay in presentation to a sub specialist, longer duration of uveitis, lack of systemic steroid use, black race and absence of early treatment institution

Different types of uveitis in sarcoidosis : Sarcoid uveitis was classified into four based on anatomy;

- isolated anterior uveitis

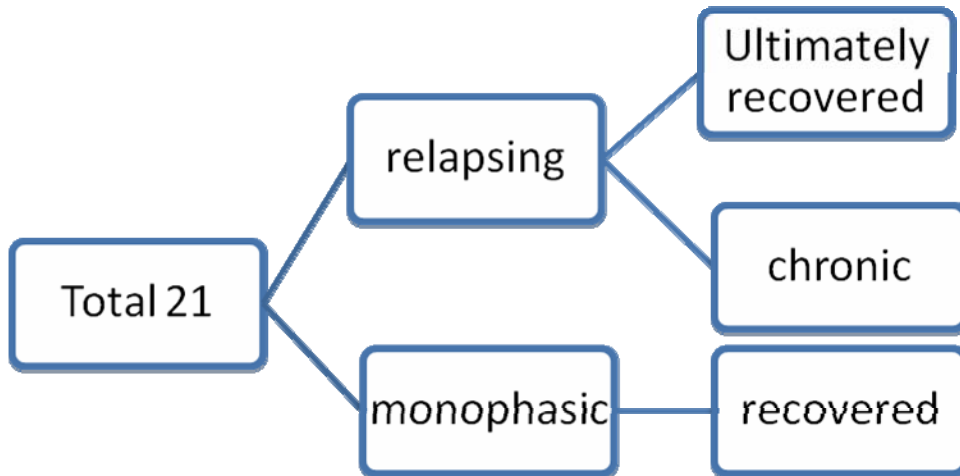


- intermediate uveitis (AVF/snowballs/snowbanks)
- Retinal vasculitis with or without panuveitis
- multifocal choroiditis( punched out chorioretinal scarring with or without posterior segment inflammation such as multifocal choroiditis and cme)

BCVA less than or equal to 6/12 was considered as poor visual outcome after adjusting the parameters for age, sex, laterality and other manifestations of systemic sarcoidosis .The worst prognosis was seen in patients with multifocal choriditis and subfoveolar neovascularisation, followed by retinal periphlebitis or retinal vasculitis<sup>25</sup>. This outcome was probably related to complications such as CME, glaucoma that were common with posterior segment involvement( 43% of all cases of glaucoma occurred in the group with MFC).Though both cataracts and glaucoma were both treated with surgery, cataract had a very good prognosis, which was lacking in glaucoma, probably due the greater inflammatory insult that occurred in glaucoma.Other uncommon complications associated with bad visual outcome were vitreous hemorrhage, retinal vascularisation , neovascularisation and ERM.Interestingly all of them occurred in patients with posterior segment involvement .

Relating to the course of uveitis:The course of sarcoidosis was broadly classified as, monophasic and relapsing,

The above pattern was observed in the study which included 21 patients<sup>26</sup>:



Monophasic uveitis remitted totally in a maximum of two years, whereas relapsing uveitis did not necessarily follow the course of systemic disease. Therefore the visual outcome was definitely favourable in those with monophasic uveitis and worse in those with relapsing uveitis.

- Comparing ocular and systemic sarcoidosis: The prognosis for patients with no clinical evidence of extraocular sarcoidosis at the onset of their uveitis was analysed and compared with those who had symptomatic pulmonary disease, and also determined which organ systems were most likely to develop disease after the onset of uveitis . Three groups of patients were studied<sup>24</sup>,

- *First group*: clinical or radiological evidence of pulmonary sarcoidosis within the first year of onset of uveitis
- *Second group*: clinical or biopsy evidence of extraocular sarcoidosis within one year of onset of uveitis but with no evidence of pulmonary sarcoidosis
- *Third group*: uveitis compatible with sarcoid uveitis , no clinical or radiological evidence of extraocular sarcoidosis at the onset of uveitis , whon had unexplained rise of ACE &/ or positive kveiems test.

Outcome variables analysed were ; BCVA,raised Intra ocular pressure requiring treatment,new symptomatic sarcoidosis in an organ involved at baseline,use of systemic steroids and immunosupressants and any intaocular surgery undertaken during the course of the disease.Only permanent changes in visual acuity were considered( temporary changes were excluded),a drop in acuity was considered permanent if it had not improved within 1 year of follow up and reversible causes such as treatable macular edema and cataracts have been excluded, the main outcome measures related to visual acuity and baseline variables were analysed by kaplan – meier analysis, along with the pattern of extraocular involvement at the onset of uveitis. In the outcome analysis,four groups were made based on the final acuity<sup>24</sup>



## SUN (Standardisation of Uveitis Nomenclature) classification

*Table 1 -SUN working group's anatomical classification of uveitis*

Type	Primary site of inflammation	includes
Anterior uveitis	Anterior chamber	Iritis, iridocyclitis, anterior cyclitis
Intrmediate uveitis	vitreous	Pars planitis, posterior cyclitis and hyalitis
Posterior uveitis	Retina or choroid	Focal or multifocal or diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis and neuroretinitis
panuveitis	Anterior chamber , vitreous , retina and choroid	

(Adapted from the international uveitis study group anatomical classification<sup>52)</sup>

*Table 2-SUN working group descriptors of uveitis*

category	descriptors	Comment
Onset	Sudden	
	Insidious	
Duration	Limited	<= 3 months duration
	Persistent	>3 months duration
Course	Acute	Episode characterised by sudden onset & limited duration
	Recurrent	Repeated episodes separated by periods of inactivity with treatment >= 3 months in duration
	Chronic	Persistent uveitis with relapse in < 3 months after discontinuing treatment

*Table 3- SUN working group grading scheme for anterior chamber cells*

Grade	Cells/ field
0	< 1
0.5+	1 – 5
1+	6 – 15
2+	16 – 25
3+	26 – 50
4+	>50

(Field size is 1 mm by 1 mm slit beam )

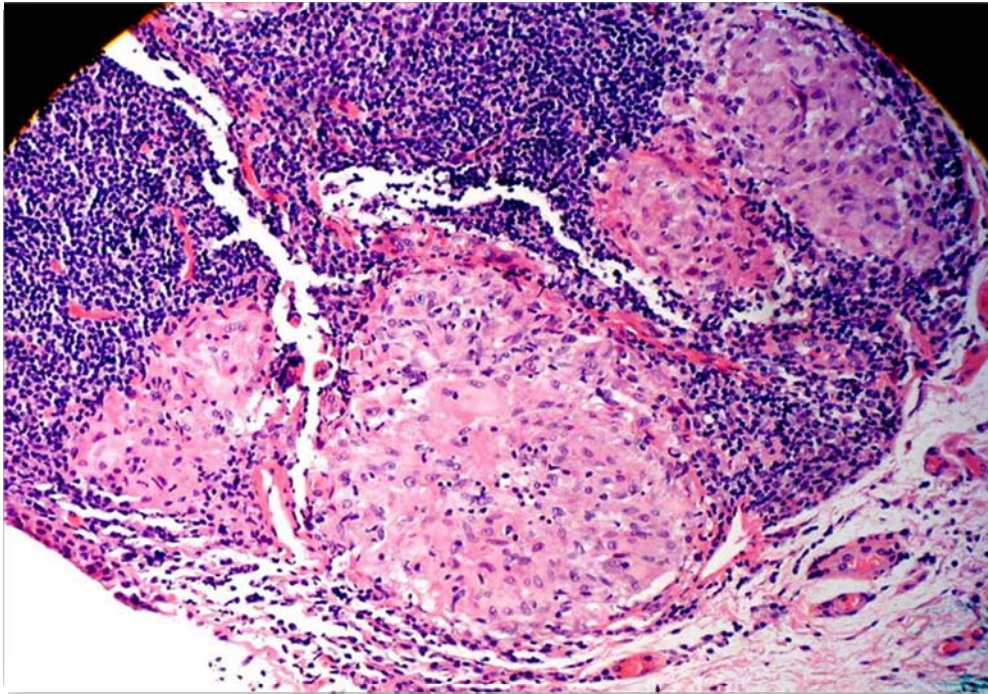
*Table 4- SUN working group grading scheme for anterior chamber flare*

