SYSTEMIC LUPUS ERYTHEMATOSUS CLINICAL PROFILE AND EVALUATION OF SUB CLINICAL ATHEROSCLEROSIS IN CHILDREN AND ADULTS

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CERTIFICATE

This is to certify that the dissertation entitled **"SYSTEMIC LUPUS ERYTHEMATOSUS CLINICAL PROFILE AND EVALUATION OF SUB CLINICAL ATHEROSCLEROSIS IN CHILDREN AND ADULTS"** presented here is the original work done by **Dr.S.BALAMEENA** in the Department of Rheumatology, Government General Hospital, Madras Medical College, Chennai-600003, in partial fulfillment of the University rules and regulations for the award of DM Rheumatology Branch IX, under our guidance and supervision during the academic period from 2003- 2006.

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INTRODUCTION

Systemic lupus Erythematosus (SLE) is an autoimmune inflammatory disorder. It is characterized by multi system involvement and is heterogenous in its presentation. It is associated with numerous antibodies and immune complex formation. It predominantly affects females in their peak reproductive period (F:M=9:1) and in other age groups (3:1). Multiple factors like environmental, genetic and hormones have been implicated in the pathogenesis of this disorder. Under the wider spectrum of molecular biology, using newer immunological techniques, many antibodies along with the epitopes have been discovered which help in further understanding the disease. This disease, which is one of the major differentiated connective tissue disorders, affects all the organs as the disease progresses. The disease activity judged by using various measures is unable to accurately anticipate the morbidity and mortality because of its heterogeneity. It has protean manifestations and encompasses a wide age range from neonates to the elderly.

AIM AND OBJECTIVES

To study the **clinical profile** of systemic lupus erythematosus in children and adults as it is seen in this part of the country.

To study the association of **Colour Duplex Doppler of the carotids** along with associated traditional risk factors like age, disease duration, smoking, family history of athersclerotic disease and laboratory variables along with SLEDAI, steroid usage and lipid profile in SLE patients.

ABBREVIATION

SLE	:	Systemic Lupus Erythematosus
CRP	:	C Reactive Protein
RF	:	Rheumatoid factor.
ACL	:	Anti cardiolipin Antibody
ANA	:	Anti Nuclear Antibody
ssDNA	:	Single Stranded Deoxyribonucleic Acid
ds DNA	:	Double Stranded Deoxy Ribo Nucleic Acid
LAC	:	Lupus Anti Coagulant
IIF	:	Indirect Immuno Fluorescence
Sm	:	Smith Antibody
U_1RNP	:	Uridyl 1 Ribonucleoprotein
SLEDAI	:	SLE Disease Activity Index
CAD	:	Coronary arterial disease
TCL	:	Total cholesterol
HDL	:	High density lipoprotein cholesterol
LDL	:	Low density lipoprotein cholesterol
TGL	:	Triglycerides
S I	:	South India - Chandrasekharan A.N. et al study
NK	:	Northern Kerala - Binoy J. Paul et al study
NI	:	North India - Malaviya A.N. et al study
IMT	:	Intimomedial thickness

REVIEW OF LITERATURE

SLE is a connective tissue disease wherein tissues and cells are damaged by auto antibodies and immune complexes, and infections are the major cause of morbidity and mortality.

History

The first historical event of describing Lupus Erythematosus was by T. Biett (1833). In 1845, Van Hebra described butterfly rash, and in 1872 Kaposi described its systemic involvement. Hargrave's et al[1] in 1948 discovered the LE cell. Lee et al[2] showed that the antibodies are of Immunoglobulin in nature and it is the LE factor, which forms the LE body. Knowledge in understanding the disease was initiated by discovery of the Immunofluorscence technique in 1957 by Hallborough using human cells. In 1961 Beck et al. used rodent tissue for immunofluoroscence and later in 1982, Tan used HEp 2 cells which improved the better understanding of the antibodies pattern. Other laboratory landmarks in SLE are, BFP (biologically false positive) VDRL reaction – Reinhart (1909), Wireloop glomeruli – Baehr, (1935), LAC – Hartmann, (1952) and ANA – Miescher, Fauconnet, (1954) Tan and Kunkel[3] described anti Sm anti body in 1966.

