OCULAR MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS AND SYSTEMIC LUPUS ERYTHEMATOSUS WITH ANTIPHOSPHOLIPID SYNDROME

DISSERTATION

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CERTIFICATE

This is to certify that the Dissertation entitled, ***"Ocular manifestations of Systemic Lupus Erythematosus and Systemic Lupus Erythematosus with Antiphospholipid Syndrome"*** is the bonafide record work done by ***Dr.J.R.S.VIJAYBABU SATHISHKUMAR,*** under our guidance and supervision in the Department of Rheumatology, Government General Hospital, Madras Medical College, Chennai, submitted as partial fulfilment for the requirements of D.M. Degree examination Branch IX, RHEUMATOLOGY AUGUST 2010, under The Dr.M.G.R. Medical University, Chennai.

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INTRODUCTION

OCULAR MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS AND SYSTEMIC LUPUS ERYTHEMATOSUS WITH ANTIPHOSPHOLIPID SYNDROME

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, relapsing and remitting, autoimmune disorder. The clinical presentations are diverse and depend on the organ systems involved. Potentially life-threatening complications may occur. A pathologic immune response involving the production of autoantibodies and immune complex mediated tissue damage is thought to play a central role in the disease process . Genetic, environmental, and possibly hormonal influences may also be contributing factors.

Women with SLE outnumber men by 9 : 1 and the peak age of onset ranges from the late teens to the fourth decade of life. Individuals of African or Asian descent appear to be at greatest risk for developing the condition. Systemic treatment options generally include antimalarial drugs, corticosteroids, and other immunosuppressive agents. A variety of newer targeted treatment modalities are under development.

The ophthalmic manifestations of systemic lupus erythematosus (SLE) are protean. They range from lesions of the eyelid and secondary Sjogren's syndrome to sight-threatening disorders such as retinal vascular disease and neuro-ophthalmic involvement. Retinal vascular disease can present as cotton wool spots, intraretinal haemorrhages or retinal vaso-occlusive disease with poor visual outcome. Severe retinal vaso-occlusive disease is reported to be significantly associated with central nervous system involvement. Visual loss from neuro-ophthalmic involvement is often due to lupus optic neuropathy. Other neuro-ophthalmic manifestations include cranial nerve palsies secondary to lupus microangiopathy and retrochiasmal disorders of vision. Choroidopathy is an

uncommon cause of visual loss but cases have been documented in which there was serous elevation of the retinal pigment epithelium and sensory retina. Decreased perfusion of the choroid has also been demonstrated in some patients with SLE.

Drugs used in the treatment of SLE can also affect the eyes. The mainstay of treatment of SLE is oral corticosteroids. Well-known complications of corticosteroid therapy include posterior subcapsular cataract formation and glaucoma.

Dysfunction in immune regulation plays the principal role in the pathogenesis of SLE. Hyperreactivity of B-cells, producing a spectrum of autoantibodies, is primarily responsive for the immune dysregulation, although T-cells are involved in the pathogenesis as well. The tissue injury is caused by immune complexes, deposition of which induces cell infiltration and damage to the tissue by proteolytic and collagenolytic enzymes.

Histopathology of affected tissue reveals vasculitis with fibrinoid necrosis and deposition of immunoglobulin and complement in small vessels and capillaries. Renal involvement begins with deposition of immune complexes in the glomeruli. Mesangial proliferation, glomerular necrosis, hyaline thrombus formation, and interstitial damage determine the severity of kidney disease.

In the eye, immune complex deposits in the vascular endothelium of the conjunctiva, sclera, choroid, ciliary body and retina alter the tissue structure and compromise function. Deposits can also develop in the basement membrane of the ciliary body, cornea and along the peripheral nerves of the ciliary body and conjunctiva.

While most patients with retinopathy have systemic disease, retinopathy can also occur independently of systemic flare-ups. SLE patients with retinopathy have a higher morbidity risk.

Unfortunately , ocular involvement is neglected in the classification criteria for SLE. Therefore a patient with arthritis, leukopenia, renal failure, and ocular involvement, as in the above reported patient, is not diagnosed with SLE. Consequently, appropriate treatment and monitoring is delayed and the generally poor prognosis of SLE becomes even worse in such cases.

This study was taken up to assess the frequency of eye changes among patients with SLE and SLE with antiphospholipid syndrome (APS).

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Autoimmune disorders affect approximately 5% of the population in the Western world and there are about 80 different autoimmune diseases[1]. An autoimmune disease is a condition in which injury to the organs or tissues is caused by autoreactive antibodies or cells. Systemic lupus erythematosus (SLE) is considered a prototypic human autoimmune disease, which manifests itself with a variety of fascinating clinical and immunological features.

Systemic lupus erythematosus (SLE) is a multisystem disease that is caused by antibody production and complement-fixing immune complex deposition that result in tissue damage.

EPIDEMIOLOGY:

Prevalence rates in SLE are estimated to be 51 per 100,000 in the United States.[2] The incidence of SLE has nearly tripled in the last 40 years, mainly as a result of improved diagnosis of mild disease.[3] Women are affected nine times more frequently than men. The disease seems to be more common in urban than rural areas. Of patients with SLE, 65% have disease onset between ages 16 and 55, 20% present before age 16, and 15% present after the age of 55.[4] Men with SLE tend to have less photosensitivity, more serositis, an older age at diagnosis, and a higher 1-year mortality compared with women.[5] SLE tends to be milder in the elderly with a lower incidence of malar rash, photosensitivity, purpura, alopecia, Raynaud's phenomenon, renal system involvement, and central nervous system (CNS) involvement, but a greater prevalence of serositis, pulmonary involvement, sicca symptoms, and musculoskeletal manifestations.[6]

CLASSIFICATION CRITERIA: Criteria for SLE classification were developed in 1971, revised in 1982, and revised again in 1997.[7]

The 1997 Revised Criteria for the Classification of Systemic Lupus Erythematosus (SLE)

Criterion	Definition
1. Malar rash	Fixed malar erythema, flat or raised
2. Discoid rash	Erythematous-raised patches with keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as an unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulcers, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a. Pleuritis (convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion)
	OR
	b. Pericarditis (documented by ECG, rub, or evidence of pericardial effusion)
7. Renal disorder	A .Persistent proteinuria(>0.5g/d or >3+)
	OR
	b. Cellular casts of any type
8. Neurologic disorder	a. Seizures (in the absence of other causes)
	OR
	b. Psychosis (in the absence of other causes)
9. Hematologic disorder	a. Hemolytic anaemia
	OR

	b. Leukopenia (<4,000/mL on two or more occasions)
	OR
	c. Lymphopenia (<1,500/mL on two or more occasions)
	OR
	d. Thrombocytopenia (<100,000/mL in the absence of offending drugs)
10. Immunologic disorder	a. Anti-double-stranded DNA
	OR
	b. Anti-Sm
	OR
	c. Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody (ANA) by immunofluorescence or an equivalent assay at any time and in the absence of drugs known to be associated with drug-induced lupus syndrome.

For identifying patients in clinical studies, a person shall be said to have SLE if any four or more of the 11 criteria are present, either serially or simultaneously, during any interval of observation.

From Hochberg MG. Updating the American College of Rheumatology revised criteria

for the classification of systemic lupus erythematosus (letter). *Arthritis Rheum* 1997;40:1725.

ACTIVITY AND DAMAGE INDICES:

SLE has a chronic course that is often complicated by exacerbations and flares of varying severity. Several validated global and organ-specific activity indices are widely used in the evaluation of SLE patients.[8] These include British Isles Lupus Assessment Group Scale, European Consensus Lupus Activity Measure (ECLAM), Lupus Activity Index, National Institutes of Health SLE Index Score, Systemic Lupus Activity Measure, and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). The Systemic Lupus International Collaborating Clinics/ACR damage index is a validated instrument specifically designed to ascertain damage in SLE.[9] The damage in SLE may be due to SLE itself or to drug therapy. The index records damage in 12 organs or systems. There is no index to measure damage caused by drugs in SLE at present.

CLINICAL FEATURES:

MUCOCUTANEOUS INVOLVEMENT:

Clearly, the cutaneous system is one of the most commonly affected, approaching 80% to 90%. The malar rash occurs in sun-exposed areas, such as nose and cheeks, and spares the nasolabial folds and below the nares. Discoid lupus lesions occur in these areas and also in the ears and scalp. Discoid lesions often heal with hypo- or hyperpigmentation. Subacute cutaneous lupus, which may be mistaken for a fungal rash, occurs as a psoriasiform type or an annular type. About half of patients with subcutaneous lupus have systemic lupus erythematosus. Livedo reticularis occurs with or without antiphospholipid antibodies. Nail fold capillary

changes can be seen. A rare lupus rash, bullous lupus, presents as blistering lesions. Lupus panniculitis (also called "lupus profundus") can heal with a cavitating appearance because of fat necrosis.

Cutaneous lesions in SLE can be classified as lupus specific and nonspecific . The lupus-specific lesions can be subclassified further as acute, subacute, and chronic lesions.[10]

The Gilliam Classification of Lupus Erythematosus (LE)-Associated Skin Lesions:

I. Histopathologically Specific (LE-Specific)

A. Acute cutaneous LE
    1. Localized
    2. Generalized
B. Subacute cutaneous LE
    1. Annular
    2. Papulosquamous
C. Chronic cutaneous LE
    1. Classical DLE
        a. Localized
        b. Generalized
    2. Hypertrophic (verrucous) DLE
    3. Lupus profundus (LE panniculitis)
    4. Mucosal LE
    5. LE tumidus

6. Chilblains LE (perniotic LE)

DLE, discoid lupus erythematosus; LE, lupus erythematosus.

Musculoskeletal:

Polyarthralgias and polyarthritis eventually occur in 90% of SLE patients. The arthritis is usually nonerosive, involving the small joints of the hands (proximal interphalangeal and metacarpophalangeal joints, but not distal interphalangeal joints) and wrists initially. If deformities occur, they are usually reversible ("Jaccoud arthropathy"), because they are due to tendon and ligament laxity, not to bone erosions. Myositis, or an overlap with dermatomyositis, is rarely found. As many as 30% of SLE patients have coexisting fibromyalgia, which is a noninflammatory chronic pain syndrome, presenting with symmetric tender points above and below the waist. Radiologic features in lupus hand arthritis include scapholunate dissociation, joint space narrowing, cystic change, and palmar/ulnar subluxation in the wrist. Tenosynovitis, tendon rupture, flexor tendon contracture, septic arthritis, subcutaneous nodules and periarticular calcification have all been reported in SLE patients.

Generalized myalgia and muscle tenderness are common. Inflammatory myositis involving the proximal muscles has been reported to occur in 5% to 11% of patients and may develop at any time during the course of the disease. The histologic features of myositis in SLE may be less striking than in idiopathic polymyositis. Histologic features include muscle atrophy, microtubular inclusions, and a mononuclear cell infiltrate. Fiber necrosis is an uncommon finding, but

immunoglobulin deposition is almost always present despite the rarity of concurrent inflammation.[11]

Avascular necrosis of bone is a major cause of significant morbidity and disability in patients with SLE. Symptomatic avascular necrosis occurs in 5% to 12% of SLE patients. Higher prevalences have been reported in series that used MRI for its detection. In SLE, factors that can induce ischemia leading to bone necrosis include Raynaud's phenomenon, vasculitis, fat emboli, corticosteroids, and antiphospholipid antibody syndrome (APS).

Renal:

The kidney is considered by many to be the signature organ affected by SLE. Renal involvement is a major cause of morbidity and hospital admissions in SLE patients and occurs in 40% to 70% of all patients. Generally, renal involvement tends to occur within the first 2 years of SLE with its frequency decreasing significantly after the first 5 years of disease. Initial categories of lupus nephritis were based on classification by the World Health Organization as assessed by histology and location of immune complexes[12]. Recently, this classification has been revised by the International Society of Nephrology and Renal Pathology Society (ISN/RPS)[13] .

WORLD HEALTH ORGANIZATION CLASSIFICATION OF LUPUS NEPHRITIS

CLASS	PATTERN	SITE OF IMMUNE COMPLEX DEPOSITION	CLINICAL CLUES[a]					
			Sediment	Proteinuria (24 h)	Serum creatinine	Blood pressure	Anti-dsdna	C3/C4
I	Normal	None	Bland	<200 mg	Normal	Normal	Absent	Normal
II	Mesangial	Mesangial only	RBC or bland	200–500 mg	Normal	Normal	Absent	Normal
III	Focal and segmental proliferative	Mesangial, subendothelial, ± subepithelial	RBC, WBC	500–3500 mg	Normal to mild elevation	Normal to elevated	Positive	Decreased
IV	Diffuse proliferative	Mesangial, subendothelial, ± subepithelial	RBC, WBC, RBC casts	1000–>3500 mg	Normal to dialysis-dependent	High	Positive to high titer	Decreased
V	Membranous	Mesangial, subepithelial	Bland	>3000 mg	Normal to mild elevation	Normal	Absent to modest titer	Normal

SOURCE: From Appel GB, Silva FG, Pirani CL (10), by permission of *Medicine*.
ABBREVIATIONS: RBC, red blood cells; WBC, white blood cells.
[a]These are only guidelines, and parameters may vary, substantiating the need for biopsy when precise diagnosis is required.