Grade	Description
0	None
1+	Faint
2+	Moderate( iris and lens details clear)
3+	Marked( iris and lens details hazy)
4+	Intense( fibrinous or plastic aqueous)

*Table 5 – SUN working group classification of activity of uveitis terminology*

terminology	Definition
Inactive	Grade 0 cells(applied to AC inflammation)
Worsening activity	2 step increase in level of inflammation ( AC cells or vitreous haze or increase in inflammation to grade 3+ or 4+)
Improving activity	2 step decrease in level of inflammation ( AC cells or vitreous haze or decrease in inflammation to grade 0)
Remission	Inactive disease $\geq$ 3 months after discontinuing all treatment for eye disease

*Fig 1 : Non caseating sarcoid granuloma*



*Fig 2 : granulomatous keratic precipitates*

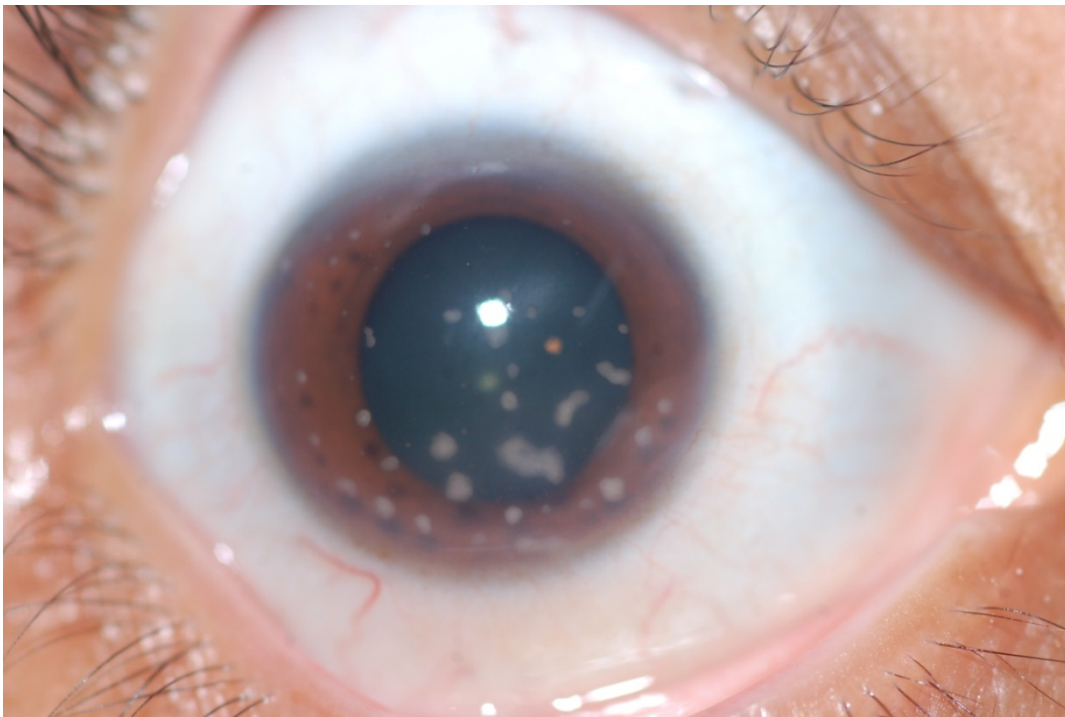




Fig 3 : Busaca nodule :



Fig 4 : Retinal vasculitis (periphlebitis):



## **Aims and Objectives**

Aims: to study the clinical manifestations, diagnostic indicators and prognostic indicators of ocular sarcoidosis

Objectives:

To study the clinical pattern of ocular sarcoidosis

To study the various parameters that are used for the diagnosis of ocular sarcoidosis

To study the prognosticators of ocular sarcoidosis

## **Materials and Methods**

Setting: University affiliated teaching centre attached to a community based eye hospital offering primary to tertiary care

Centre: Aravind Eye Hospitals, Madurai

Department: Uvea clinic and Uveitis services, Aravind Eye Hospitals, Madurai

Period of study: May 2009 to December 2010

Sample size: 50 patients, 73 eyes

Procedure for data collection: case selection, clinical examination and filling up of proforma. Data was entered into microsoft excel spreadsheets and analysed using STATA software.

Patients and uveitis workup:

Inclusion criteria: All patients who presented to uvea clinic of Aravind eye hospital between april 2009 to december 2010 with definitive signs of intraocular inflammation compatible with a diagnosis of ocular sarcoidosis<sup>42</sup> were included in the study.

Exclusion criteria: Patients with classical systemic features pointing to other differentials, those with established histological or serological evidence of other entities, patients with no follow up, patients with other co existing, co-morbid conditions

Clinical evaluation: The records of the uveitis services of Aravind eye hospital, Madurai during the years 2009 and 2010 were reviewed to identify patients who fulfilled the inclusion criteria. Charts of eligible patients were studied retrospectively and had been worked up according to the standard uveitis workup<sup>49</sup>. Demographic data like age, gender, occupation were noted. History included details of ocular symptoms, duration, disease severity, laterality, chronicity, course of illness, any ocular therapy taken prior to presentation at our clinic, response to treatment, systemic symptoms and signs if any with duration and the number of recurrences of ocular symptoms

Complete ocular examination at each visit included best corrected visual acuity, slit lamp examination, tonometry and indirect ophthalmoscopy. The assessment of visual acuity was done on the basis of best corrected visual acuity by Snellen's chart at a distance of six metres, during each visit to uvea clinic at Aravind. Ocular parameters included were ocular signs at initial diagnosis, location of the inflammation such as anterior, intermediate, posterior or panuveitis, presence of granulomatous type of keratic precipitates, severity of anterior chamber reaction, presence of anterior or posterior synechiae, severity of vitritis, presence of vitreous exudates either snow balls or snow banking, presence of retinal periphlebitis as segmental vasculitis with candle wax

drippings, peripheral multifocal choroiditis, presence of papillitis , the level of intra ocular pressures and the number of episodes of ocular inflammation.

Complications studied were complicated cataract, secondary glaucoma(both open angle and angle closure), retinal ischemia with neovascularisation and chronic corneal degenerative changes such as band shaped keratopathy. Anatomical location was based on SUN classification of uveitis<sup>52</sup>. Laterality was graded as unilateral or bilateral. Chronicity was graded as acute- sudden onset ,less than three months duration, chronic- more than or equal to three months duration, recurrent- more than three months with complete resolution between episodes, uveitis was graded granulomatous as there were large greasy mutton fat keratic precipitates with anterior chamber reaction of grade 2 to 3 with or without iris nodules(koeppe and busaca). Visual outcome was considered favourable if there was no decrease in visual acuity at final followup or two line improvement from prior visual acuity.Unfavourable if there was decrease in visual acuity by two lines or no improvement compared to initial acuity.

The final outcome was measured according to change in number of snellen lines read when comparing baseline and final acuity. The visual acuities then were analysed and correlated.