Cazenave described Lupus Erythemateaux in 1851 in France. Kaposis first showed visceral involvement in SLE in 1872. TAN in 1982 proposed the revised American College of Rheumatology criteria for classification of SLE.

Epidemiology

SLE prevalence varies in different geographical areas. Johnson et al. reported in his study that the prevalence rates 36.2, 90.6 and 206

per100, 000 among women of Caucasian, Asian and Afro Caribbean origin respectively[4,5].

In certain countries like San Fransico, Sweden and Nottingham the prevalence is 51, 36.3 and 24.6 per one lakh and the incident rate which denotes new cases every year is 7.6, 4.5 and 4 per one lakh respectively. The incidence in children is 0.6 – 0.8 per one lakh[6,10]. The F:M sex ratio in children is 1.4 – 5.8: 1 and in adults 8:1 to 13:1.

The frequency of presentation of SLE in different age groups is as follows 1) between 16–55 it is 65%, 2) below 16 it is 20% and 3) above 55 it is 15%.

SLE is 3 times more common in Blacks who have more Sm and RNP antibodies, discoid skin lesions, cellular casts and serositis[7].

Immunopathogenesis

Genetics

Support for genetic factors comes from the following facts like high prevalence among monozygotic twins (24%) and the highest reported is 58%. 5-12% of the relatives of SLE patients develop the disease[6,8].

Genetic

a.	Complement	C_1, C_4 def.	> 75% prevalence, severe disease
		C_2 def.	35% prevalence
		C_4	50-80% patients partially deficient
b.	MHC Association	HLA : A_1, B_8, DR_3	English patients
		DR_2, DQw_4 (DQw_6), DQ_2	Susceptibility to nephritis

		DRw_8	Early onset SLE (<20 yrs)
		$DQw_{6, 7, 8}$	Lupus anticoagulant
		DQB1 0201, 0302	Antids DNA
		DQw_6	Anti Sm
		DR-7	More severe disease
		DR-3	AntiRo/antiLa, neonatal lupus
c.	Non HLA genes	T cell receptor genes	(assoc; with anti-Ro)
		Ig heavy chain (Gm)	Km light chain genes
		Homozygons deletion of Ig VH gene	
d.	Newer Polymorphism	TNF 308 A, FC ϒIIA, FC ϒIIIA and FC ϒIIIB, MBL, IL 4, IL 10, PARP, CR 1. Fas, Fas ligand	

Environmental factors

Definite- Ultra Violet B-rays in the range 300-360 nanometers penetrate the deeper layers of the skin and cause necrosis of the basal layer. This leads to antigen flip-flop towards the outside of the membrane through Apoptotic bleb and thus when exposed to the antibodies form antigen antibody complexes. Circulating ANA's will further cause inflammation even after the initiating stimuli is withdrawn[8,12].

Hormonal-Sex hormones F:M ratio is 9:1 between menarche and menopause & 3:2 in the young & old.

Dietary factors like alfalfa (L-canavanine), high calorie diet, high intake of saturated fats and infections–retroviruses, bacterial lipopolysaccharide, EBV (James, et al, 1997) have been implicated.

Drugs–hydralazine, procainamide, INH, hydantoin, Alpha methyldopa, chlorpromazine, D-penicillamine and α-interferon.

Abnormal immune response and pathogenesis

The immunopathogenesis is multi factorial. SLE is a CD4 T cell dependent disease. The foreign antigens are presented to the T cells through MHC class II molecules. Clones of auto reactive B cells have been seen in active SLE. They depend on IL 6 cytokine for their proliferation. They are dependent on the T helper cells (CD 4). These T cells also show hyperactivity due to stimulation of antigen presented by the various antigen-presenting cells like dendritic cell. They belong to the groups like CD 5 marker B1 cell, CD -4-8-(double negative) and CD 4+8- cells which escape the central and peripheral tolerance. Due to this dysregulation of immune system occurs. This is modified by infection and genetic abnormalities which eventually leads on to generation of various anti bodies by epitope spreading[6,12].

Abberations in the recombination of VDJ region genes of immunoglobulin heavy chain and VJ of light chain generate antibodies.

Pathogenic antibodies mutations arise from the invariable region often in frame work area. The anti ds DNA through its cationic charge, increase acidity, charge to charge hydrogen bonding and interaction with the molecules in the antigen produces increased avidity.