The most severe form of lupus nephritis is diffuse proliferative glomerulonephritis. There are subendothelial immune complex deposits. This disorder can rapidly lead to renal failure. Usually, the urinalysis shows proteinuria, hematuria, and if a first morning urine is obtained, red blood cell casts . Focal lupus nephritis (class III) is less severe, but occasional patients do progress to renal failure. In membranous lupus nephritis there are subepithelial immune complex deposits with concomitant mesangial deposits. Patients usually have nephrotic syndrome. Its course is more indolent, but there is eventual progression to renal insufficiency and failure. Nephrotic syndrome is not to be considered benign, because it causes hyperlipidemia and hypercoagulability.

NERVOUS SYSTEM INVOLVEMENT:

SLE affects the CNS and the peripheral nervous system. Approximately 40% of the NPSLE manifestations develop before the onset of SLE or at the time of diagnosis, and 63% develop within the first year after the diagnosis.[15]

Neuropsychiatric Syndromes in Systemic Lupus Erythematosus

Central Nervous System
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache (including migraine and benign intracranial hypertension)
Movement disorder (chorea)
Myelopathy
Seizure disorder
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis
Peripheral Nervous System
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
Autonomic disorder
Mononeuropathy, single/multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

Adapted from The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndrome. Arthritis Rheum 42:599, 1999.

Cardiopulmonary:

Pleuritic pain (sometimes with pleural effusions) and pericardial pain (with or without effusion) occur in SLE. Pleurisy is more common than pericarditis, but they can occur together. Rare cardiac manifestations include Libman-Sacks endocarditis with valvular vegetations, myocarditis, and coronary arteritis. Pulmonary hypertension can be primary or secondary to pulmonary emboli. Pulmonary hypertension in lupus is usually mild, but it can progress. Interstitial pneumonitis, both acute and chronic, may occur. Life-threatening pulmonary hemorrhage is an unusual finding.

Gastrointestinal:

Oesophageal dysmotility occurs in SLE, but is usually mild. Hepatomegaly and splenomegaly may occur, especially in children. Pancreatitis is a rare manifestation. Mesenteric vasculitis can lead to postprandial pain, abdominal pain, infarcts, and bowel perforation. Colitis and protein-losing enteropathy are extremely rare. A few SLE patients will have overlap with primary biliary cirrhosis or autoimmune hepatitis. About one-third of SLE patients have a mild elevation of liver function tests.

Constitutional:

Many SLE patients have low-grade fever (a few with temperatures higher than 39°C). Weight loss can occur, especially at presentation, but is rare. Lymphadenopathy can be found, usually small and symmetric. An acute fatigue can occur with lupus flares. Chronic fatigue is common, often as part of fibromyalgia, which occurs in as many as 30% of SLE patients.

Hematologic:

Anemia is very common in SLE but is multifactorial. The classic anaemia, a hemolytic anaemia with increased reticulocyte count, direct Coombs test, and low haptoglobin, is not the most common. Anemia of chronic disease is the most common finding. Anemia may also be due to iron deficiency, renal insufficiency or failure, or to sickle cell (or trait) and thalassemia. Leukopenia is common but usually mild. It is rare for the white blood cell count to be below 1000/L. Lymphopenia is frequent (glucocorticoids also cause lymphopenia). Neutropenia can occur but is rare. Mild or profound thrombocytopenia can occur. Antiphospholipid antibodies are also associated with thrombocytopenia. The partial thromboplastin time may be prolonged due to a lupus anticoagulant. The erythrocyte sedimentation rate or C-reactive protein level may be elevated. The erythrocyte sedimentation rate and C-reactive protein do not correlate with or predict clinical disease activity.

Lymphadenopathy occurs in approximately 40% of patients usually at the onset of disease or during disease flares. The nodes are typically soft, nontender, and discrete, and usually are detected in the cervical, axillary, and inguinal area. Biopsy specimens reveal areas of follicular hyperplasia and necrosis.[16] The appearance of hematoxylin bodies is highly suggestive of SLE, but is uncommon.

Splenomegaly occurs in 10% to 45% of patients, particularly during active disease, and is not associated with cytopenias. Periarterial fibrosis, or “onionskin” lesions, in the spleen has been considered pathognomonic of SLE and is thought to represent healed vasculitis. Splenic atrophy and functional hyposplenism also have been reported in SLE and may predispose to severe septic complications.[17]

Laboratory Findings in Systemic Lupus Erythematosus:

Test	**Typical**	**Unusual**
Hematologic	Anemia of chronic disease	Neutropenia
	Hemolytic anaemia with elevated reticulocyte count	
	Leukopenia	
	Thrombocytopenia	
	Elevated erythrocyte sedimentation rate or C-reactive protein	
	Prolonged partial thromboplastin time, DR VVT, or other tests for lupus anticoagulant	
Comprehensive metabolic panel	Elevated blood urea nitrogen or creatinine	Elevated liver function tests
Other chemistry	Elevated creatine kinase or aldolase	
	Elevated homocysteine	
	Elevated cholesterol	
Urinalysis	Proteinuria	
	Red blood cells or red blood cell casts	

Imaging Studies:

Magnetic resonance imaging of the brain is preferred over computed tomography in the evaluation of central nervous system lupus. The most common finding is small white matter lesions, which may represent immune complex deposition. Cerebral atrophy can also occur.

Magnetic resonance imaging of the hip is the best way to find osteonecrosis at an early stage, when it may be ameliorated by core decompression. Bone scan can detect subclinical involvement of other sites.

Special Tests:

Autoantibodies:

Most (96% or more) SLE patients have a positive antinuclear antibody (ANA) test result. Because up to 20% of healthy young women also have a positive ANA, the presence of an ANA alone is not given much weight. Titers of 1:640 or higher are more indicative of a connective tissue disease of some sort. Some autoantibodies are very specific for lupus, such as anti-dsDNA (which occurs in about 30%) or anti-Sm (this is an abbreviation for Smith, not smooth muscle). Other autoantibodies, such as anti-Ro/SS-A, anti-La/SS-B, and anti-ribonucleoprotein, occur in SLE but also in rheumatoid arthritis and in Sjogren syndrome. Antiphospholipid antibodies are found in 10% to 40% of SLE patients during the course of disease. They are associated with an increased risk of thrombosis and pregnancy loss. A recently identified autoantibody, anti-SR, has received Food and Drug Administration approval for testing in SLE.

AUTOANTIBODIES AND CLINICAL FEATURES

ANTIBODIES	FREQUENCY	CLINICAL ASSOCIATIONS	RELATIONSHIP TO DISEASE ACTIVITY
ANA	> 90%	Nonspecific	For diagnostic purposes only
Anti-dsDNA	40%–60%	Nephritis	May predict disease flare and associates with flare
Anti-RNP	30%–40%	Raynaud's, musculoskeletal	Does not track disease
Antiribosomal P	10%–20%	Diffuse CNS, psychosis, major depression	Does not track disease
Anti-SSA/Ro	30%–45%	Dry eyes and mouth, SCLE, neonatal lupus, photosensitivity	Does not track disease
Anti-SSB/La	10%–15%	Dry eyes and mouth, SCLE, neonatal lupus, photosensitivity	Does not track disease
Antiphospholipid	30%	Clotting diathesis	Varied

Complement:

Reduction in the complement components C3 and C4 or in total hemolytic complement occurs frequently, but is not specific for lupus.

Special Examination:

A skin biopsy with immunofluorescence is helpful in the diagnosis of SLE cutaneous lesions.

In patients with nephritis, a renal biopsy can determine the ISN subtype (mesangial, focal proliferative, diffuse proliferative, or membranous) and give information on both activity and chronicity (damage).

In patients with neuropathy, a nerve conduction study and biopsy may be necessary to document vasculitis. An electromyelogram and muscle biopsy may be needed in the evaluation of myositis.

REVIEW OF OCULAR MANIFESTATIONS IN SLE

SLE can affect the eye, optic nerve, other areas in the central nervous system (CNS), and ocular adnexa. Severe vision loss is often the result of vaso-occlusive insults to the retina or optic nerve. Ocular manifestations occur in approximately 15% of patients with SLE. Children with SLE may have a higher risk (~35%) of ocular manifestations. Ophthalmic problems may be an important part of overall disease activity, and are thus featured in the latest version of the British Isles Lupus Assessment Group index of disease activity (BILAG 2004)[18].

ANTERIOR SEGMENT MANIFESTATIONS	POSTERIOR & NEURO MANIFESTATIONS
Keratoconjunctivitis Sicca (KCS)	Vascular complications/retinopathy
Uveitis	Vein Occlusions
Generalized orbital inflammation	Non-specific Retinopathy
Acute proptosis	Neuro-ophthalmic complications
Lid edema	Retrobulbar optic neuritis (RON)
Limited ocular motility	Anterior ischemic optic neuropathy
Episcleritis/scleritis	Acute papillitis

PATHOPHYSIOLOGY OF OCULAR DISEASE:

SLE may cause ocular disease by a number of mechanisms including immune complex deposition and other antibody related mechanisms, vasculitis and thrombosis. Immune complex deposition has been identified in blood vessels of the conjunctiva, retina, choroid, sclera, ciliary body, in the basement

membranes of the ciliary body and cornea, in the peripheral nerves of the ciliary body and conjunctiva [19]. Antibody dependent cytotoxicity may cause retinal cell death and demyelination of the optic nerve. Pathogenic circulating antibodies include anti-phospholipid antibodies (APA) and antineuronal antibodies. Similar mechanisms centred on the lacrimal gland may result in secondary Sjogren's syndrome with consequent dry eyes (keratoconjunctivitis sicca) due to inadequate tear production; this is in marked contrast to most cases of dry eyes in the general population where it is primarily a problem of disturbance of the lipid layer of the tear film resulting in increased tear evaporation.

PRESENTATION OF OPHTHALMIC DISEASE:

Ocular manifestations in SLE are fairly common, potentially sight threatening and may be the presenting feature of their disease[20]. SLE may affect almost any part of the eye and visual pathway. Additionally drugs used in the treatment of SLE may cause ocular problems such as cataract or retinopathy. The patient will usually be aware that there is an 'eye problem', and will report it to their rheumatologist (or General Practitioner). It is therefore important that the implications of these symptoms are recognized and appropriate help is sought. In general terms, pain (often accompanied by visible inflammation or redness) usually indicates significant external/anterior segment disease, whereas problems with vision (blurring, distortion, double vision usually indicates posterior segment/neuro-ophthalmic disease. All such complaints warrant urgent referral to an ophthalmologist for more detailed assessment.

CAUSES OF RED EYE IN SLE

Common	Dry eye (kerato-conjunctivitis sicca)
Less common	Episcleritis Scleritis Conjunctivitis (non-infective)
Rare	Keratitis (other than kerato-conjunctivitis sicca) Anterior uveitis

CAUSES OF LOSS OF VISION IN SLE:

Anterior segment	Severe kerato-conjunctivitis sicca
Lens	Cataract (secondary to inflammation and/or corticosteroids)
Vitreous	Vitreous haemorrhage (secondary to proliferative retinopathy)
Retina	Severe vaso-occlusive retinopathy Central retinal vein occlusion (CRVO) Branch retinal vein occlusion (BRVO) Central retinal arteriole occlusion (CRAO) Branch retinal arteriole occlusion (BRAO) Exudative retinal detachment Toxic maculopathy (secondary to anti-malarial treatment)
Choroid	Lupus choroidopathy Choroidal effusion Choroidal infarction Choroidal neovascular membranes
Neuro-ophthalmic	Optic neuritis Anterior ischaemic optic neuropathy Posterior ischaemic optic neuropathy Optic chiasmopathy Cortical infarcts

Keratoconjunctivitis sicca, or dry eye, is a common ocular manifestation of SLE[21] . Secondary Sjogren's syndrome is also associated with the disease[22] . In a study by Jensen et al. [23] 60% of 20 patients with SLE reported at least one symptom of dry eye. Typical findings on ophthalmic examination include corneal epitheliopathy, abnormal tear film, and decreased tear production. More

significant manifestations such as filamentary keratitis, corneal scarring, or ulceration can occur. Typical treatment options include lubricating drops and ointments, punctual occlusion, and topical cyclosporine drops. Other corneal manifestations of SLE, including peripheral ulcerative keratitis, interstitial keratitis, and keratoendotheliitis with corneal edema, are uncommon[24] .