Treatment : The corner stone of therapy for all sarcoid patients is with steroids. Steroid eye drops (1%Prednisolone acetate), topical mydriatic agents(0.5% Homatropine) to prevent the formation of posterior synechiae and for symptomatic relief was given in cases of mild anterior uveitis. Patients with severe anterior chamber disease, intermediate uveitis and limited posterior uveitis recieved periocular steroids( 0.5 mg of Triamcinolone acetate) and oral steroids(tab.Prednisolone 1mg/kg/wt ) tapered over a few weeks. Patients with severe complications and severe posterior segment involvement recieved immunosuppressants (tab.Methotrexate 15mg/kg or tab.Azathioprine 1-2 mg/kg/wt) in addition to oral steroids. duration of treatment was based on the level of inflammation control. Cataract surgery was performed for visually significant complicated cataract. Antiglaucoma medications (eye drops Timolol maleate 0.5%, 0.2% Brimonidine and 1% Dorzolomide ) were added to decrease elevated intraocular pressures.

Statistical analysis: To determine visual acuity improvement , last available best corrected visual acuity was compared to visual acuity at the time of presentation. Visual acuity improvement was defined as an improvement of atleast two snellen line in visual acuity from initial visit to last follow up visit. Proportions were compared using chi square test. Value of p less than

0.05 was taken as statistically significant. Data was initially entered in microsoft excel spreadsheets and analysed using STATA software.

## Results

73 eyes of 50 patients with a probable diagnosis of ocular sarcoidosis , who fitted into our inclusion criteria were studied. The mean duration of follow up for these patients was 6 months. Demographic characteristics studied have been summarised in tables 1. The mean age of presentation was 38 years ranging from 12 to 67 years. The mean age of presentation among males was 32 years and among females was 46 years. There was a predilection for female gender with 62% and males attributing to 38%. These values have also been represented in terms of pie chart(fig 5). On evaluating the systemic features associated, no exact symptomatic presentation was noted. Findings of bilateral hilar lymphadenopathy and elevated liver enzymes were noticed in 18(out of 50) and 1(out of 7) of patients respectively.

*Table 1-demographic parameters including age and sex*

Variable	frequency	Percentage %	Age range
female	31	62	12- 67 years
male	19	38	16-56 years

The various ocular disease characteristics have been summarised in tables 2a and 2b. Unilateral involvement was seen in 27 patients and bilateral



involvement was seen in 23 patients. Acute onset was noticed in 19.17% of eyes, chronic in 72.6% of eyes and recurrence was seen in 8.2% of eyes. Defective vision was seen in 82.1% of eyes, pain and redness was seen in 34.2% and 31.5 % respectively. Photophobia was noticed in 21.9% of the eyes studied and floaters were seen in 26.5% of eyes. Amongst the clinical signs , granulomatous keratic precipitates and anterior chamber reaction were observed in 93.1% of eyes. Grade 2 and grade 3 anterior chamber reaction were seen in 38.35% and 41.09% of the eyes respectively , whereas grade 1 reaction was seen in 13.69% of the patients. Iris nodules were noticed in 24.6% of eyes of which koeppes nodules alone contributed to 15.06%, busacas to 5.5% , koeppes and busacas together to about 4.1% and angle granuloma was seen in 1.3% of the patients. Peripheral anterior synechiae and posterior synechiae were seen in 6.85 and 12.3% of the eyes respectively constituting a total of 19.1%. conjunctival nodules were noticed in 2.7% of the patients. Corneal involvement was seen in 5.47% of the eyes out of which dry eye was noticed in 2.7% and band shaped keratopathy was seen in 2.7% of the eyes. Secondary glaucoma in the form of open angle and angle closure types were noticed in 1.3% and 5.4% of the eyes respectively. Complicated cataract was seen in 2.7% of the eyes studied. Vitritis was seen in 47.9% of the eyes , of which grade 3 , grade 2 and grade 1 were seen in 27.39%, 13.69% and

6.8% of the eyes respectively.vitreous exudates in the form of snow balls were seen in 27.39% of the eyes, snowbanking was noticed in ,

Table 2a- summarising various symptoms of ocular sarcoidosis among 73 eyes studied

Symptoms	Frequency	Percentage
Defective vision	60	82.9
Photophobia	16	21.9
Floaters	19	26.0
Pain	25	34.2
Redness	23	31.5

1.3% of the eyes and snowballs together with snowbanking was observed in

1.3% of the eyes studied

*Table 2b- various ocular signs of sarcoidosis amongst 73 eyes studied*

Ocular signs	frequency	Percentage(%)
<b>Anterior segment</b>		
<i>Granulomatous keraticprecipitates</i>	68	93.1
<i>Anterior chamber reaction</i>	68	93.1
Grade 1	30	41.0
Grade 2	28	38.3
Grade 3	10	13.6
<i>Iris nodules</i>	18	24.6
Koeppes	11	15.0
Busacas	03	5.4
Both	04	4.1
Angle granuloma	01	1.3
<i>Synechia</i>	14	19.1
Peripheral anterior	09	12.3
Posterior	05	6.8
<i>Conjunctival nodules</i>	02	2.7
<i>Corneal involvement</i>	04	5.4
Dry eye	02	2.7
Band shaped keratopathy	02	2.7
<i>Glaucoma</i>	05	6.8
Open angle	01	1.3
Angle closure	04	5.4
<i>Complicated cataract</i>	02	2.7

Ocular signs	frequency	Percentage(%)
<b>Posterior segment</b>		
<i>Vitritis</i>	35	47.9
Grade 3	20	27.3
Grade 2	10	13.6
Grade 1	5	6.8
<i>Vitreous exudates</i>	22	30.1
Snow balls	20	27.3
Snow banking	1	1.3
Both	1	1.3
<i>Peripheral multifocal choroiditis</i>	2	2.7
<i>Periphlebitis</i>	9	12.3
<i>Cystoid macular edema</i>	6	8.2
<i>Papillitis</i>	8	10.9
<i>Optic nerve head granuloma</i>	1	1.3

Peripheral multifocal choroiditis was seen in 2.7% of the eyes, segmental periphlebitis as candle wax drippings was observed in 12.3% of the eyes, cystoid macular edema in 8.2% of the eyes, papillitis and optic nerve head granuloma were noticed in 10.95 and 1.35 of the eyes respectively.

Table 3 – various laboratory investigations performed in relation to ocular sarcoidosis

Investigations	Frequency	Percentage (%)
Chest x-ray(n =50)		
Bilateral hilar lymphadenopathy	18	36
Only fibrosis	2	4
Both	2	4
Normal	28	56
Mantoux test(n=50)		
Positive	7	14
Negative	43	86
Serum ACE(n=22)		
Elevated	11	50
Normal	11	50
Liver function tests(n=7)		
Altered	1	14.2
Normal	6	85.6

Systemic investigations performed were chest x-ray, mantoux test, serum ACE levels and liver function tests. Serum ACE was done in 22 patients and liver function tests were performed in 7 patients whereas, the other two investigations were done in all the patients. Radiologically evident bilateral hilar lymphadenopathy was noticed in 36% of the patients, lung fibrosis was seen in 4% of the patients and both together was seen in 4% of the patients studied. Mantoux test was reactive in 14% of the patients and not reactive in 86% of the patients. Serum levels of ACE was found to be elevated in 50% of the tested individuals and liver function tests were altered in 1 out of 7 Patients tested for the same.

Treatment modalities offered have been summarised in the table below,

*Table 4 – treatment pattern of 73 eyes studied*

Treatment modality	No of eyes out of 73
Topical steroids	73
Periocular steroids	20
Oral steroids	40
Cycloplegics	55
Immunosuppressants	7

Topical steroids were given in all 73 eyes, 68 eyes were given cycloplegics for symptomatic relief, 10 eyes were given periocular steroid injections in

addition to topical steroids , 40 patients recieved systemic steroids along with topical medications and 5 patients also needed systemic immunosuppressants in the form of azathioprine and methotrexate.