Cytokines involved in SLE are interleukin (IL) –4, IL 10, along with defective IL 2 production in the regulatory cells CD4+25+, which promotes CD4 T cells proliferation. During inflammation of tissues there is an increase of Th1 cytokines like interferon ϒ, TNF α by T cell and IL 1 is produced by macrophages spontaneously. This persistent Tcell activation prevents anergy induction.

Diagnostic criteria

The presence of 4 or more of Revised American College of Rheumatology Criteria (1982) is essential to make a diagnosis of SLE with 98% specificity & 97% sensitivity[1]. Appendix[1].

Auto antibodies in SLE

They primarily target nucleic constituents including DNA, RNA proteins & RNP complexes. They also bind to cell surface and cellular antigens[11,12].

Intracellular Ag-Antibodies to ds DNA (80%), ss DNA (90%), Ribosomal (10-15%), Histone (42-50%), Ro (SS-A), (40-50%), La/SS-B (15%), Sm (30%), U_1RNP (30-50%), 28 S RNA, RNA polymerase II (12%), Ku (20-40%) and Proteasome (58%).

Membrane level-Antibodies against Lymphocyte (>50%), RBC (10-50%), Platelet (10%), APLS-ACL (30%) and APLS LAC (50%).

These antibodies are of diagnostic, prognostic significance as well as produce immunopathological changes characteristics of disease.

Antibodies to nucleosome is the recent finding in lupus nephritis. Initiated by these antibodies, and extended by epitope spreading, antids DNA and histones are generated by stimulated autoreactive B cells.

J.A.Simon et al in 2003 described the potential utility of nucleosome antibodies and concluded that it can be used as diagnostic tool and disease activity marker[66].

ANA is detected by ELISA which is sensitive 98%-100% but immunofluorescent assay by HEp2 cells at dilution of 1:160 is more

specific and sensitive. The sensitivity using rodent cell is about 70% only. Anti ds DNA is detected by ELISA, RIA (Farr–gold standard) are more sensitive than Crithidia lucillae assay, which is specific. Antibodies to extractable nuclear antigens like Sm, U1RNP, Ro, La, Jo1and Scl-70 are identified by immuno precipitation and ELISA. Presence of antibodies to Jo1 and Scl-70 in SLE may be seen in overlap and increases the severity of the disease.

CLINICAL FEATURES

1. Constitutional: Fever is seen in childhood onset SLE in 70%[10]. Fatiguability is seen during flare. Lupus crisis denotes active lupus. Chills, leukocytosis and increased CRP favour infection.

2. Mucocutaneous: Skin and mucous membrane is involved in 80% of cases. SLE skin lesions are described as SLE specific and nonspecific under Gilliam's classification.

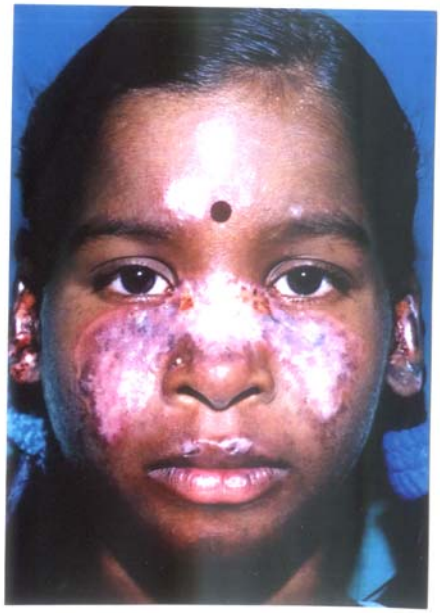
LE specific lesions Acute: (30-50), Malar rash, Generalised erythema and Bullous LE/TEN like lesion

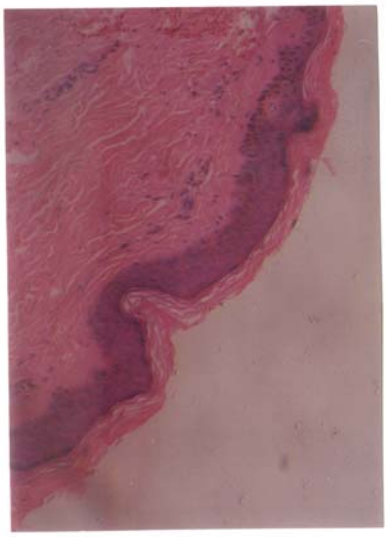
Subacute cutaneous lupus (SCLE) (10-15), Annular polycyclic, Papulosquamous.