The retina is a common site of ocular involvement in patients with lupus. The proportion of patients with SLE who manifest retinal involvement varies depending on the population studied and ranges from 3% in well controlled patients to 29% in patients with more active systemic disease[25-30] . Retinal vascular changes are a significant ophthalmic finding, as they appear to correlate to the degree of systemic disease activity[27] . In one prospective study by Stafford-Brady et al.[26] , 88% of patients with retinopathy had active systemic disease, and 73% had active CNS involvement. Furthermore, these authors showed that patients with retinopathy had a lower overall rate of survival during their follow-up interval as compared with individuals without retinopathy. The retinal microangiopathy associated with SLE is thought to result from immune complex-mediated vascular injury and microvascular thrombosis. Antiphospholipid antibodies may play a critical role in some patients. In a study by Montehermoso et al. [25] antiphospholipid antibodies were found in 77% of patients with lupus related retinal or optic nerve disease, compared with only 29% of SLE patients without such ocular involvement. Retinal findings most commonly associated with lupus are cotton wool spots and intraretinal hemorrhages[31] .

Other retinal manifestations may include microaneurysms, vascular tortuosity, arteriolar narrowing, retinal edema, or exudates[28-30] . Fluorescein angiography may be helpful in patient evaluation[30] . Most patients with mild retinopathy are at low risk for vision loss[26,30].

In contrast, severe vaso-occlusive retinopathy is a rare but well described entity that is associated with widespread retinal capillary nonperfusion, multiple branch retinal artery occlusions, ocular neovascularization, vitreous hemorrhage, and significant resultant visual loss[32,33] . A study by Jabs et al.[31] showed that 55% of eyes with severe retinal vaso-occlusive disease suffered vision loss, often to a visual acuity of worse than 20/200. The authors also found that CNS involvement by lupus was a frequent association in patients with such marked retinal vascular changes. Central retinal vein or artery occlusions can also occur, either independently or together, and may be unilateral or bilateral[34].

Systemic immunosuppression with corticosteroids and steroid-sparing agents are the primary treatment modalities for patients with significant retinal disease. Intravenous corticosteroid pulse therapy may be needed in acute settings to control severe retinal involvement. Patients with significant vaso-occlusive disease or antiphospholipid antibodies may benefit from treatment with antiplatelet agents such as aspirin or through anticoagulation with warfarin[32] . Plasmapheresis has been used together with immunosuppressive agents in managing patients with severe retinal vasculitis . Panretinal photocoagulation and vitrectomy surgery should be used as appropriate to control neovascularization and vitreous hemorrhage in order to limit further vision loss and other complications of ocular ischemia.

Choroidopathy, uveal effusions, and serous retinal detachment may occasionally occur in patients with SLE[35]. Significant uveal effusions may also lead to secondary angle-closure glaucoma[36]. Nguyen et al.[35] reported on a total of 28 patients with lupus choroidopathy, all of whom had active systemic vascular disease. Choroidopathy resolved in 82% of patients once systemic control of the disease was achieved.

SLE can have many neuroophthalmic manifestations. Optic nerve involvement occurs in approximately 1% of patients with SLE[37]. Optic neuritis and neuropathy can potentially lead to severe loss of vision[38-39]. Optic neuritis may occur together with transverse myelitis in patients with SLE, thus raising clinical suspicion for demyelinating diseases such as multiple sclerosis[39] . Ischemic optic neuropathy[40] and chiasmopathy[41] have also been described. Optic nerve dysfunction can be the initial manifestation of systemic disease in some patients. Patients may present with painless vision loss, impaired colour vision, visual field defects, pupillary abnormalities, and may have optic disc edema or pallor on examination.

Lin et al.[42] described eight patients with SLE-associated optic neuritis. Eighty-seven percent of these patients had visual acuities worse than 20/200 at onset, and final visual outcomes were highly variable despite corticosteroid pulse therapy followed by a tapering oral corticosteroid course. The authors emphasize the importance of differentiating SLE-associated optic neuritis from idiopathic optic neuritis. Patients with SLE may experience severe visual impairment with long-term dependence on immunosuppressive therapy. Treatment options for optic nerve disease include systemic corticosteroids and immunosuppressives such as cyclophosphamide and methotrexate[41]. Other neuro-ophthalmic manifestations are less common. Eye movement abnormalities[43] , intranuclear ophthalmoplegia[44] , and retrochiasmal involvement[45] leading to visual hallucinations and vision loss have been described.

Episcleritis, scleritis, and conjunctivitis have been reported in association with SLE[46]. Scleritis, in particular, can cause significant ocular morbidity and can be associated with active systemic disease. Pathologic studies

using immunohistochemical stains in conjunctival biopsy specimens have implicated an underlying immune-complex mechanism[47].

Lupus may affect the ocular adnexal structures as well. Cutaneous involvement may lead to a discoid-type, scaly rash on the eyelids[48]. The clinical picture may resemble chronic blepharitis or eczema[49]. Lupus should be considered in the differential diagnosis of chronic blepharitis that fails to respond to traditional treatment measures and skin biopsy can be performed to confirm the diagnosis. Immunohistochemical stains typically demonstrate immunoglobulin deposition at the dermoepidermal junction[48]. Mistaken diagnosis may lead to eyelid margin deformities and may delay the diagnosis of systemic lupus[50]. Cutaneous involvement from SLE typically responds well to systemic hydroxychloroquine[48,49]. Protection from excessive sunlight should be emphasized. Local corticosteroids, including intralesional triamcinolone in some cases, may be of benefit as well[51].

Orbital disease is a rare presentation of SLE. Orbital inflammation, infarction, myositis, panniculitis, proptosis, and periorbital edema have been described[52]. A tissue biopsy and systemic evaluation may be necessary to confirm the diagnosis and to exclude other diseases such as thyroid-related orbitopathy, other inflammatory conditions, infection, and neoplastic processes.

OPHTHALMIC DISEASE AND THE ROLE OF ANTI-PHOSPHOLIPID ANTIBODIES:

The presence of APA is associated with vaso-occlusive disease (both retinal and CNS) in SLE[53]. Interestingly retinal vascular occlusions and even a similar retinopathy may also be seen in primary anti-phospholipid syndrome. In general, the presence of APA is linked to focal thrombotic events that may prompt the use of anti-coagulation or low dose aspirin in addition to immunosuppression.

OPHTHALMIC DISEASE IN DRUG INDUCED LUPUS:

Ocular complications are rare in drug-induced lupus, although retinal vasculitis and occlusive disease have been reported in hydralazine and procainamide induced lupus syndrome.

OPHTHALMIC DISEASE AS A SIDE-EFFECT OF TREATMENT:

Ophthalmic side effects and disease can also result from the medications used to treat SLE. Both topical and systemic corticosteroids may accelerate cataract formation and may cause steroid-induced glaucoma. Central serous retinopathy is also associated with corticosteroid use. Other immunosuppressive agents are usually more costly, have their own side-effects and need careful monitoring. Overwhelming septic cavernous sinus thrombosis has been reported after a combination of high dose steroid and intravenous cyclophosphamide therapy for lupus nephritis[54].

The aminoquinolones, chloroquine and, to a lesser extent, hydroxychloroquine can cause reversible visually insignificant changes in the cornea (vortex keratopathy) and, more importantly, an irreversible sight-threatening maculopathy. Initial changes are subtle (loss of foveal reflex and a fine granular appearance) and often asymptomatic, but can progress to a 'bull's eye' maculopathy and even generalized atrophy of the retina and optic nerve[55]. This retinopathy may continue to progress despite cessation of the drug. Although both drugs can cause identical changes the risks are much lower with hydroxychloroquine, particularly at recommended doses of up to 6.5 mg/kg/day[56,57]. Below this level, hydroxychloroquine, toxicity is extremely rare. One prospective cohort study of 400 patients receiving long-term hydroxycholoroquine of up to 6.5 mg/kg/day found only two patients to be affected, in both cases only after 6 yrs of treatment[58]. Indeed Lee[59] estimated that at these recommended levels there have been only 20 affected

cases in over a million patients receiving the drug; all 20 cases had been taking the drug for over 5 yrs.

In the UK, the Royal College of Ophthalmologists have advised that the prescribing rheumatologist should carry out the baseline assessment of lean body weight (if overweight), renal and liver function, asking about any visual impairment which is not corrected by glasses and testing reading vision[56]. Any apparent visual impairment or eye disease should be first confirmed by an optometrist, and then referred on to the local ophthalmologist before starting treatment. If visual problems occur once treatment has started, patients should be advised to stop treatment, attend their optometrist and seek advice from the prescribing physician who would refer on to the ophthalmologist. Annual evaluation should be by the prescribing rheumatologist and includes enquiry about visual symptoms and measuring reading acuity[56]. In the USA, screening by an ophthalmologist is recommended for those patients on hydroxychloroquine who are at higher risk: dose >6.5 mg/kg/day, duration of treatment >5 yrs, renal or hepatic disease, pre-existing retinal disease or age >60 yrs[57]. Chloroquine has a less clear safety profile and should be avoided where possible. All patients taking chloroquine should have regular ophthalmic examination according to locally arranged protocol.

Chloroquine and hydroxychloroquine are well known to cause sight-threatening macular disease, leading to decreased vision, abnormal colour vision, reproducible and permanent visual field defects[60,61]. Corneal verticillata is a common finding in patients taking chloroquine, but this rarely affects vision[62].

Thus SLE may have many ocular manifestations. A high clinical suspicion for lupus should be maintained as ocular involvement may be the initial presentation of systemic disease and may parallel overall disease activity.

Significant ocular morbidity and vision loss may occur, and close monitoring and appropriate local and systemic treatments are necessary. As our knowledge of the underlying immunologic mechanisms of SLE improves, newer biologic agents may play an increasingly important therapeutic role. Collaboration with primary care providers and other medical subspecialists may be necessary to best manage the disease.

AIM

AIM

The aim of the work was to assess

1] the frequency of eye changes among patients with SLE,

2] the association between anti-phospholipid antibodies and ocular lesions,

3] the correlation of the ocular manifestations with disease activity,

4] the relationship between the presence of circulating autoantibodies and eye changes.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DESIGN: Prospective study

STUDY CENTRE: Department of Rheumatology,
Madras Medical College& Government General Hospital,
Chennai -3.

STUDY PERIOD: March - 2009 to March – 2010

STUDY POPULATION: Consecutive cases of lupus patients who are attending the Department of Rheumatology, GGH Chennai.

STUDY SAMPLE: 110 patients.

INCLUSION CRITERIA:

1] Patients who satisfied the 1997 Revised Criteria for the Classification of Systemic Lupus Erythematosus (SLE)

2]AGE: All age group

3]SEX: Both genders

EXCLUSION CRITERIA:

1] Patients who do not satisfy the 1997 Revised Criteria for the Classification of Systemic Lupus Erythematosus (SLE)

2] Patients with overlap syndrome

STUDY PROCEDURE:

ETHICAL CONSIDERATION:

The study was commenced after obtaining approval from the Institutional Ethical Committee. Patients with SLE attending Rheumatology OPD or got admitted in Rheumatology ward , Government General Hospital were included in this study and were explained about the purpose of the study. Written informed

consent was obtained from those who were willing to participate in the study in the prescribed format in regional language. Left thumb impression was obtained from those patients who are illiterates.

SCREENING:

Apart from age and sex, detailed medical history including mode of onset, duration of illness, constitutional, mucocutaneous, musculoskeletal and symptoms pertaining to the ocular involvement i.e. dry eyes, red eyes, swelling over eye lids, decreased visual acuity, floaters, ocular pain, headaches, itching, flashes, watering, double vision (diplopia) and relevant history of other organ involvement was obtained. History of recurrent abortion if relevant, venous or arterial thrombosis were noted. All patients were questioned for hypertension, diabetes, CAHD and pulmonary tuberculosis. Alcohol and smoking habits were also enquired. Detailed clinical examination was done in all patients.

Laboratory investigations including complete blood count, urine analysis, blood sugar, urea, creatinine, serum electrolytes, liver function tests, muscle enzyme analysis and fasting lipid profile were done for all patients.

IMMUNOLOGICAL INVESTIGATIONS:

C-reactive protein was done by latex agglutination method, ANA by either ELISA [Cal Biotech] or indirect immunofluorescence method, Anti-ds DNA by ELISA [Warpole lab] or *Crithidia* test and aCL IgG and IgM by ELISA method were done in all patients.

PRINCIPLE:

Microwells are pre-coated with purified antigen/antigens. The pre-diluted controls, together with diluted patient samples are added to the wells, autoantobodies recognizing one or a combination of antigens bind during the first

incubation. After washing the wells to remove all unbound proteins, peroxidase labelled rabbit anti-human IgG conjugate is added. The conjugate binds to the captured human autoantibody and the excess unbound conjugate is removed by a further wash step. The bound conjugate is visualised with 3,3',5,5' tetramethylbenzidine(TMB) substrate which gives a blue reaction product, the intensity of which is proportional to the concentration of autoantibody in the sample. Acid is added to each well to stop the reaction. This produces a yellow end point colour, which is read at 450nm by using ELISA reader.