The visual outcome analysed at the end of the study by comparing the best corrected visual acuity between the initial and the final visits, at the end of six months followup, have been described below in table

*Table 5 – visual outcome for 73 eyes at the end of 6 months*

Visual outcome	Number	Percentage (%)
Improved	21	28.76
Same	49	67.2
Decreased	3	4.1

The actual values of best corrected visual acuity recorded , during the initial visit and during the final visit at the end of 6 months follow up have been represented in the following two tables

*Table 6a – values of visual acuity at the time of presentation ( n=73)*

Initial visual acuity	Frequency	Percentage (%)
6/6	38	52.0
6/6-6/12	21	28.7
6/18-6/36	8	10.9
6/60- 1/60	5	6.8
<1/60	1	1.3

*Table 6b – values of visual acuity at the end of 6 months follow up*

Final visual acuity	Frequency	Percentage (%)
6/6	46	63.1
6/9- 6/12	15	20.5
6/18- 6/36	8	10.9
6/60- 1/60	3	4.1
<1/60	1	1.3

The proportions comparing the initial and final visual acuities were then analysed using chi square test of independence , whose p value was < 0.001 and was highly significant,



The values for visual acuity were compared with the parameters relating to anatomical location of uveitis, development of new complications and the type of complications. The following table describes their correlation,

*Table 7 – analysis of visual outcome at the end of the study against anatomical location of uveitis and presence of complications during initial visit*

Parameter	Good visual outcome(6/6+ atleast one line improvement foll treatment)	Bad visual outcome( decrease in visual acuity+ no improvement foll treatment)
Only anterior uveitis	88.2%	11.76%
Anterior uveitis + posterior uveitis	91.4%	8.5%
Pure posterior segment involvement	0%	100%
Presence of complications at initial visit	50%	50%

*Table 8 – analysis of visual improvement at the end of the study as apposed to the various complications*

Complications	Percentage improved	Percentage not improved
Secondary glaucoma( 5 eyes)	80	20
Complicated cataract(2 eyes)	100	0
Retinal ischemia(3 eyes)	0	100
Band shaped keratopathy(2 eyes)	0	100

The above table describes in detail the various complications and their respective visual outcomes, complicated cataract and secondary glaucoma had 100% and 80% improvement in the final visual acuity amongst the affected eyes, whereas retinal isxhemia and band shaped keratopathy had poor outcome with nil improvement in visual acuity amongst the affected eyes.

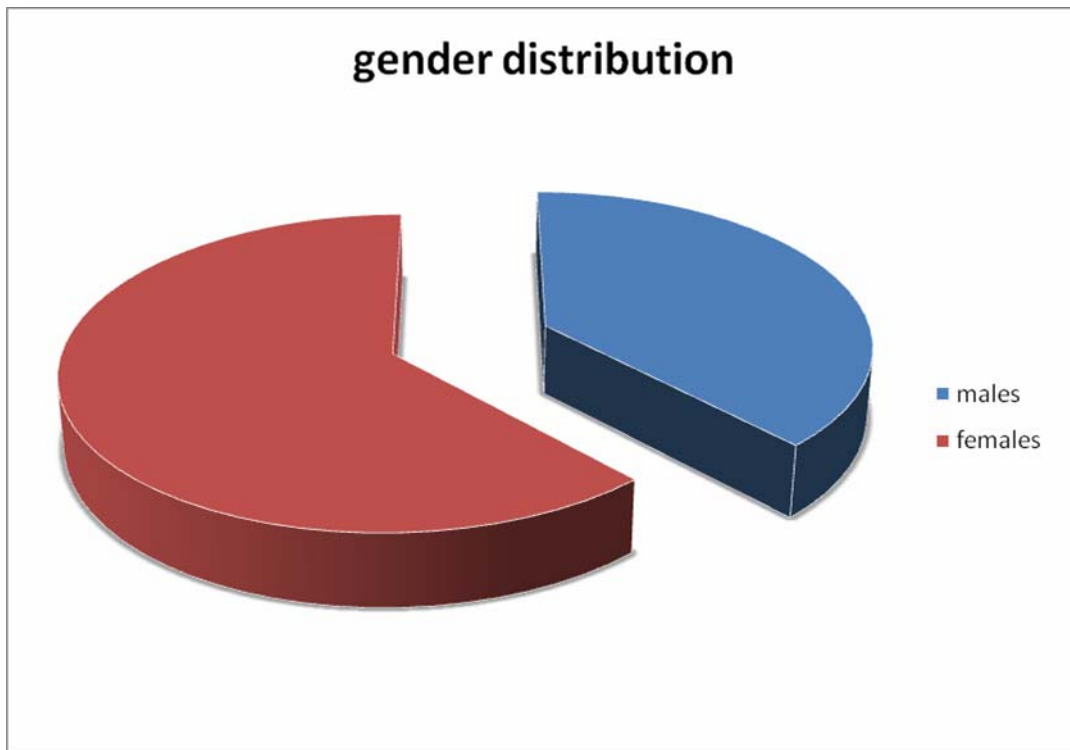
Statistical analysis was carried out to derive significant correlation between these parameters and final visual outcome using chi square test , but there was no statistical significance as the values were greater than 0.05.

There was also significant reduction in decrease of disease severity in terms of anterior chamber reaction and vitreous cells and haze between the initial and final visits as seen in the table below,

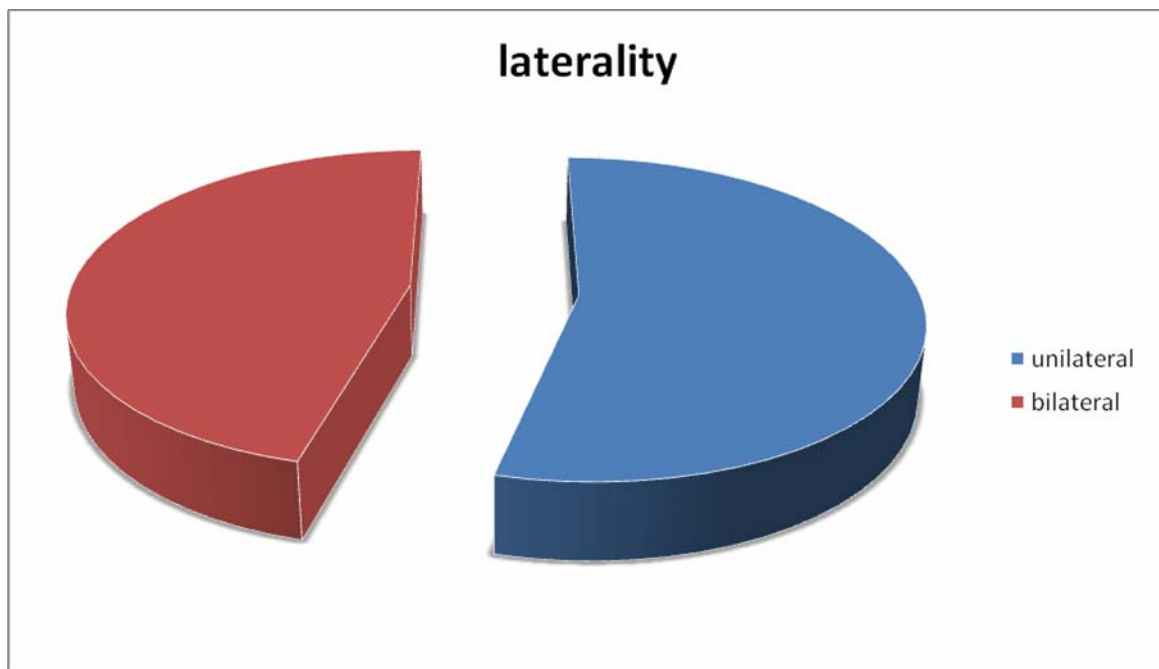
*Table 9 – severity of inflammation between initial and final visits*