Chronic lupus (CLE) (10-15), Localised discoid, Generalised discoid and Lupus profundus.

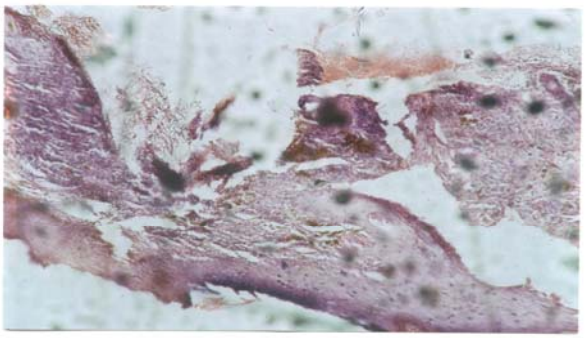
LE Nonspecific lesions: Panniculitis, Urticaria, Vasculitis, Livedo reticularis, Nonscarring alopecia, Hyperpigmentation, Pruritus, Leg ulcer, S/C nodules.

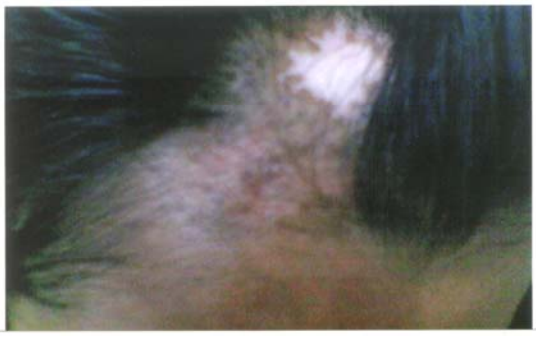
ACUTE LE LESION





CHRONIC LE LESION





Pathogenesis

Anti Ro(SSA) & La(SSB) antibodies correlate with the development of SCLE skin lesions. In the skin IL-1 and TNF-α are increasingly produced along with heat shock proteins.

Lupus band test is positive in non lesional unexposed and lesional skin in SLE whereas only lesional skin is positive in DLE (described by Burnham in 1907). In 10- 20% of SLE patients have discoid lesions. 2-10% of DLE evolve into SLE. ANA is positive in 22-62% of DLE and along with anti ss DNA in 90% denotes more severe disease. SCLE lesions are nonfixed, nonscarring, with remissions and exacerbations, occurs in sun-exposed areas of the extensor aspect of forearms, upper neck and chest and is associated with HLA DR3 and is anti Ro(SSA) antibody positive.

Histopathology of ACLE shows liquefactive and vacuolar degeneration of basal cell layer, pigmentary incontinence, hyperkeratosis, edema of the upper dermis and perivascular infilteration of monocytes, as seen in the photograph Plate 1.

SCLE lesions shows variable degrees of hyperkeratosis, focal basal cell degeneration, dermal edema and rarely vesicular changes can occur particularly at the active border of the annular SCLE.

DLE lesions show follicular plugging, atrophy, scarring, erythema and telangiectasia, which commonly occurs in the scalp and trunk. SCLE is due to antibody-mediated cytotoxicity and DLE is due to T-cell mediated cytotoxicity. Plate 2.

In children malar rash 55%, alopecia 20%, oral ulcer 50% and photosensitivity seen in 50%[6,10]. Non specific lesion palmar erythema,

atrophic blanche, urticarial lesion, livedoreticularis, chilblain, epidermolysis bullosa, dermatitis herpetiformis, pemphigoid and epidermolysis bullosa acquisita have been reported in adults[14,15,16].

3. ***Musculo skeletal*** manifestation is seen in about 95% of patients[8,9]. At the onset, arthritis is seen about 45-65% in various studies. During the disease course, arthritis is seen in 71% deformities in 30% and nodules in 5%. Jaccoud's involving small joints of the hands is seen in 15-20%. In children arthritis is seen in 75% and is non erosive. Spontaneous tendon rupture and septic arthritis have been reported. Avascular necrosis is seen commonly in the hips because of APLS, steroids usage, fat embolism and vasculitis of small vessels. Myositis is seen in 20%, it may be due to disease, drugs commonly steroids and chloroquine and overlap syndromes. Muscles involved are the proximal group usually but rarely the distal group, as seen in dermatomyositis SLE overlap 3-5%. Fibromyalgia is seen in 2-5%, which also contributes to the fatiguability. Vacuolar and nemaline rod myopathy are seen rarely.