Cut-off value for ANA:

ANA result	Interpretation
≤0.90	Negative
0.91 to 1.09	Equivocal
≥1.10	Positive

Cut-off value for Anti-ds DNA:

Interpretation	
≤0.90	Negative
0.91 to 1.09	Equivocal
≥1.10	Positive

Interpretation of results for aCL IgG and IgM antibodies

aCL IgG		aCL IgM	
<10 GPL units/mL	Negative	<15 MPL units/mL	Negative
10 – 15 GPL units/mL	Borderline Positive	15 – 20 MPL units/mL	Borderline Positive
>15 – 80 GPL units/mL	Moderate Positive	>20 – 80 MPL units/mL	Moderate Positive
>80 GPL units/mL	High Positive	>80 MPL units/mL	High Positive

The complement levels were measured using Single Radial Immune Diffusion plates. The procedure consists of immunoprecipitation in agarose gel between an antigen and its homologous antibody. It is performed by incorporating the anti C3 and anti C4 antibodies uniformly throughout a layer of agarose gel and antigen is added into the wells duly punched in the gel. Antigen

diffuses radially out of the well into the surrounding gel and a visible ring of sharp precipitation forms where the antigen and antibody reacted in the zone of equivalence. A quantitative relationship does exist between ring diameters and complement concentration. The reference value for C3 is 80 – 160 mg/dl and for C4 is 20 – 40 mg/dl.

Lupus Anticoagulant Study including activated partial prothrombin time, dilute Russel Viper venom test and Kaolin clotting time were done.

OPHTHALMIC EVALUATION:

All the patients underwent detailed ophthalmic examination at Government Ophthalmic Hospital And Regional Institute Of Ophthalmology, Chennai. Each eye was assessed individually.

1] VISUAL ACUITY:

The assessment of distant and near visual acuity was done by asking the patient to cover one of the eyes with a cardboard or with the palm of his hand.

DISTANT VISUAL ACUITY:

Distant visual acuity was more accurately recorded with Snellen's chart. It is read at six metres, with the letters diminishing in size from above. The patient has normal vision if he is able to read the line of letters designated as 6/6 at or near the bottom of the chart. The scale for decreasing distant visual acuity is 6/9, 6/12 (industrial vision), 6/18, 6/24, 6/36 and 6/60 (legal blindness in some countries).

If the patient is unable to read the letters, he is asked to count the examiner's fingers which are held a metre away. If his answers are correct, he has distant visual acuity of "counting fingers" at a metre. If he is unable to count

the fingers, the examiner should move his hand in front of the patient's eyes. The visual acuity is then said to be "hand movement". If he can see only light, visual acuity is recorded as "perception of light". If he cannot see any light, visual acuity is recorded as "no perception of light" which is total blindness.

NEAR VISUAL ACUITY:

The common near visual acuity tests used are the Jaegar test and the 'N' chart, usually read at a distance of 30 cm. The Jaegar test is recorded as J1, J2, J4, J6, etc., and the 'N' chart as N5, N6, N8, N10, etc. Standard small newsprint is approximately J4 or N6. Each eye is tested in turn with the other covered. Middle-aged patients (presbyopic age) were tested with their reading glasses.

2] VISUAL FIELDS:

The visual fields can be recorded approximately by using the confrontation test. The patient covers the eye which is not being tested with his palm and fixes the other at the examiner's nose, ear or eye. A target is then brought into his field of vision from the side and the point at which the patient sees the object is noted. The eye is tested in the different meridians, usually 8.

EXTERNAL EYE EXAMINATION:

This is done with good illumination from either a window or a bright torch. A magnifying glass facilitates examination and should be used whenever available. Common problems screened include drooping of the upper eyelid (ptosis), lid retraction, inability to close the lids (lagophthalmos), eversion of the lid margins (ectropion) and inversion of lid margins (entropion). Detailed examination of the eye lids, conjunctiva, cornea, iris, pupils, anterior chamber and lens were done.

PUPIL RESPONSE:

The response of light directed at one pupil in a darkened room is known as the direct pupillary response. The reaction of light by the fellow pupil is called the consensual pupillary response. If there is no pupillary reaction to light, the reaction to accommodation is tested by asking the patient to fix his eyes on an object at a distance and then to focus on another object at about 10 cm away from him.

EXTRAOCULAR MUSCLES:

The extraocular muscles are examined by observing the position of the eyeballs with the patient looking straight ahead. One eye may be observed to be turned inwards (convergent squint) or outwards (divergent squint). Occasionally, one of the eyes may be seen to be higher than the other (vertical squint).

OCULAR MOVEMENTS:

When the extraocular muscles are severely paralysed, the restriction in movement is tested by asking the patient to look in 7 different directions (positions of gaze).

Movement	Right Eye	Left Eye
Right	Right lateral rectus	Left medial rectus
Up and right	Right superior rectus	Left inferior oblique
Down and right	Right inferior rectus	Left superior oblique
Left	Right medial rectus	Left lateral rectus
Up and left	Right inferior oblique	Left superior rectus
Down and left	Right superior oblique	Left inferior rectus

The six cardinal positions of gaze and their corresponding primary extraocular muscle actions.

OPHTHALMOSCOPY:

The ophthalmoscope is used to observe abnormality in the ocular media, optic disc, retinal vessels, fundal background and the macula.

RED REFLEX:

With the lens power of the ophthalmoscope turned to 0 and the ophthalmoscope held one metre away from the patient's eye a red reflex is seen through the pupil. Alternatively the lens power can be turned to about +5 dioptres and the eye examined approximately 10 cm away. This is caused by the reflection of the light of the ophthalmoscope from the choroidal vessels. It appears as a bright red round area which is evenly lighted. Any opacity in the cornea, lens (cataract) or vitreous will be seen as a dark area. In retinal detachment, the reflex appears grey instead of red.

FUNDUS:

Examination of the fundus is usually done with the direct ophthalmoscope. The refractive error in both the patient and examiner has to be compensated for by adjusting the lens power of the ophthalmoscope. Alternatively, the examiner and patient may use their glasses or contact lenses in which case no adjustment will be required. The patient is then instructed to look at a distant object. When the right fundus is examined, the ophthalmoscope is held in the right hand. The examiner uses his right eye to examine the patient's right eye approaching from the right side. The patient's left fundus is examined with the examiner's left eye and the patient is approached from the left. It is important to get near enough so that the examiner's forehead touches his own thumb which is used to lift the upper lid of the eye being examined.

It is best to approach the eye from the temporal side so that a good view of the disc can be seen before the pupil contracts when light is shone on the macula. The nasal retinal vessels and the temporal retinal vessels are examined before the macula. Because of the extreme sensitivity of the macula to light which results in rapid constriction of the pupil, examination of the macula is difficult and usually requires a mydriatic eyedrop to dilate the pupil.

BINOCULAR SLIT-LAMP MICROSCOPY:

The binocular slit-lamp microscope enables accurate observation of the eye up to a magnification of 40 times. It consists of two parts, an oblique light which can be adjusted to a slit and a binocular microscope. Other uses of the slit-lamp include examination of the retina with magnification from a Hruby or contact lens and checking the filtrating angle of glaucoma patients (gonioscopy).

TONOMETRY:

A tonometer is used to measure intraocular pressure. The most widely used tonometer is the Goldmann Applantation Tonometer. The Schiotz Indentation Tonometer is less accurate but it is portable. The new non-contact tonometers do not require local anaesthesia.

PERIMETRY AND SCOTOMETRY:

Perimetry gives a more exact record of the visual fields than the confrontation test. The ability of the patient to see a small 5 mm target on an arc moving into his view from the periphery at different meridians is recorded on to a chart. Scotometry is used to assess the central 30° part of the field of vision. It involves using a small 1–5 mm target on a screen (Bjerrum or Tangent screen) placed 1 or 2 metres away and noting when the test target appears. The normal blind spot is found 15° lateral to the fixation point.

TESTS FOR COLOUR VISION:

The Ishihara test is most commonly used for colour vision. It is very sensitive test. Lantern colour matches or Farnsworth Munsell 100 hue test are other tests for colour vision.

REFRACTION:

It can be objective with retinoscopy. Subjective tests are done with a trial frame and a set of lenses. Alternatively, the lenses may be mounted on a series of rotating discs (phoropter).

SCHIRMER'S TEST:

Schirmer's test is done to measure the quantity of tears produced by eyes. In Schirmer's test a 35 mm× 5mm Whatman filter paper is used to measure the amount of tears that is produced over a period of 5 minutes. The strip is placed at the junction of middle and lateral thirds of the lower eye lid. The test is done under ambient light. The patient is instructed to look forward and to blink normally during the course of the test.

Interpretation:

1. Normal which is =>15 mm wetting of the paper after 5 minutes.
2. Mild which is 14-9 mm wetting of the paper after 5 minutes.
3. Moderate which is 8-4 mm wetting of the paper after 5 minutes.
4. Severe which is <4 mm wetting of the paper after 5 minutes.

Ultrasonography, CT scan and Magnetic Resonance Imaging (MRI), Macular potential acuity, electrophysiology including electroretinography (ERG), electrooculography (EOG) and visual evoked response study (VER) were done if relevant.

Statistical analysis:

he statistical analysis was performed using the SPSS version 17.0. Results are presented as the mean±S.D., except for frequencies, which are expressed as percentages. Comparison between groups were made by means of 2-sample t-test, and Chi square test used when appropriate. P values less than 0.05 were considered significant.

RESULTS

RESULTS

The present study consisted of 110 SLE patients. There were 11 males and 99 females in the study group [Fig. 1]. The age of the patients varied from 9 years to 65 years [Fig. 2]. The mean age of the patients was 25.9±9.2 years. The mean duration of disease was 29±30.8 months with disease onset in the second or third decade being the commonest. 12[10.9%] patients had childhood onset of the disease [Fig. 3] with mean age being 13±2.13 years. The mean disease duration in childhood onset was 12.25±7.84 months.

TABLE 1

Cross tabulation: Disease duration Vs Ophthalmic manifestation

Disease duration	Ophthalmic status				Total
	Normal		Abnormal		
≤3 yrs	57	67.06%	28	32.94%	85
>3 yrs	13	52%	12	48%	25
Total	70		40		110

Chi squared equals 1.893 with 1 degree of freedom.

The two-tailed P value equals 0.1689. This implies that the ophthalmic involvement is independent of disease duration in SLE patients.