Parameters	Initial visit/ percentage%	Final visit/ percentage %
Grade 3- AC cells	38( 47.9)	10(13.6)
Grade 2 - AC cells	28( 27.9)	10(13.6)
Grade 1- AC cells	10( 13.69)	6(8.2)
Grade 0- AC cells		42 ( 57.5)
Grade 3- vitreous cells	20(27.3)	6( 8.2)
Grade 2 – vitreous cells	10(13.6)	3 (4.1)
Grade 1- vitreous cells	5(6.8)	1( 1.3)
Grade 0 – vitreous cells		25( 34. 2)

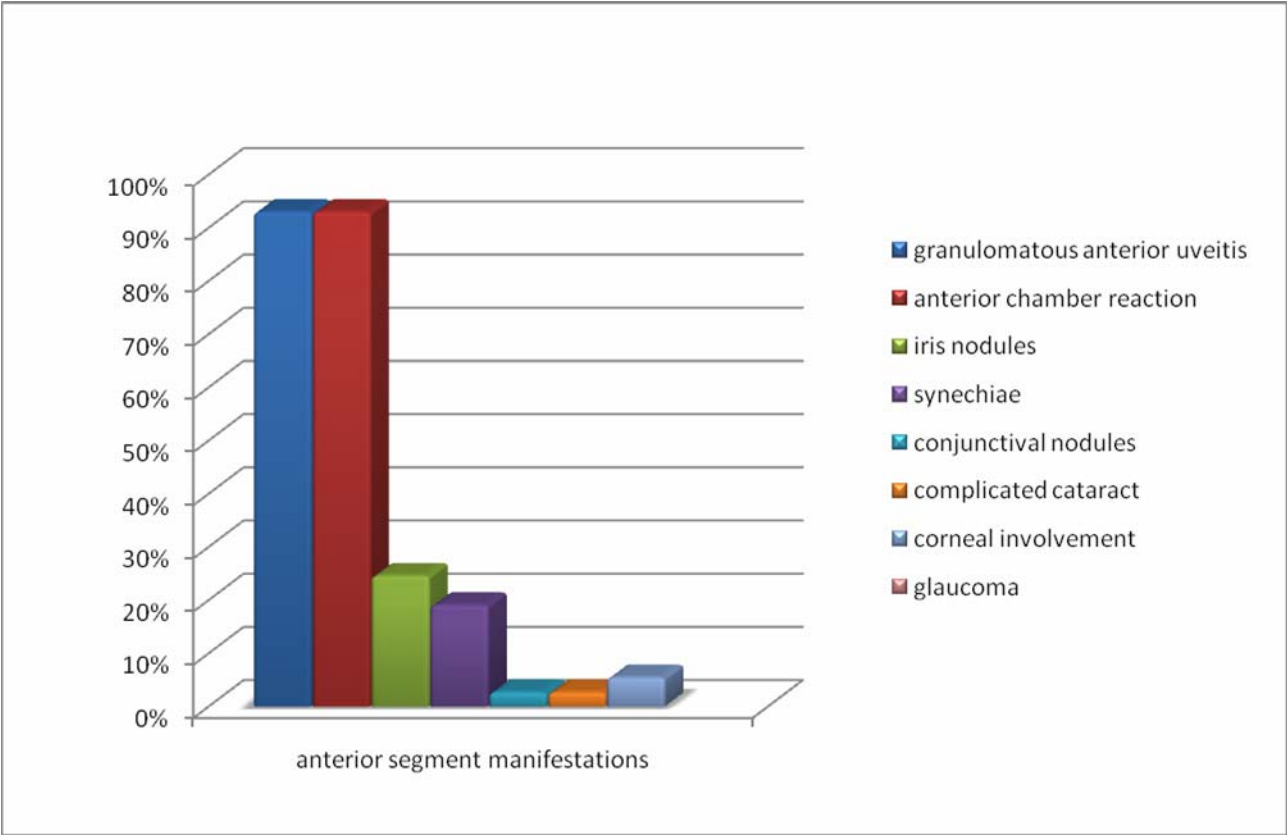
*Chart 1 : Gender distribution among 50 patients*



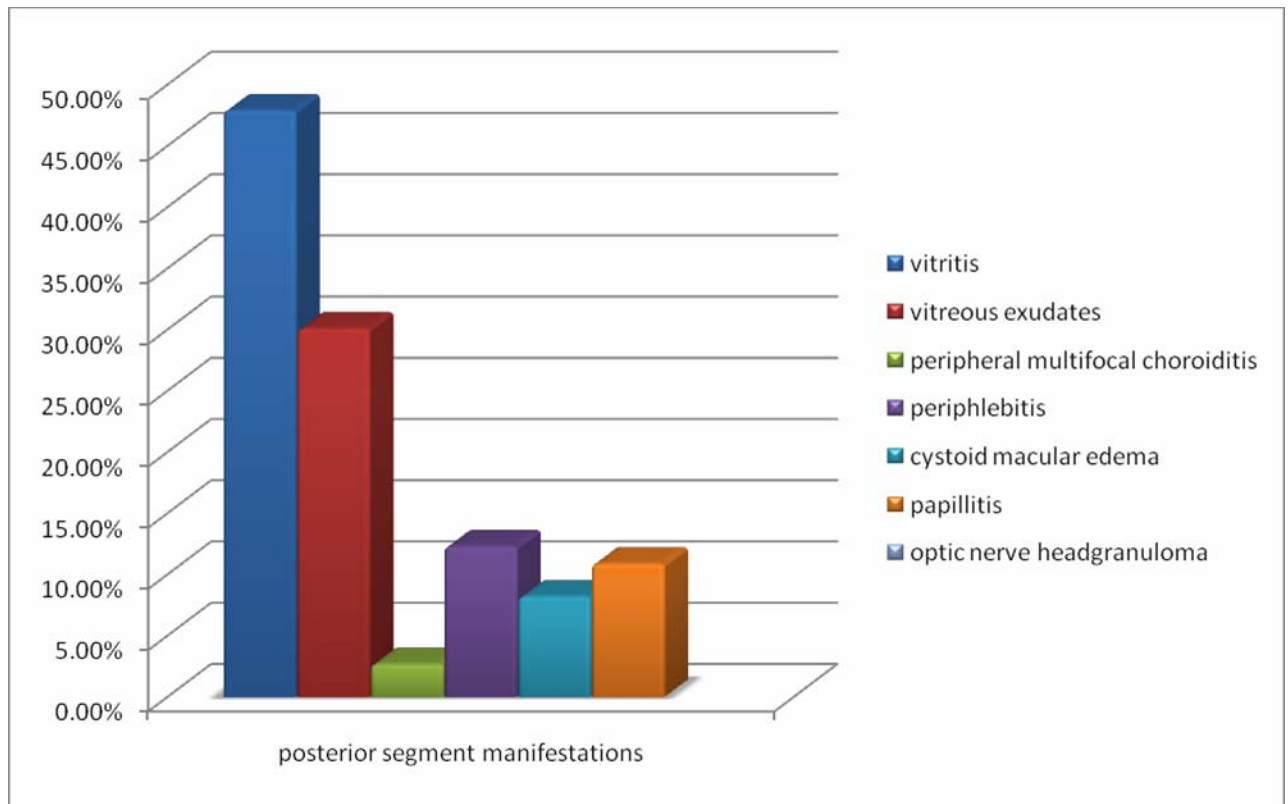
*Chart 2 :Llaterality among 73 eyes studied*



*Chart 3 : Anterior segment manifestations of ocular sarcoidosis among studied patients*



*Chart4: Posterior segment manifestations of ocular sarcoidosis among studied patients*



## Discussion

It is of vital importance to know the various clinical manifestations, diagnostic indicators and prognosticators of ocular sarcoidosis, especially in south Indian population where the disease has not been largely studied so far. Most of the demographic and other epidemiological parameters studied in relation to sarcoidosis are from caucasian population studies. Moreover the diagnostic profile that has been put forward recently originates from Japanese population<sup>2</sup>. Visual prognostic indicators can range from demographic indices of the patient and extend to complications associated with ocular sarcoidosis. The ophthalmologist can then profile the patient into categories based on whether the vision is likely to improve or not, taking several factors into consideration. The study of prognostic indicators requires comparison between a group of patients who had bad final visual outcome with a group of patients who had improvement in visual acuity with respect to that seen at presentation. Apart from improvement in visual outcome, adequate control of intraocular inflammation and development of sight threatening complications are necessary factors to be evaluated. The cumulative effect of these multiple factors that may lead to favourable or unfavourable outcome could thus be studied.