FIGURE 1

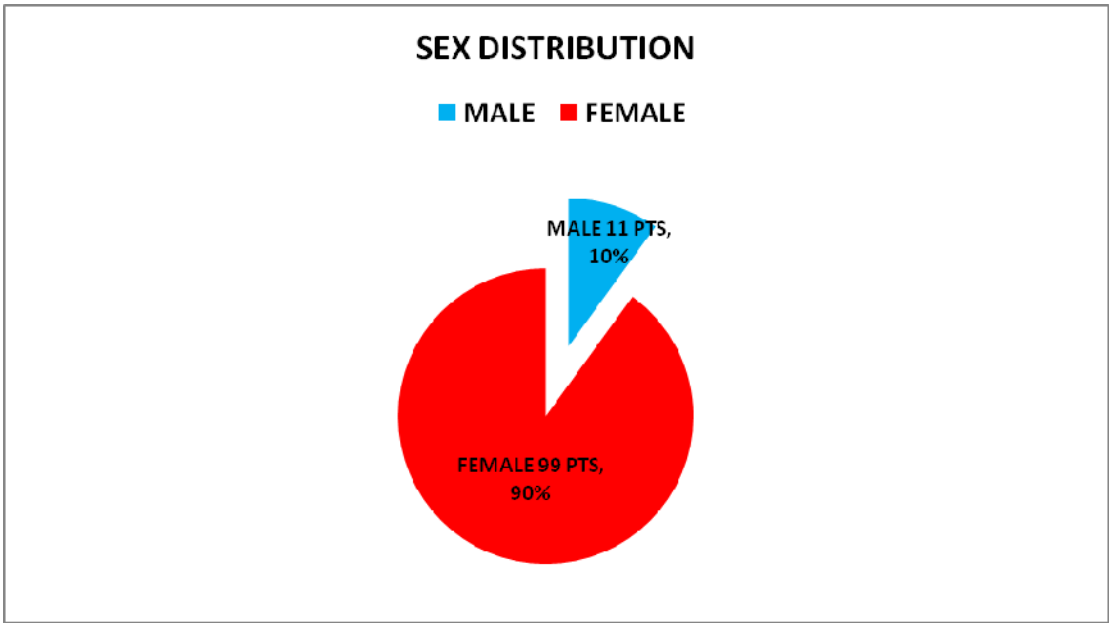


FIGURE 2

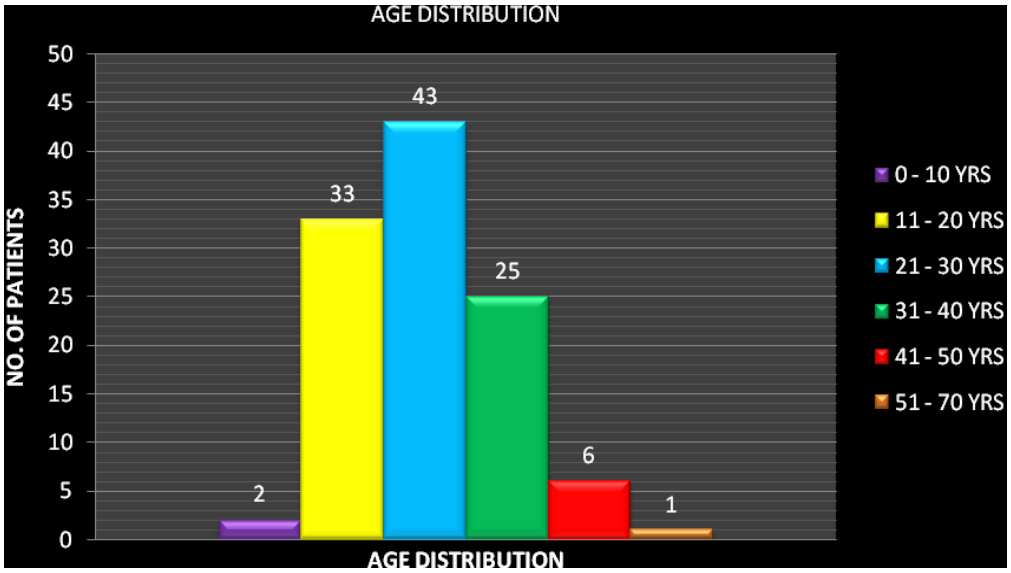


FIGURE 3

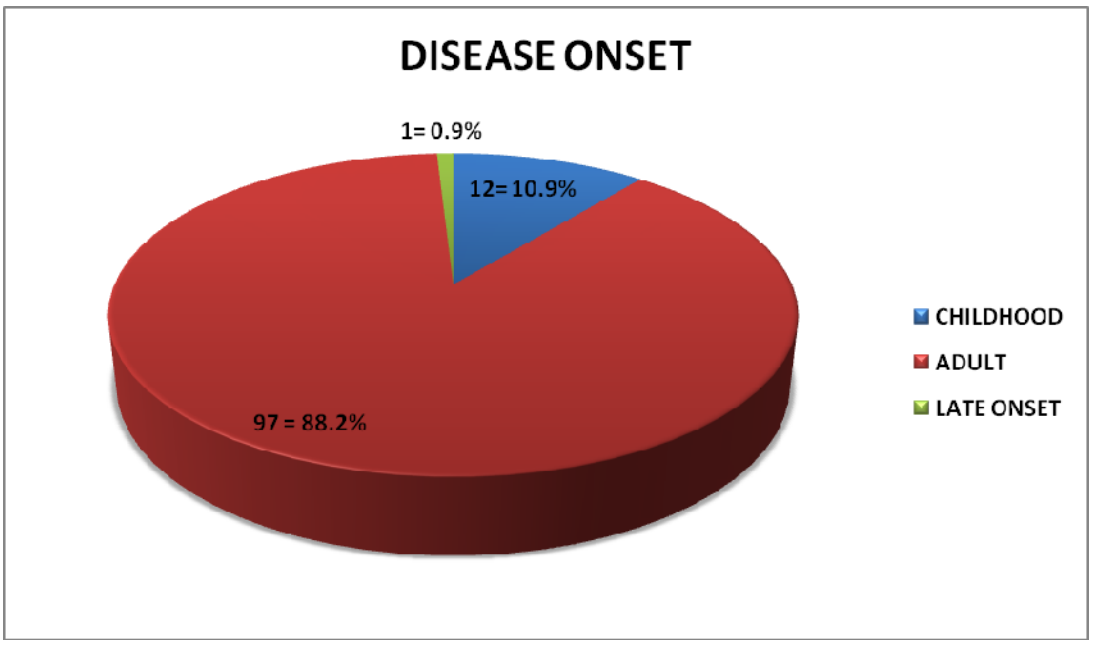
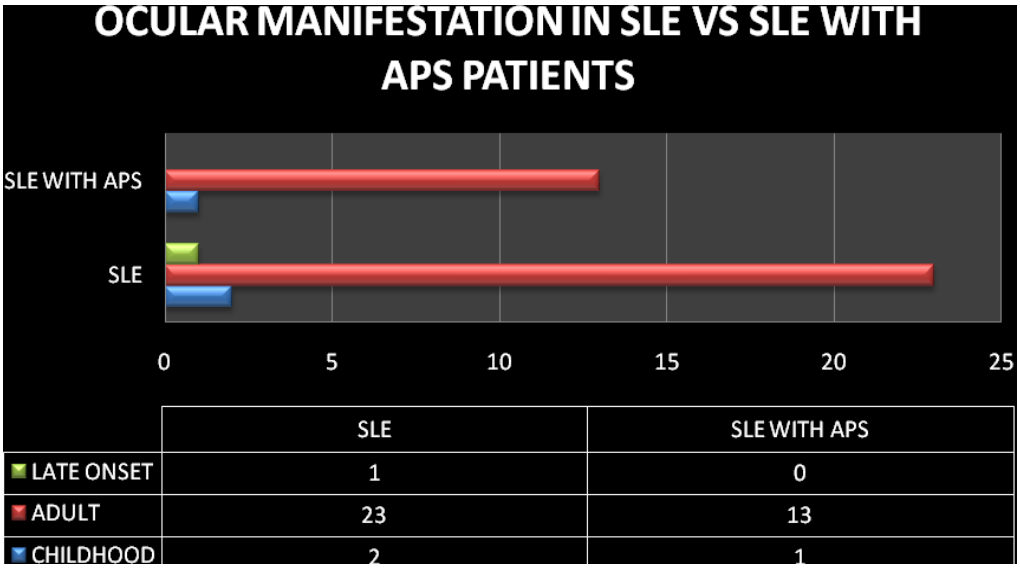


FIGURE 4



	SLE	SLE WITH APS
LATE ONSET	1	0
ADULT	23	13
CHILDHOOD	2	1

TABLE 2

SEX WISE DISTRIBUTION OF PATIENTS

Group	SLE		Childhood SLE		SLE with APS		cSLE with APS	
	Male	Female	Male	Female	Male	Female	Male	Female
Number	9	67	1	6	Nil	22	1	4
%	8.18%	60.9%	0.9%	5.45%	Nil	20%	0.9%	3.63%

Out of the 110 patients 23 patients[20.9%] had ocular complaints remaining 87 patients[79.1%] had no ocular symptoms. The common ocular complaints were blurring of vision – 12 patients[10.9%], dry eyes – 3 patients[2.7%], red eyes – 3 patients[2.7%], swelling over eye lid – 2 patients[1.8%] , itching, eye discharge and restriction of eye movements – each 1 patient[0.9%].Refractive error was seen in 11[10%] of patients.

Ocular abnormalities were seen in 40 patients [36.4%]. 70 patients [63.6%] had no ocular abnormalities. Among the 40 patients with ocular abnormality 14 patients [35%] were found to have associated APS. Among the 40 patients 36 patients [90%] were females, 1 patient[2.5%] was male and 3 patients[7.5%] had childhood onset of disease. The most common abnormalities were dry eyes [11.8%], retinal vasculitis[3.6%], posterior subcapsular cataract[3.6%] and cotton wool spots in fundus [2.7%]. The other ocular abnormalities found were post neuritic optic atrophy[0.9%], filamentary keratitis[0.9%], subconjunctival hemorrhage[1.8%], hypertensive retinopathy [1.8%], blepharitis [0.9%], macular edema [1.8%], meibonitis[0.9%], conjunctivitis[0.9%], retinal detachment[0.9%], complicated cataract[0.9%], fibrovascular proliferative uveitis[0.9%], anterior

uveitis[0.9%], CRAO[0.9%], chloroquine maculopathy[1.8%], hordeolum internum[0.9%], herpes zoster ophthalmicus[0.9%], dacryocystitis[0.9%], lateral rectus palsy[0.9%], multiple punctate erosion of cornea[0.9%] and cherry red spot[0.9%].

TABLE 3

OCULAR MANIFESTATIONS IN SLE AND SLE WITH APS PATIENTS

s.no	Ocular manifestation	SLE [N=83]	%	SLE WITH APS [N=27]	%	Total no. of patients [N=110]	%
1	Post neuritic optic atrophy			1	3.7%	1	0.9%
2	Dry eyes	9	10.8 %	4	14.8%	13	11.8 %
3	Filamentary keratitis	1	1.2%			1	0.9%
4	SCH	1	1.2%	1	3.7%	2	1.8%
5	Hypertensive retinopathy			2	7.4%	2	1.8%
6	Cotton wool spots	3	3.6 %			3	2.7%
7	Retinal vasculitis	3	3.6 %	1	3.7%	4	3.6%
8	Blepharitis	1	1.2%			1	0.9%
9	Macular edema	2	2.4 %			2	1.8%

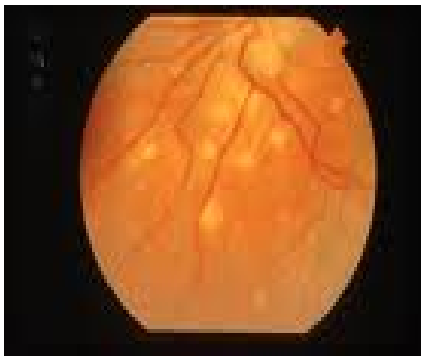
10	Meibonitis	1	1.2%			1	0.9%
11	Conjunctivitis	1	1.2%			1	0.9%
12	Retinal detachment			1	3.7%	1	0.9%
13	Complicated cataract			1	3.7%	1	0.9%
14	Fibrovascular proliferative panuveitis			1	3.7%	1	0.9%
15	Anterior uveitis	1	1.2%			1	0.9%
16	Posterior subcapsular cataract	2	2.4 %	2	7.4%	4	3.6%
17	CRAO	1	1.2%			1	0.9%
18	Chloroquine maculopathy	2	2.4 %			2	1.8%
19	Hordeolum internum	1	1.2%			1	0.9%
20	Herpes Zoster Ophthalmicus	1	1.2%			1	0.9%
21	Dacryocystitis	1	1.2%			1	0.9%
22	Lateral rectus palsy	1	1.2%			1	0.9%
23	Multiple Corneal erosion	1	1.2%			1	0.9%

24	Cherry red spots	1	1.2%			1	0.9%
25	Vitreous strands			1	3.7%	1	0.9%
26	Corneal opacity			1	3.7%	1	0.9%

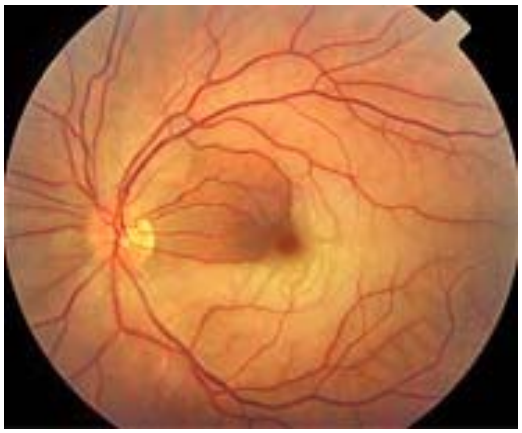
Only one patient had ocular manifestation as the first sign of SLE. One SLE patient with APS had CRAO. She was detected to have LAC and found to have aCL positivity. Another patient with optic atrophy had LAC and aCL positivity. One patient presented with features of Steven Johnson syndrome like picture and was found to have exudative retinal detachment of both eyes, complicated cataract of left eye and fibrovascular proliferative panuveitis of right eye with ANA and aCL positivity. Cystoid macular edema of both eyes was seen in one patient with SLE. No patient in our study had cavernous sinus thrombosis. 4 SLE patients with APS [14.8%] had dry eyes compared with 9 patients [10.8%] with SLE. 2 SLE patients with APS [7.4%] had hypertensive retinopathy.