In our study the demographic profile including age and gender were consistent with the reports of previous investigators<sup>1,3</sup>. The common age group affected was between 35 and 50 years and there was a definite predilection for female sex. Racial distribution is not applicable for our population. The occupation amongst affected were of multifarious sectors. There was no significant relationship between any particular working group and occurrence of the disease. There was an increased percentage of housewives, which can probably be attributed to the increased incidence among females. The course of the disease as described by its mode of presentation in our study had more patients in the chronic group consisting of 56 eyes out of 73 having a chronic presentation, whereas only 17 eyes had an acute presentation. Recurrences were noted in 6 eyes. Young patients had predominant acute presentation, while older individuals had chronic involvement. Similar presentation has been reported earlier in other studies<sup>1,2</sup>. Laterality was more in favour of bilateral presentation of about 63% and unilateral presentation of about 37% of the patients studied. This also correlates with other prior studies where bilateral presentation was seen in upto 90% of the population studied<sup>4</sup>.

The patients studied were then analysed for the various symptoms and signs relating to this condition. Common symptom was defective vision(



blurred vision) constituting 60% of the study group, followed by pain and redness of about 25% and 23% respectively. Photophobia and floaters were also noticed in 16% and 19% of the population studied respectively. These symptoms correlate well with the common clinical findings of chronic anterior uveitis and intermediate uveitis as explained later.

Sarcoidosis presents with a wide variety of clinical features affecting every part of the ocular system, starting from the lids and adnexa to the retina and optic nerve. Uveitis in sarcoidosis can be classified into anterior, intermediate and posterior and pan uveitis. This categorical differentiation is very important for treatment purposes. Most studies have shown that the commonest clinical presentation in ocular sarcoidosis is of chronic anterior uveitis<sup>1,3,4</sup>. These findings correlated well with our study, where chronic anterior uveitis was the commonest clinical presentation with granulomatous keratic precipitates seen in 93.1% , AC reaction with presence of cells in the anterior chamber ranging from grades 1 to 3 seen in 93.1%, iris nodules( both koepe & busaca) seen in 24.6% and synechiae( peripheral anterior and posterior) seen in 19.1% of the population studied. The next common clinical finding was of intermediate uveitis, where vitritis with vitreous exudates(snow balls and snowbanking) were seen in 47.9% and 30.1% of the population studied. Previous studies<sup>4,5</sup> done report the presence of vitritis in

30 to 100% of the patients with sarcoidosis, but only the presence of vitritis of grade 2 to 3 associated with either vitreous exudates and or cystoid macular edema( constituted 8.2% of our study poulation) favours a diagnosis of intermediate uveitis. The commonest posterior segment finding according to previous studies was of segmental periphlebitis commonly referred to as taches de bougies which was noticed in almost 70% of fundus findings in spalton's study. Segmental periphlebitis was noticed only in 12.3% of our study population. These values differ from other investigators wher association of vitritis with peripheral segmental vasculitis was more common than intermediate uveitis, which turned out to be the second commonest clinical presentation in our study. Other clinical findings noted were as of conjunctival nodules in 2.7%, corneal involvement in the form of keratoconjunctivits of about 2.7%, peripheral multifocal choroiditis in 2.7%, papillitis in 10.9% and optic nerve head granuloma was seen in 1.3% of the population studied.

Vision threatening complications noted in our study were glaucoma (open angle and closed) seen in 6.8% of the poulation, complicated cataract in 2.7% band shaped keratopathy in 2.7% and retinal ischemia proven by angiography seen in 2.7% of the population studied. Glaucoma was the commonest complication notes as evident from the numerical data cited. From

the data analysed by prior investigators<sup>4,5</sup>, it is seen that cystoid macular edema was the commonest sight threatening complication leading to significant visual loss, though cystoid macular edema was noticed in more number of patients than glaucoma, the visual recovery was good in all these patients, probably because none of these patients had associated peripheral periphlebitis or other posterior segment involvement and had only associated vitritis and vitreous exudates were noticed among 2 patients with cystoid macular edema.

Special investigations that were performed for patients with suspected sarcoidosis in our study population were chest xray, mantoux test, serum levels of Angiotensin converting enzyme and liver function tests. Of these chest xray and mantoux were performed in all patients, whereas ACE levels were tested in 22 out of 50 patients and liver function tests were done only in 7 patients. Amongst them, cutaneous anergy, in the form of negative skin response to tuberculo-protein in previous BCG immunised individuals was seen in 86% of the study population. Radiological evidence of bilateral hilar lymphadenopathy (and /or fibrosis) by chest xray was seen in 44% of the patients. Elevation of serum ACE levels was seen in 50% of those who were tested. Altered liver function tests were noticed in only one subject. The above three parameters have been put forward in the list of major diagnostic

criteria for ocular sarcoidosis by Herbort et al<sup>42</sup> . None of the study patients had histopathological evidence or biopsy proven sarcoidosis. Therefore these three parameters of cutaneous anergy to tuberculo-protein, radiological features suggestive of sarcoidosis in the absence of profound symptoms and elevated serum ACE levels can be used to make a diagnosis of sarcoidosis in a patient with bilateral granulomatous panuveitis, where histopathological diagnosis is either inaccessible or not possible<sup>48</sup> , especially in a country like India where tuberculosis is quite an endemic disease and has similar presentation.

To determine prognosticators for any condition it is essential to determine acuity end points based on initial presenting vision and final visual acuity at the end of treatment. This determines the visual improvement that was attained over the course of the disease. The main goal of treatment is to control the ongoing pathological process and to limit or reverse the visual loss brought about by the disease. Therefore as visual improvement cannot be considered as the only prognostic factor, other parameters like adequate control of intraocular inflammation in terms of decreasing severity of inflammation , absence of sight threatening complications inspite of adequate and appropriate treatment, fall in visual acuity from initial levels and the ability to maintain good vision as in the initial presentation (as discussed

earlier) were also taken into account to analyse the prognosis of ocular sarcoidosis.

The proportions comparing the initial and final visual acuities were statistically correlated by chisquare test. It shows an improvement in the final visual outcome in terms of improvement of atleast two snellen lines from the initial presenting vision to thre last best corrected visual acuity. On apposing these values to many other parameters , both demographic and clinical some positive correlations were drawn , thereby determining useful prognostic indicators. *It was found that patients with predominant chronic anterior uveitis or intermediate uveitis or both improved well in terms of visual potential , subjective improvement and did not develop any new complications.* Those patients who had sight threatening complications in the initial visit ( poor visual potential in the initial presentation), early age of presentation and therefore chronicity along with multiple recurrences had an unsatisfactory outcome. Amongst the various complications, complicated cataract had the best prognosis and retinal ischemia had the worst prognosis, others had variable outcome depending upon their severity.

*Control of inflammation was adequate ( decreasing severity of inflammation and remission as defined by SUN classification<sup>52</sup>) in patients with predominant anterior and intermediate uveitis.* They also responded well

to steroids. patients with severe posterior segment involvement in the initial presentation required stronger agents such as Methotrexate and Azathioprine to control the inflammation. Ultimately the intraocular inflammation was well controlled in all patients.