Herpes zoster ophthalmicus

Retinal vasculitis



Central retinal artery occlusion



Chloroquine maculopathy

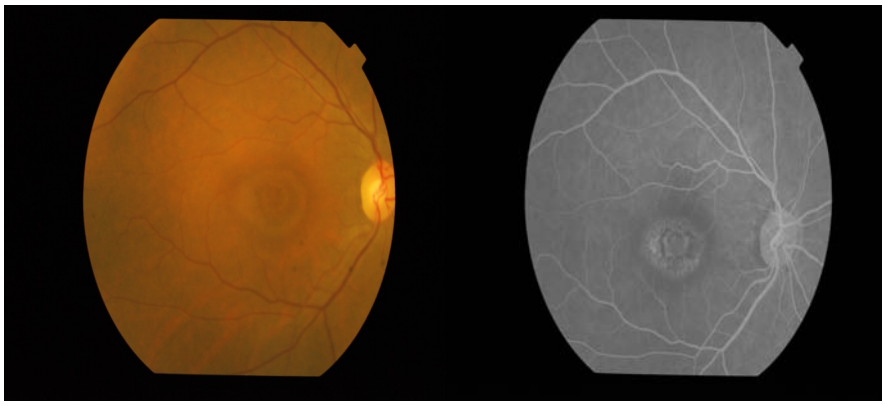


TABLE 4

COMPARISON OF DEMOGRAPHIC AND CLINICAL PARAMETERS-

OCULAR INVOLVEMENT VS WITHOUT OCULAR INVOLVEMENT

s.no	Parameters	SLE with ocular involvement [N=40]	%	SLE without ocular involvement [N=70]	%	T-Value	P-Value
1	Age in yrs [mean±SD]	27.38±10.52		25.07±8.35		1.2658	NS
2	M:F	1:39		10:60			
3	Duration of disease in months [mean±SD]	33.33±25.13		26.97±33.45		1.0442	NS
4	Recurrent abortions [no. of patients]	5	12.5 %	2	2.8 %	1.9930	0.0463
5	Gangrene/DVT	3	7.5%	4	5.7 %	0.3691	NS
6	Hypertension	9	22.5 %	11	15.7 %	0.8876	NS
7	Neurological manifestation[no. of patients]	10	25%	10	14.3 %	1.4015	NS

P significant < 0.05.

The analysis in the Tables 4 & 5 show that there exists no statistically significant difference between SLE patients with ocular involvement Vs without Ocular involvement in demographic, clinical and laboratory parameters except for recurrent abortions, thrombocytopenia, Anti-dsDNA positivity, aCL positivity, low complement levels and SLEDAI score which were significantly higher in the former group.

TABLE 5

Comparison of lab parameters - Ocular involvement Vs without ocular involvement

s.no	Parameter	SLE with ocular involvement [N=40]	%	SLE without ocular involvement [N=70]	%	T-value	P-value
1	Hb in gms [mean±S.D]	9.66±1.37		9.97±1.59		1.0329	NS
	Anaemia Hb<10gm [no. of patients]	20	50%	27	38.57%	1.1656	NS
2	Platelets in lakhs/cumm [mean±S.D]	1.73±0.69		1.75±0.63		0.1547	NS
	Thrombocytopenia < 1lakh/cumm [no. of patients]	0	0	9	12.85%	2.3667	0.0179
3	ESR in mm/hr [mean±S.D]	62.42±35.34		54.73±29.94		1.2126	NS
4	CRP positivity [no. of pts]	21	52.5%	39	55.7%	0.3257	NS
5	Anti – dsDNA [no. of pts]	28	70%	31	44.28%	2.6016	0.0093
6	aCL positivity [no. of pts]	14	35%	12	17.14%	2.1206	0.0340
7	LAC study detected [no. of pts]	6	15%	7	10%	0.7814	NS
8	Low complement [no. Of patients]	25	62.5%	27	38.57%	2.4181	0.0156
9	SLEDAI score [mean±S.D]	28.05±10.19		22.62±9.34		2.8373	0.0054

P significant < 0.05.

TABLE 6

Comparison of demographic and clinical parameters -

aCL positive Vs aCL negative patients

s.no	Parameter	SLE with aCL positivity [N=26]	%	SLE with aCL negativity [N=84]	%	T-value	P-value
1	Age in yrs [mean±S.D]	24.03±8.18		26.48±9.48		1.1872	NS
2	M:F	1:25		10:74			
3	Duration of disease in months [mean±S.D]	29.92±24.43		28.79±31.06		0.1698	NS
4	Recurrent abortion[no. of patients]	4	15.38%	3	3.57%	2.1564	0.0311
5	Gangrene/DVT	2	7.69%	5	5.95%	0.3176	NS
6	Hypertension	3	11.53%	17	20.23%	1.0050	NS
7	Ocular manifestation	14	53.84%	26	30.95%	2.1206	0.0340
8	Neurological manifestation	7	26.92%	13	15.47%	1.3224	NS

P significant < 0.05.

In Tables 6 & 7 – comparison of demographic, clinical parameters and SLEDAI score between SLE patients with aCL positivity Vs aCL negativity show that recurrent abortions, ocular manifestations and LAC study were significantly higher in the former group.

TABLE 7

Comparison of lab parameters – aCL positive Vs aCL negative patients

s.no	Parameters	SLE aCL positivity [N=26]	%	SLE with aCL negativity [N=84]	%	T-value	P-value
1	Hb in gms [mean±S.D]	10.28±1.14		9.75±1.60		1.5681	NS
	Anaemia <10gms [no. of patients]	9	34.61 %	38	45.23 %	0.9568	NS
2	Platelets in lakhs/cumm [mean±S.D]	1.62±0.43		1.78±0.70		1.1009	NS
	Thrombocytopenia <1 lakh /cumm [no. of patients]	1	3.84%	8	9.52%	0.9230	NS
3	ESR in mm/hr [mean±S.D]	50.19±29.91		59.69±32.90		1.3133	NS
4	CRP positivity [no. of patients]	17	65.38 %	43	51.90 %	1.2702	NS
5	Anti-dsDNA positivity [no. of patients]	11	42.30 %	48	57.14 %	1.3256	NS
6	LAC study detected[no. of patients]	12	46.15 %	1	1.19%	6.2062	0.0000005
7	Low complement [no. of patients]	14	53.84 %	38	45.24 %	0.7683	NS
8	Ocular manifestation [no. of patients]	14	53.84 %	26	30.95 %	2.1206	0.0340
9	SLEDAI score [mean±S.D]	27.15±12.63		23.80±8.92		1.5073	NS

P significant < 0.05.

TABLE 8

Comparison of demographic and clinical parameters –

LAC detected Vs LAC not detected patients

s.no	Parameters	LAC detected [N=13]	%	LAC not detected [N=97]	%	T-value	P-value
1	Age in yrs [mean±S.D]	24.46±7.25		26.10±9.46		0.6009	NS
2	M:F	1:12		10:87			
3	Duration of disease in months [mean±S.D]	24.46±18.24		29.92±32.03		0.6001	NS
4	Recurrent abortions [no. of patients]	3	23.07%	4	4.1%	2.628	0.0086
5	Gangrene/DVT [no.of patients]	1	7.69%	6	6.18%	0.2090	NS
6	Hypertension [no.of patients]	1	7.69%	19	19.58%	1.0442	NS
7	Ocular manifestation [no.of patients]	6	46.15%	34	35.05%	0.7814	NS
8	Neurological manifestation [no.of patients]	2	15.38%	18	18.55%	0.2785	NS

P significant < 0.05.

In Tables 8 & 9 – comparison of demographic, clinical parameters and SLEDAI between LAC detected Vs LAC not detected SLE patients show that recurrent abortions and aCL positivity were significantly higher in the former group.

TABLE 9

Comparison of lab parameters – LAC detected VS LAC not detected patients

s.no	Parameters	LAC detected [N=13]	%	LAC not detected [N=97]	%	T-value	P-value
1	Hb in gms [mean±S.D]	10.13±0.88		9.84±1.58		0.7359	NS
	Anaemia <10gms [no. of patients]	5	38.46%	42	43.29%	0.3311	NS
2	Platelets in lakhs/cumm [mean±S.D]	1.77±0.33		1.73±0.68		0.2082	NS
	Thrombocytopenia <1 lakh/cumm [no. of patients]	0	0	9	9.3%	1.1462	NS
3	ESR in mm/hr [mean±S.D]	49.46±25.38		57.8±32.83		0.8800	NS
4	CRP positivity [no. of patients]	10	76.92%	50	51.54%	1.7256	NS
5	Anti – dsDNA positivity[no. of patients]	4	30.77%	55	56.70%	1.7607	NS
6	aCL positivity [no. of patients]	12	92.30%	14	14.43%	6.2062	0.000000005
7	Low complement[no. of patients]	7	53.85%	45	46.39%	0.5055	NS
8	SLEDAI score [mean±S.D]	23.30±9.12		24.73±10.09		0.4848	NS

P significant < 0.05.

DISCUSSION

DISCUSSION

Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune, multisystem disease which may affect the eyes and/or visual system in one third of patients. These ocular manifestations cause significant morbidity in their own right, but can also be a useful indicator of underlying systemic disease activity. Although early recognition and treatment have led to a reduction in severe ocular complications, ocular involvement in SLE is still a potentially blinding condition.

The present study was done on 110 patients who satisfied the 1997 ACR revised classification criteria for Systemic Lupus Erythematosus. There were 99 females and 11 males. The female to male ratio was 9 : 1. Indian series by Malaviya et al[67] had a female to male ratio of 8 : 1.

The age of the patients varied from 9 years to 65 years. The mean age of the patients was 25.9±9.2 years. Disease onset in the second or third decade was common. Median age at disease onset was 21.32±5.38 years. Masi et al and Hochberg et al observed a median age of disease onset at 31 and 30 years respectively[63]. In India, Binoy J. Paul et al and Ghosh B et al noted a median age of onset of 21.6 and 26.5±9 years respectively[64,65]. The median disease duration of study patients was 29±30.8 months. About 12[10.9%] patients had childhood onset of disease. The mean disease duration in childhood onset SLE was 12.25±7.84 months.

Musculoskeletal and mucocutaneous involvement were the commonest clinical manifestations noted in the study group as reported in studies from India and abroad[66,67].

Ocular complaints were given by 23[20.9%] of patients. The common ocular complaints were blurring of vision in 12 patients[10.9%], dry eyes – 3 patients[2.7%], red eyes – 3 patients[2.7%], swelling over eye lid – 2 patients[1.8%] , itching, eye discharge and restriction of eye movements – each 1 patient[0.9%]. EY Yap et al[68], reported ocular symptoms in 7% of patients.

Keratoconjunctivitis sicca or dry eyes was the most common finding affecting 13 (11.8%) patients and is less than the figures found by Yap et al and other authors[69-71]. KIMURA ITARU et al also reported a prevalence of 32.5% of keratoconjunctivitis sicca in their study involving 329 patients[72]. There was no correlation between the presence of dry eyes and age, duration of disease, number or type of system involvement. This variable was independent and not related to any other parameters. Although the musculoskeletal system is linked to arthritis and collagen vascular disease, there was no significant correlation between the musculoskeletal system involvement and dry eyes.[73,74] With an estimated prevalence of between 3 - 29%, retinal vascular lesions were detected in 4.5% our patients.[75,76]

Cotton wool spots were seen in 2.7% of our patients. Gold et al[68] reported that 3% of ambulatory SLE patients had cotton wool spots. Shearn and Pirofsky and Lanham et[68] al found that 28%- 29% of hospitalised patients with SLE had retinal vascular findings[68].

The number of patients (3.6%) with steroid-induced cataracts was not comparable with the 20% reported by Yap et al. The presence of a cataract was not related to the duration of the disease, activity of the disease or the age of the patients. The cataracts were bilateral and were always associated with

systemic steroid therapy. There was no case of corticosteroid induced glaucoma from our study population.

Optic neuropathy was seen in 0.9% of patients. This prevalence of clinical optic neuropathy is similar to the 1% - 2% reported in other series[68]. Optic neuropathy in SLE patients can present as optic neuritis, ischaemic optic neuropathy or slowly progressive visual loss[68].

Ocular movement abnormality due to lateral rectus palsy was seen in 0.9% of patients. Ocular motor signs in SLE are uncommon and often transitory. When present, they help to ascertain the location, and often the cause, of neurologic involvement[77].

Chloroquine induced maculopathy was seen in 1.8% of our patients which is comparable with the reports of R Araiza-Casillas et al[78]. Infections of the eye are not common in our study. The common eye infections seen were blepharitis[0.9%], meibonitis[0.9%], conjunctivitis[0.9%], hordeolum internum[0.9%], herpes zoster ophthalmicus[0.9%] and dacryocystitis[0.9%].

In our study, 12[10.9%] childhood onset SLE patients were involved. Out of 12 patients 3[25%] had ocular involvement. One patient had herpes zoster ophthalmicus, another patient had cherry red spot with retinal vasculitis. One patient with associated APS had Gr II hypertensive retinopathy. In comparison with Al-Mayouf SM, Al-Hemidan AI. et al[79] study, which involved 52 childhood SLE patients, ocular manifestations were less common in our study because of low number of childhood patients involved in the present study. The conclusion of their study was ocular manifestations including sight threatening

complications are not rare in children with SLE and optic neuropathy has a strong prediction for CNS lupus.