## Conclusion

Sarcoidosis is a chronic granulomatous inflammation having various systemic and ocular manifestations. In our study we have analysed the different clinical manifestations , diagnostic parameters and prognosticators relating to ocular sarcoidosis in our population.

From our results we find that the commonest clinical presentation of ocular sarcoidosis was of chronic anterior uveitis with intermediate uveitis. Significant diagnostic indicators were cutaneous anergy to tuberculo-protein, radiological evidence of hilar lymphadenopathy and elevated serum ACE levels. Favourable prognosticators were location of the uveitis as anterior and intermediate uveitis, absence of sight threatening complications in the the initial visit, absence of multiple recurrences over the course of disease. Treatable complications like complicated cataract and glaucoma also had a favourable outcome. But no statistically significant correlation could be drawn between these parameters as the initial presenting visual acuity was good in majority of the cases. These results seem to correlate well with the results drawn from Japanese and European population studies that were conducted .

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## **ABBREVIATIONS**

ICT	Intra Cranial Tension
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PSI	Posterior Segment Inflammation
ACE	Angiotensin Converting Enzyme
FFA	Fundus Florescein Angiography
ICG	Indocyanine Green Angiography
HRCT	High Resolution Computerised Tomography
HPE	Histopathological Examination
TB	Tuberculosis
BAL	Bronchioalveolar Lavage
CME	Cystoid Maculae Edema
AVF	Anterior Vitreous Face
MFC	Multifocal Choroiditis
BCVA	Best Corrected Visual Acuity
ERM	Epiretinal Membrane
IL1,2,6	Interleukins 1,2,6
TNF	Tumour Necrosis Factor
ESR	Erythrocyte Sedimentation Rate
PCR	Polymerase Chain Reaction



MASTER CHART

patient no	no of eyes	Name	Age	sex	mr no	occupation	laterality	onset	defective vision	photophobia	pain	floaters	redness	keratic precipitates	anterior chamber reaction	iris nodules	conjunctival nodules	synechiae	complicated cataract	corneal involvement	periorbital swellings	secondary glaucoma	vitreous haze	vitreous exudates	peripheral multifocal choroiditis	periphlebitis	cystoidmacular edema	papillitis	optic nerve head granuloma	BCVA	intraocular pressure	FFA	serum ACE	serum Lysozyme	chestxray	mantoux reaction	LFT	biopsy	retinal ischemia	neovascularisation	topical steroids	posteriorsteronons	systemicsteroids	cycloplegics	immunosuppressants	BCVA at 6 months	anteriorchamberreactionat6months	vitreoushaze at6months					
1	1	nagarathinam	26	female	2917134	housewife	2	2	2	1	2	2	1	1	1c	2	2	2	2	2	2	2	1b	1a	2	1	1	1	2	6/6	12mmhg	1a	1b	2	1b	2	1b	2	2	2	1	1	1	2	2	6/6.	1c	1c					
1	2	nagarathimamma	26	female	2917134	housewife	2	2	2	1	2	2	1	1	1c	2	2	2	2	2	2	2	2	1b	1a	2	1	1	1	2	6/6	12 mmhg	1a	1b	2	1b	2	1b	2	2	2	1	1	1	2	2	6/6.	1c	1c				
2	3	devaki	60	female	2927559	housewife	2	1	2	1	2	1	1	1	1a	1a	2	1b	2	2	2	2	1b	2	2	2	1	2	2	6/6p	13mmhg	2	1b	2	1a	2	1b	2	2	2	1	2	1	2	2	6/6.	1a	2					
2	4	devaki	60	female	2927559	housewifeyes-ul	2	1	2	1	2	1	1	1	1a	1a	2	1b	2	2	2	2	1b	2	2	2	1	2	2	6/6p	13mmhg	2	1b	2	1a	2	1b	2	2	2	2	1	2	1	2	2	6/6.	1a	2				
3	5	jeyalakshmi	64	female	2935041	housewife	2	2	2	1	2	1	1	1	1a	2	1a	2	2	2	2	2	1b	2	2	2	2	2	2	6/9p	14mmhg	2	1b	2	1a	2	2	2	2	2	2	1	2	1	2	2	6/6p	2	2				
3	6	jeyalakshmi	64	female	2935041	housewife	2	2	2	1	2	1	1	1	1a	2	1a	1	2	2	2	2	1b	2	2	2	2	2	2	6/9p	13mmhg	2	1b	2	1a	2	2	2	2	2	2	1	2	1	2	2	6/6.	2	2				
4	7	mallika arjun rao	40	male	2962126	shop keeper	1	2	1	1	2	2	2	1	1b	1 (angle granulo ma)	2	1b	2	2	2	2	1c	2	2	2	2	2	2	6/60	13 mmhg	2	1b	2	1a	2	2	2	2	2	2	1	1	1	2	2	6/12.	2	2				
5	8	ganeshram	26	male	2953704	engineer	1	2	1	2	2	1	2	1	1b	2	2	2	2	2	2	2	1c	1a	2	2	2	1	2	6/6p	18mm hg	2	2	2	1b	2	2	2	2	2	2	1	2	1	2	2	6/6.	2	2				
6	9	jeyaraman	21	male	2955472	electrician	1	2	1	1	2	2	2	1	1b	1c	2	2	2	2	2	2	1c	1a	2	2	2	2	2	6/9p	16mmhg	2	2	2	1b	2	2	2	2	2	2	1	2	1	2	2	6/6.	1a	1c				
7	10	saibulla	45	male	2962738	businessman	2	1	2	1	2	2	1	1	1a	1c	2	1b	2	2	2	1a	1a	2	2	2	2	2	2	6/18	48mmhg	2	2	2	1a	2	2	2	2	2	2	1	2	1	2	1	2	1	6/6.	1a	1c		
7	11	saibulla	45	male	2962738	businessman	2	1	2	1	2	2	1	1	1a	1c	2	1b	2	2	2	1a	1a	2	2	2	2	2	2	6/6p	40mmhg	2	2	2	1a	2	2	2	2	2	2	1	2	2	2	2	1	6/12.	2	2			
8	12	pathirakali	56	female	2902102	sweeper	1	2	1	2	2	1	2	1	1b	1c	2	1a	2	2	2	2	1c	2	2	2	2	2	2	6/12 p	12mmhg	2	2	2	1a	1	2	2	2	2	2	1	2	2	2	2	2	2	6/12.	2	2		
9	13	kalarani	40	female	2987578	housewife	2	1	2	1	2	1	1	1	1a	2	1a	2	2	2	2	2	1c	2	2	2	2	2	2	6/6	13mmhg	2	2	2	1a	2	2	2	2	2	2	1	2	1	1	2	2	6/6.	2	2			
9	14	kalarani	40	female	2987578	housewife	2	1	2	1	2	1	1	1	1a	2	1a	2	2	2	2	2	1c	1a	2	2	2	1	2	6/6p	15mmhg	2	2	2	1a	2	2	2	2	2	2	1	2	1	1	2	2	6/6.	2	2			
10	15	ramakrishnan	34	male	2936994	owner of tea stall	1	2	1	2	1	1	2	1	1b	2	2	2	2	2	2	2	1a	1a	1	1	2	1	2	6/6p	8 mmhg	2	2	2	1a	2	2	2	2	2	2	1	1	1	1	2	2	6/6.	1a				
11	16	shahjahan	42	male	2943286	secretary	1	2	1	2	1	2	2	1	1b	2	2	2	2	2	2	2	1a	1a	2	2	2	2	2	6/6p	17 mmhg	1a	2	2	1b	2	1b	2	2	2	2	1	1	1	1	2	2	6/6p	1a				
12	17	sabitha sarkar	39	female	2991801	housewife	2	2	2	1	2	2	2	1	1a	2	2	1a	2	2	2	1a	1a	1a	2	2	2	2	2	6/36	20mmhg	2	2	2	1b	2	1b	2	2	2	2	1	2	1	1	2	2	6/6p	1b				
12	18	sabitha sarkar	39	female	2991801	housewife	2	2	2	1	2	2	2	1	1a	2	2	1a	2	2	2	1a	1c	1a	2	2	2	2	2	6/60	14mmhg	2	2	2	1c	2	1b	2	2	2	2	1	2	1	1	2	2	6/12.	1b				
13	19	nagalakshmi	65	female	3062841	housewife	1	2	1	1	2	2	1	1	1b	1b	2	1a	2	2	2	2	1c	2	2	2	2	2	2	6/6p	15mmhg	2	1a	2	1b	1	2	2	2	2	2	1	2	1	1	2	2	6/36.	1b	1b			
14	20	chandrasekar	32	male	2020913	businessman	2	2	2	1	2	2	1	1	1c	1b	2	2	2	2	2	2	1b	2	2	2	2	2	2	6/6p	12mmhg	2	1b	2	1b	2	2	2	2	2	2	1	2	1	1	2	2	6/6p	1b	1b			
14	21	chandrasekar	32	male	2020913	businessman	2	2	2	1	2	2	2	1	1b	2	2	2	2	2	2	2	1b	1a	2	1	2	2	1	6/6p	13mmhg	2	1b	2	1a	2	2	2	2	2	2	1	1	1	2	2	2	6/6.	2	2			
15	22	rauther	23	male	2334567	fisherman	1	2	1	2	2	2	1	1	1b	2	2	2	2	2	2	2	1b	1a	2	1	2	2	2	6/6p	16 mmhg	2	2	2	1a	2	2	2	2	2	2	1	1	1	2	1	2	2	6/6.	2	2		
16	23	babina	12	female	2305269	student	2	2	2	1	2	1	1	1	1c	2	2	1a	2	1b	2	2	1b	1a	2	2	2	2	2	6/24	13mmhg	2	1a	2	1a	2	2	2	2	2	2	1	2	1	1	1	2	2	6/6.	2	2		
16	24	babina	12	female	2305269	student	2	2	2	1	2	1	2	1	1b	2	2	1a	2	1b	2	1b	1c	1a	2	2	1	2	2	6/24	14mmhg	2	1a	2	1a	2	2	2	2	2	2	1	2	1	2	1	2	1	2	1	6/9.	1b	1c
17	25	shantha	67	female	2672159	housewife	1	2	1	2	1	2	1	1	1b	1a	2	2	2	2	2	2	1c	1a	2	2	1	2	2	6/12	12mmhg	1b	2	2	1a	2	2	2	2	2	2	1	2	1	1	2	2	6/9.	1b	1c			
18	26	mubash	28	male	2916086	shop keeper	2	2	2	2	1	2	1	1	1c	2	2	2	2	2	2	2	1c	2	2	1	2	2	2	6/6	10mmhg	2	2	2	1a	2	2	2	2	2	2	1	2	1	1	2	2	6/6.	1c	1b			
18	27	mubash	28	male	2916086	shop keeper	2	2	2	2	1	2	2	1	1b	2	2	2	2	2	2	2	1c	2	1	1	2	2	2	6/6	12mmhg	2	2	2	1a	2	2	2	2	2	2	1	2	1	1	2	2	6/6.	1c	2			
19	28	ilayaraja	21	male	2412984	student	1	2	1	2	1	1	1	1	1b	2	2	2	2	2	2	2	1c	2	2	2	2	2	2	6/6	12mmhg	2	2	2	1a	2	2	2	2	2	2	1	2	1	1	2	2	6/6.	1c	2			
20	29	samjohn	33	male	3051944	businessman	1	2	1	1	2	2	1	1	1b	2	2	2	2	2	2	2	1c	2	2	2	2	2	2	6/6	15mmhg	2	2	2	1a	2	2	2	2	2	2	1	2	1	2	2	2	6/6.	1c	2			
21	30	fazeela noushad	31	female	3049909	housewife	2	1	2	1	2	2	1	2	2	1a	2	2	2	1a	2	2	1c	2	2	2	2	2	2	6/6	16mmhg	2	1a	2	1a	2	2	2	2	2	2	1	2	1	2	2	2	6/6p	1b	2			
21	31	fazeela noushad	31	female	3049909	housewie	2	1	2	1	2	2	2	1	1b	1a	2	2	2																																		



# PROFORMA

*Study describing Clinical Manifestations , Diagnostic Indicators and Prognostic Indicators Of Ocular Sarcoidosis*

Study no:

Date:

Age / Sex :

MR no :

Occupation :

Hospital : paying/ free

History :

A. Laterality : unilateral ( 1 )      bilateral ( 2 )

B. Onset : acute ( 1 )      chronic ( 2 )

C. Defective vision : yes  1      No  2

D. Photophobia : yes  1      No  2

E. Floaters : yes  1      No  2

F. Pain : yes  1      No  2

G. Redness : yes  1      No  2

Ocular findings :

A. Granulomatous keratic precipitates : yes  1 No  2

B. AC reaction : yes  1 No  2

Grade 1- 1a

Grade 2- 1b

Grade 3- 1c

C. Iris nodules : yes  1 No  2

Koeppe - 1a

Busaca - 1b

Both - 1c

D. Conjunctival nodules : yes  1 No  2

E. Posterior synechiae/ peripheral anterior synechiae : Yes  1 No  2

Posterior synechiae : 1a

Peripheral anterior synechiae : 1b

F. Complicated cataract : yes  1 No  2

G. Corneal involvement : yes  1 No  2

Dry eye- 1a

BSK - 1b

H. Periorbital lesions : yes  1 No  2

I. Vitritis : yes  1 No  2

Grade 1- 1a

Grade 2- 1b

Grade 3 – 1c

J. Vitreous exudates : Yes  1 No  2

Snow balls- 1a

Snowbanking-1b

K. Peripheral multifocal choroiditis : Yes  1 No  2

L. Periphlebitis : Yes  1 No  2

M. Retinal edema ( cystoid macular edema) : Yes  1 No  2

N. Papillitis / disc edema : Yes  1 No  2

O. Optic nerve head granuloma : Yes  1 No  2

Best corrected visual acuity at the time of presentation :

RE  LE

Intra ocular pressure( applanation tonometry) :

RE  LE

Investigations :

A. FFA : Done  1 Not Done  2

Normal – 1a

Abnormal – 1b

B. Serum ACE : Done  1 Not Done  2

Elevated – 1a

C. Serum Lysozyme : Done  1 Not Done  2

D. Chest x ray : Done  1 Not Done  2

Normal - 1a

Bilateral hilar lymphadenopathy – 1b

Others – 1c

E. Mantoux : Reactive  1 Not reactive  2

F. Liver function tests : Done  1 Not Done  2

Elevated – 1a

Normal - 1b

G. Tissue biopsy : Done  1 Not Done  2

Complications :

A. Secondary glaucoma : Yes  1 No  2

Open angle – 1a

Angle closure – 1b

B. Complicated cataract : Yes  1 No  2

C. Band shaped keratopathy : Yes  1 No  2

- D. Cystoid macular edema : Yes  1 No  2
- E. Retinal ischemia : Yes  1 No  2
- F. Neovascularisation : Yes  1 No  2

Treatment :

- A. Topical steroids : Yes  1 No  2
- B. Periocular steroids : Yes  1 No  2
- C. Systemic steroids : Yes  1 No  2
- D. Cycloplegics : Yes  1 No  2
- E. Immunosuppressants : Yes  1 No  2
- F. Others : Yes  1 No  2

( cataract surgery, PRP,  
intravitreal steroid injections)

Follow up :

BCVA : first visit second visit third visit(6 months)

RE : \_\_\_\_\_

LE : \_\_\_\_\_

Anterior segment during third visit : \_\_\_\_\_

Vitritis and vitreous haze during third visit : \_\_\_\_\_