There exists no relationship between ophthalmic status of SLE patients, age of the patient and disease duration .

There was a statistically significant difference in the parameters [table 4 & 5] between the patients who had ocular involvement and patients without ocular involvement in recurrent abortions, thrombocytopenia, Anti-dsDNA positivity, aCL positivity, low complement levels and SLEDAI score which were significantly higher in the former group[with ocular involvement].

In the present study the frequency of anticardiolipin antibodies was 23.6% and LAC positivity was 11.8%. Two studies from our country, in the north and Madras reported a frequency of 28% and 41% respectively for anticardiolipin antibodies.

In Tables 6 & 7 – comparison of demographic, clinical parameters and SLEDAI score between SLE patients with aCL positivity Vs aCL negativity show that recurrent abortions, ocular manifestations and LAC study were significantly higher in the aCL positive group. Ocular manifestations were seen in 14[53.8%] of aCL positive patients. The common ocular abnormalities were dry eyes in 4[15.4%] patients, hypertensive retinopathy in 2[7.7%],retinal vasculitis in 2[7.7%],posterior subcapsular cataract in 2[7.7%], CRAO with chloroquine maculopathy in 1[3.8%],optic atrophy in 1[3.8%],SCH in 1[3.8%], and retinal detachment with complicated cataract in 1[3.8%] patient.

In Tables 8 & 9 – comparison of demographic, clinical parameters and SLEDAI between LAC detected Vs LAC not detected SLE patients

show that recurrent abortions and aCL positivity were significantly higher in the former group. Ocular manifestations were seen in 6[46.2%] patients with positive LAC study. The common ocular manifestations seen were dry eyes 2[15.4%],SCH 1[7.7%],optic atrophy 1[7.7%], retinal vasculitis 1[7.7%] and posterior subcapsular cataract in 1[7.7%] patient with LAC positivity.

Only one patient had ocular manifestation as the first sign of SLE. The SLE patient with APS who had CRAO was found to have LAC and aCL positivity which is similar to reports of previous studies[31]. Another patient with optic atrophy had LAC and aCL positivity which is similar to reports of Lin et al.[42] . One patient presented with features of Steven Johnson syndrome like picture and was found to have exudative retinal detachment of both eyes, complicated cataract of left eye and fibrovascular proliferative panuveitis of right eye with ANA and aCL positivity. Cystoid macular edema of both eyes was seen in one patient with SLE. No patient in our study had cavernous sinus thrombosis. 7.4% of SLE patients with APS had hypertensive retinopathy.

CONCLUSION

CONCLUSION

1] There was a female predominance in the patients with ocular involvement due to Systemic Lupus Erythematosus.

2] Ocular manifestations were seen in 36.4% of our study patients.

3] Ocular complaints were given by 20.9% of patients.

4] Keratoconjunctivitis sicca or dry eyes was the most common finding affecting 11.8% of patients. Retinal vasculitis was seen in 4.5% of our patients. Posterior sub capsular cataract due to steroid use was seen in 3.6% of our patients. Chloroquine maculopathy was seen in 1.8% of our patients.

5] Neuro-ophthalmic manifestations were less common involving 1.8% of our patients.

6] Ocular infections involving 5.5% of our patients, were less common and are not life or vision threatening.

7] There exists no relationship between ophthalmic status of SLE patients, age of the patient and disease duration .

8] The frequency of anticardiolipin antibodies was 23.6% and LAC study was 11.8% in our patients. Their presence is positively correlated with ocular involvement.

9] Ocular involvement is positively associated with recurrent abortions, thrombocytopenia, Anti-dsDNA positivity, aCL positivity, low complement levels and high SLEDAI score.

10] Sight-threatening complications of SLE include optic neuropathy and retinal vascular disease.

BIBLIOGRAPHY

BIBLIOGRAPHY

1] Jacobson, D. L., Gange, S. J., Rose, N. R., and Graham, N. M. (1997). Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin. Immunol. Immunopathol.* 84, 223.

2] Lawrence R.C., Helmick C.G., Arnett F.C., et al: Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998; 41:778-799.

3] Uramoto K.M., Michet Jr. C.J., Thumboo J., et al: Trends in the incidence and mortality of systemic lupus erythematosus, 1950-1992. *Arthritis Rheum* 1999; 42:46-50.

4] Ballou S.P., Khan M.A., Kushner I.: Clinical features of systemic lupus erythematosus: Differences related to race and age of onset. *Arthritis Rheum* 1982; 25:55-60.

5] Miller M.H., Urowitz M.B., Gladman D.D., et al: Systemic lupus erythematosus in males. *Medicine (Balt)* 1983; 62:327-334.

6] Boddaert J., Huong D.L., Amoura Z., et al: Late-onset systemic lupus erythematosus: A personal series of 47 patients and pooled analysis of 714 cases in the literature. *Medicine (Balt)* 2004; 83:348-359.

7] Hochberg M.C.: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40:1725.

8] Urowitz M.B., Gladman D.D.: Measures of disease activity and damage in SLE. *Baillieres Clin Rheumatol* 1998; 12:405-413.

9] Gladman D., Ginzler E., Goldsmith C., et al: The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39:363-369.

10] Gilliam J.N., Sontheimer R.D.: Skin manifestations of SLE. *Clin Rheum Dis* 1982; 8:207-218.

11] Cronin M.E.: Musculoskeletal manifestations of systemic lupus erythematosus. *Rheum Dis Clin N Am* 1988; 14:99-116.

12] Appel GB, Silva FG, Pirani CL. Renal involvement in systemic lupus erythematosus (SLE): a study of 56 patients emphasizing histologic classification. Medicine 1978;75: 371–410.

13] Weening, JJ, D'Agati VD, Schwartz MM, et al. Classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15:241–250.

14] Alarcon GS, Calvo-Alen J, McGwin G, et al. Systemic lupus erythematosus in a multiethnic cohort: LUMINA XXXV. Predictive factors of high disease activity over time. Ann Rheum Dis 2006;65:1168 - 1174.

15] De Marcaida J.A., Reik Jr. L.: Disorders that mimic central nervous system infections. *Neurol Clin* 1999; 17:901-941.

16] Kojima M., Nakamura S., Morishita Y., et al: Reactive follicular hyperplasia in the lymph node lesions from systemic lupus erythematosus patients: A

clinicopathological and immunohistological study of 21 cases. *Pathol Int* 2000; 50:304-312.

17] Dillon A.M., Stein H.B., English R.A.: Splenic atrophy in systemic lupus erythematosus. *Ann Intern Med* 1982; 96:40-43.

18] Isenberg DA, Rahman A, Allen E et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology 2005;44:902–6.

19] Karpik AG, Schwartz MM, Dickey LE, Streeten BW, Roberts JL. Ocular immune reactants in patients dying with systemic lupus erythematosus. Clin Immunol Immunopathol 1985;35:295–312.

20] Nguyen QD, Foster CS. Systemic lupus erythematosus and the eye. Int Ophthalmol Clin 1998;38:33–60.

21] Klejnberg T, Moraes Junior HV. Ophthalmological alterations in outpatients with systemic lupus erythematosus. Arq Bras Oftalmol 2006; 69:233– 237.

22] Prabu A, Marshall T, Gordon C, et al. Use of patient age and anti-Ro/La antibody status to determine the probability of patients with systemic lupus erythematosus and sicca symptoms fulfilling criteria for secondary Sjogren's syndrome. Rheumatology (Oxford) 2003; 42:189–191.

23] Jensen JL, Bergem HO, Gilboe IM, et al. Oral and ocular sicca symptoms and findings are prevalent in systemic lupus erythematosus. J Oral Pathol Med 1999; 28:317–322.

24] Varga JH, Wolf TC. Bilateral transient keratoendotheliitis associated with systemic lupus erythematosus. Ann Ophthalmol 1993; 25:222–223.

25] Montehermoso A, Cervera R, Font J, et al. Association of antiphospholipid antibodies with retinal vascular disease in systemic lupus erythematosus. Semin Arthritis Rheum 1999; 28:326–332.

26] Stafford-Brady FJ, Urowitz MB, Gladman DD, et al. Lupus retinopathy: patterns, associations, and prognosis. Arthritis Rheum 1988; 31:1105–1110.

27] Klinkhoff AV, Beattie CW, Chalmers A. Retinopathy in systemic lupus erythematosus: relationship to disease activity. Arthritis Rheum 1986; 29: 1152–1156.

28] Ushiyama O, Ushiyama K, Koarada S, et al. Retinal disease in patients with systemic lupus erythematosus. Ann Rheum Dis 2000; 59:705–708.

29] Gold DH, Morris DA, Henkind P. Ocular findings in systemic lupus erythematosus. Br J Ophthalmol 1972; 56:800–804.

30] Lanham JG, Barrie T, Kohner EM, et al. SLE retinopathy: evaluation by fluorescein angiography. Ann Rheum Dis 1982; 41:473–478.

31] Jabs DA, Fine SL, Hochberg MC, et al. Severe retinal vaso-occlusive disease in systemic lupus erythematous. Arch Ophthalmol 1986; 104: 558–563.

32] Au A, O'Day J. Review of severe vaso-occlusive retinopathy in systemic lupus erythematosus and the antiphospholipid syndrome: associations, visual outcomes, complications and treatment. Clin Experiment Ophthalmol 2004; 32:87–100.

33] Read RW, Chong LP, Rao NA. Occlusive retinal vasculitis associated with systemic lupus erythematosus. Arch Ophthalmol 2000; 118:588–589.

34] Leibovitch I, Goldstein M, Loewenstein A, et al. Combined central retinal artery and vein occlusion in a patient with systemic lupus erythematosus. Rheumatology (Oxford) 2001; 40:1195–1196.

35] Nguyen QD, Uy HS, Akpek EK, et al. Choroidopathy of systemic lupus erythematosus. Lupus 2000; 9:288–298.

36] Wisotsky BJ, Magat-Gordon CB, Puklin JE. Angle-closure glaucoma as an initial presentation of systemic lupus erythematosus. Ophthalmology 1998; 105:1170–1172.

37] Sivaraj RR, Durrani OM, Denniston AK, et al. Ocular manifestations of systemic lupus erythematosus. Rheumatology (Oxford) 2007; 46:1757–1762.

38] Buckley R, Graham E, Jones S, Silman A, Tullo A. Ocular toxicity and hydroxychloroquine: guidelines for screening 2004. wwww.rcophth.ac.uk/docs/publications/oculartoxicity2004.pdf

39] Marmor MF, Carr RE, Easterbrook M et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy. A report by the American Academy of Ophthalmology. Ophthalmology 2002;109:1377–82.

40] TogashiM, Numata K, Yamamoto S, et al. Anterior ischemic optic neuropathy in a patient with positive antinuclear antibody and lupus anticoagulant findings. Ophthalmologica 1996; 210:132–135.

41] Frohman LP, Frieman BJ, Wolansky L. Reversible blindness resulting from optic chiasmitis secondary to systemic lupus erythematosus. J Neuroophthalmol 2001; 21:18–21.

42] Lin YC, Wang AG, Yen MY. Systemic lupus erythematosus-associated optic neuritis: clinical experience and literature review. Acta Ophthalmol 2008 [Epub ahead of print].

43] Keane JR. Eye movement abnormalities in systemic lupus erythematosus. Arch Neurol 1995; 52:1145–1149.

44] Rheu CW, Lee SI, Yoo WH. A catastrophic-onset longitudinal myelitis accompanied by bilateral internuclear ophthalmoplegia in a patient with systemic lupus erythematosus. J Korean Med Sci 2005; 20:1085–1088.

45] Brandt KD, Lessell S, Cohen AS. Cerebral disorders of vision in systemic lupus erythematosus. Ann Intern Med 1975; 83:163–169.

46] Read RW, Weiss AH, Sherry DD. Episcleritis in childhood. Ophthalmology 1999; 106:2377–2379.

47] Frith P, Burge SM, Millard PR, et al. External ocular findings in lupus erythematosus: a clinical and immunopathological study. Br J Ophthalmol 1990; 74:163–167.

48] Donzis PB, Insler MS, Buntin DM, et al. Discoid lupus erythematosus involving the eyelids. Am J Ophthalmol 1984; 98:32–36.

49] Mseddi M, Marrekchi S, Meziou TJ, et al. Discoid lupus erythematosus with eyelid involvement: a series of nine patients. J Fr Ophtalmol 2007; 30:247–249.

50] Ena P, Pinna A, Carta F. Discoid lupus erythematosus of the eyelids associated with staphylococcal blepharitis and Meibomian gland dysfunction. Clin Exp Dermatol 2006; 31:77–79.

51] Gunasekera V, Jayaram H, Kashani S, et al. Refractory discoid lupus erythematosis of the eyelid successfully treated with intra-lesional triamcinolone. Eye 2008 [Epub ahead of print].

52] Serop S, Vianna RN, Claeys M, et al. Orbital myositis secondary to systemic lupus erythematosus. Acta Ophthalmol (Copenh) 1994; 72:520–523.

53] Asherson RA, Merry P, Acheson JF, Harris EN, Hughes GR. Antiphospholipid antibodies: a risk factor for occlusive ocular vascular disease in systemic lupus erythematosus and the ‘primary’ antiphospholipid syndrome. Ann Rheum Dis 1989;48:358–61.

54] Chen YC, Cheng TT, Lai MH, Wu CH. Overwhelming septic cavernous sinus thrombosis in a woman after combination of high-dose steroid and intravenous cyclophosphamide therapy for lupus nephritis. Lupus 2000;9:78–9.

55] Hobbs HE, Sorsby A, Freedman A. Retinopathy following chloroquine therapy. Lancet 1959;2:478–80.

56] Buckley R, Graham E, Jones S, Silman A, Tullo A. Ocular toxicity and hydroxychloroquine: guidelines for screening 2004. wwww.rcophth.ac.uk/docs/publications/oculartoxicity2004.pdf

57] Marmor MF, Carr RE, Easterbrook M et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy. A report by the American Academy of Ophthalmology. Ophthalmology 2002;109:1377–82.

58] Mavrikakis I, Sfikakis PP, Mavrikakis E et al. The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine: a reappraisal. Ophthalmology 2003;110:1321–1326.

59] Lee AG. Hydroxychloroquine screening. Br J Ophthalmol 2005;89:521–2.

60] Easterbrook M. Ocular effects and safety of antimalarial agents. Am J Med 1988; 85 (4A):23–29.

61] Mavrikakis M, Papazoglou S, Sfikakis PP, et al. Retinal toxicity in long term hydroxychloroquine treatment. Ann Rheum Dis 1996; 55:187–189.

62] Hollander DA, Aldave AJ. Drug-induced corneal complications. Curr Opin Ophthalmol 2004; 15:541–548.

63] Masi AT, Kaslow RA. Sex effects in SLE - a clue to pathogenesis. Arthritis Rheum 1978; 21: 480.

64] Binoy J Paul, Muhameed Fassaludeen, Nandakumar et al. Clinical profile of Systemic lupus Erythematosus in Northern Kerala. J Indian Rheumatology Assoc 2003; 11: 94 – 97.

65] B Ghosh, K Saha, A Ghosh, S Dhar. Cardiovascular evaluation in patients with Systemic Lupus Erythematosus – a cross sectional study. Indian Journal of Rheumatology 2008; 3(4):139 – 43.

66] Madhavan R, Porkodi R, Ramakrishnan S et al. Systemic Lupus Erythematosus – the Madras experience. J Assoc Physicians India 1988; 36: 473 – 75.

67] Malaviya AN, Singh RR,Kumar A et al. SLE in Northern India. A review of 329 cases. J Assoc Phys India 1988; 36: 476 – 80.

68] Yap EY, Au Kong KG, Fong KY et al. Ophthalmic manifestations in Asian patients with systemic lupus erythematosus. Sing Med J 1998; 39: 557 - 559.

69] Yap EY, Au Kong KG, Fong KY et al. Ophthalmic manifestations in Asian patients with systemic lupus erythematosus. Sing Med J 1998; 39: 557 - 559.

70] Reddy CV, Foster CS. Systemic lupus erythematosus. In: Albert DM, Jakobiec FA (eds). Principles and Practice of Ophthalmology. WB Saunders: Philadelphia, 1994, pp 2894 - 2901.

71] Farris RL. Sjogren's syndrome. In: Gold DH, Weingeist TA (eds). The Eye in Systemic Disease. JB Lippincott: Philadelphia, 1990, pp 70 - 71.

72] KIMURA ITARU et al incidence of Ocular Complications in Systemic Lupus Erythematosus. Folia Ophthalmologica Japonica; VOL.50;NO.4;PAGE.293-297(1999).

73] Karesh JW, Baer JC, Hemady RK. Noninfectious orbital inflammatory disease. In: Tasman W, Jaeger EA (eds). Duane's Clinical Ophthalmology. JB Lippincott: Philadelphia, 1994 vol. 2, chap 35, pp 28 - 30.

74] Lemp MA, Marquardt R. The Dry Eye. Springer-Verlag: Berlin, 1992, pp 9 - 11.

75] Stafford-Brady FJ, Urowitz MB, Gladman DD, Easterbrook M. Lupus retinopathy. Patterns, associations and prognosis. Arthritis Rheum 1988; 31: 1105 - 1110.

76] Klinkhoff AV, Beattie CW, Chalmers A. Retinopathy in systemic lupus erythematosus: relationship to disease activity. Arthritis Rheum 1986; 29: 1152 - 1156.

77] James R. Keane, MD et al Eye Movement Abnormalities in Systemic Lupus Erythematosus *Arch Neurol.* 1995;52(12):1145-1149.

78] R Araiza-Casillas, F Cárdenas, Y Morales and M H Cardiel et al. Factors associated with chloroquine-induced retinopathy in rheumatic diseases; *Lupus* 2004; 13; 119.

79] Al-Mayouf SM, Al-Hemidan AI et al Ocular manifestations of systemic lupus erythematosus in children. Saudi Med J. 2003 Sep;24(9):964-6.

APPENDICES

ABBREVATIONS

ANA	Antinuclear antibody
Anti-ds DNA	Anti double stranded antibody
aCL IgM, IgG	Anticardiolipin antibody IgM, IgG
LAC	Lupus anticoagulant
C3, C4	Complement
CRP	C-reactive protein
SLE	Systemic Lupus Erythematosus
cSLE	Childhood SLE
DLE	Discoid Lupus Erythematosus
ACR	American College Rheumatology
SLEDAI	SLE Disease Activity Index
APS	Antiphospholipid Antibody Syndrome
Anti-Sm	Anti-Smith antibody
CNS	Central Nervous System
CRAO	Central Retinal Artery Occlusion
CRVO	Central Retinal Vein Occlusion
BRAO	Branch Retinal Artery Occlusion
BRVO	Branch Retinal Vein Occlusion
ELISA	Enzyme Linked Immunoabsorbant Assay
S.D.	Standard Deviation
Hb	Haemoglobin
Grms	Grams

PATIENT CONSENT FORM

STUDY TITLE

Ocular manifestations of Systemic Lupus Erythematosus and Systemic Lupus Erythematosus with Antiphospholipid Syndrome.

Study Centre : Department of Rheumatology,

Madras Medical College, Chennai – 600 003

Patient's Name :

Patient's Age :

Identification Number : Patient may check (✓) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study on "**Ocular manifestations of Systemic Lupus Erythematosus and Systemic Lupus Erythematosus with Antiphospholipid Syndrome"** ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological and urine examination. ☐

Signature / Thumb Impression _____ Place _____ Date _____

Patient's Name and Address: _____

Signature of the Investigator : _____ Place _____ Date _____

Study Investigator's Name : _____

PROFORMA

Clinical Profile of Systemic Lupus Erythematosus

NAME: **AGE/SEX:** **OP/ IP No:** **RCC No :**

ADDRESS: **OCCUPATION:**

H/O PRESENT ILLNESS: **TOTAL DURATION OF ILLNESS:**

Fever Malaise Fatigue

Malar rash Discoid lesion Oral ulcer Alopecia
photosensitivity

Purpura Raynaud's Gangrene

Joint Symptoms

Myalgia Weakness Headache dry eyes/red eyes

Mood Seizures insomnia blurring of vision

Swelling over eyelids restriction of eye movements

Chest pain Palpitation Dyspnoea Syncope
Pedal edema

Cough Expectoration Hemoptysis Hematuria
Oliguria Facial puffiness

OTHERS

PAST HISTORY:

PERSONAL HISTORY:

TREATMENT HISTORY:

PHYSICAL EXAMINATION:

Fever Anaemia clubbing cyanosis LN PE JVP

MUCOCUTANEOUS

OTHERS

PULSE BP RR

CVS RS ABDOMEN

CNS MSS:

Ophthalmic examination: Right eye Left eye

Visual Acuity

Lids

Ocular Movement

Conjunctiva

Cornea

Iris

Anterior Chamber

Pupils

Lens

Tension

N.L.Duct

Slit Lamp Exam

Retinoscopy

Fundus

Visual Field

Tonometry

Schirmer's Test

INVESTIGATIONS:

Hb TC DC ESR 1 hr Platelets BT CT
PT INR APTT

Urea Cr Uric acid Sugar T.Bilirubin ALT AST

SAP LDH CPK Electrolytes Na K HCO 3 Cl

Lipid profile

Urine R/E

ANA Anti dsDNA ACL

LAC VDRL CRP

Complement

ECG CXR PA View

ECHO

ASSESSMENT

SLEDAI SLICC

MANAGEMENT

NSAIDS STEROIDS Pulse Oral

IMMUNOSUPPRESSANTS ANTICOAGULANTS/ANTIPLATELETS

Systemic Lupus Erythematosus Disease Activity Index

Descriptor	Definition	Weighted Score
Seizure	Recent onset; exclude metabolic, infectious, or drug-related causes	8
Psychosis	Altered ability to function in normal activity owing to severe disturbance in the perception of reality; includes hallucinations, incoherence marked by loose associations, impoverished thought content, marked illogical thinking, and bizarre disorganized or catatonic behavior; exclude the presence of uremia and offending drugs	8
Organic brain syndrome	Altered mental function with impaired orientation or impaired memory or other intellectual function, with rapid onset and fluctuating clinical features; includes clouding of consciousness with reduced capacity to focus and inability to sustain attention on environment, and at least two of the following—perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, and increased or decreased psychomotor activity; exclude metabolic infectious and drug-related causes	8
Visual	Retinal changes from systemic lupus erythematosus cytoid bodies, retinal hemorrhages, serous exudate or hemorrhage in choroid, optic neuritis (not due to hypertension, drugs, or infection)	8
Cranial nerve	New onset of sensory or motor neuropathy involving a cranial nerve	8
Lupus headache	Severe, persistent headache; may be migrainous, unresponsive to narcotic analgesia	8

Descriptor	Definition	Weighted Score
Cerebrovascular accident	New syndrome; exclude arteriosclerosis	8
Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages; vasculitis confirmed by biopsy or angiogram	8
Arthritis	More than two joints with pain and signs of inflammation (tenderness, swelling, or effusions)	4
Myositis	Proximal muscle aching or weakness associated with elevated creatine phosphokinase/aldolase levels, electromyographic changes, or biopsy specimen showing myositis	4
Casts	Heme, granular, or erythrocyte	4
Hematuria	>5 erythrocytes per high-power field; exclude other causes (stone, infection)	4
Proteinuria	>0.5 g of urinary protein excreted per 24 hr; new onset or recent increase of >0.5 g/24 hr	4
Pyuria	>5 leukocytes per high-power field; exclude infection	4
New malar rash	New onset or recurrence of inflammatory type of rash	4
Alopecia	New or recurrent; patch of abnormal, diffuse hair loss	4
Mucous membrane	New onset or recurrence of oral or nasal ulceration	4
Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening	4
Pericarditis	Pericardial pain with at least one rub or effusion; confirmation by ECG or echocardiography	4
Low complement	Decrease in CH50, C3, or C4 levels (to less than the	2

Descriptor	Definition	Weighted Score
	lower limit of the laboratory-determined normal range)	
Increased DNA binding	>25% binding by Farr assay (to more than the upper limit of the laboratory-determined normal range, e.g., 25%)	2
Fever	>38°C after exclusion of infection	1
Thrombocytopenia	<100,000 platelets	1
Leukopenia	Leukocyte count <3000/mm^3 (not due to drugs)	1

ECG, electrocardiogram.

INSTITUTIONAL ETHICAL COMMITTEE
GOVERNMENT GENERAL HOSPITAL & MADRAS MEDICAL COLLEGE,
CHENNAI-600 003.

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Fax : 044 – 25305115

K.Dis.No.006859/P & D3/Ethics/Dean/GGH/09 Dated:23-03-2009

Title of the work "Ocular manifestations of systemic Lupus erythematosus and systemic Lupus Erythematosus with Antiphospholipid syndrome"

Principal Investigator Dr. J.R.S. vijaybabu sathish kumar M.D., PG in DM

Department Rheumatology, MMC, Ch-3

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting which is held on 31st March at 2 P.M in Government General Hospital, Deans, Chamber, Chennai-3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s)
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, GGH,CHENNAI

CHAIRMAN
IEC, GGH,CHENNAI

DEAN
GGH &MMC, CHENNAI

DM 30-03 (3)