Drug induced myopathy may be differentiated by predominantly affection of type 2 fibres (electron microscopy) but muscle enzymes are normal.

4. ***Gastrointestinal*** manifestations in SLE include, recurrent oral ulcers, pharangitis, oesophagitis, pepticulcer, ascites, hepatomegaly (50%), transaminitis (20%)[18].

BuddChiari Syndrome, lupoidhepatitis, pseudo intestinal obstruction, mesenteric vasculitis, protein loosing enteropathy, peritonitis, pancreatitis (4%), biliarycirrhosis, cholangitis and cholecystitis have also been reported[19].

5. Cardiovascular: Pericarditis including pericardial effusion in 30% to 45%, myocarditis in 5-10%, endocarditis15%, Libman-sack's in 2-5% and valvular heart disease AR & MR 18-74% are seen[8,9,11,24].

Lagana et al, 1999 studied autonomic dysfunction to be associated with microvascular disease or metabolic alteration.

Coronary artery heart disease is seen as an effect of accelerated atherosclerosis in patients even < 35 years because of steroid induced dyslipidemia, hypertension and immune complex mediated intracellular cholesterol accumulation[20,21]. The microcirculation can be affected by vasculitis, APLS, Raynaud's and atherosclerosis.

Pulmonary hypertension can be seen as a reversible entity. When it is secondary to ILD it is of severe type with irreversible changes of the capillary bed. Pulmonary capillaritis and plexogenic arterial transformation has been reported with poor prognosis. Pulmonary embolism and acute reversible hypoxemia has been reported**.** Raynaud's phenomenon is seen in 75% of patients with SLE and pulmonary hypertension. There is high incidence of anti U1 RNP, rheumatoid factor and APL antibody in patients with pulmonary hypertension[11].

6. Pulmonary involvement: SLE can involve any part of the respiratory system[22,23]. Upper Airway involvement is seen in 10-15% of SLE and the manifestation are epiglottitis, subglottic stenosis, vocal cord paralysis, laryngeal oedema or ulceration, inflammatory mass lesions or nodules, cricoarytenoid arthritis and as necrotising vasculitis. Pleural Disease is seen in 36% of the patients. About 38% to 40% of patients with normal chest x-ray have abnormal CT findings[12].

Parenchymal Disease is seen in 7% as acute lupus pneumonitis, alveolar haemorrhage syndrome, chronic interstitial lung disease, lymphocytic interstitial pneumonia (LIP), Bronchiolitis obliterans with or without organising pneumonia. Acute reversible hypoxemia in lupus pneumonitis is due to increased levels of complement split products that activate neutrophils which aggregate within pulmonary vasculature causing decreased oxygenation capacity which resolves with steroids. Alveolar haemorrhage and acute lupus pneumonitis are life threatening. Shrinking lung syndrome was described by Hoff brand in 1965. This is due to diaphragmatic weakness, basal pleural or pulmonary fibrosis and primary myopathy, disease activity and phrenic nerve involvement[13]. Chest X-ray shows progressive elevation of diaphragm with normal parenchyma. Normal corrected Carbon monooxide transfer with restrictive pattern in PFT is characteristic feature of this condition[23].

7. Hematologic Features : Anaemia of chronic disease is seen in 60-80%, autoimmune haemolytic anaemia (AIHA) in 10% with positive Coomb's test in 20-60%. Leukopenia seen in 30% is associated with neutropenia or lymphopenia; generally between 2500-4000/mm^3 and is associated with active disease. Thrombocytopenia is seen in 30-50% and is related to antiplatelet antibody or APL antibody. Immune thrombocytopenia (ITP) is seen in 5–10% of SLE cases at the onset of disease. ANA positivity in ITP is about 15-20%. Other antibodies seen are those to factor II, VIII, IX, XI or XII, protein C, S and antithrombin III. Pancytopenia is seen in 2-4% of the cases at the onset[8,9,11]. Anecdotal reports of TTP have been reported.

Nescher et al in his study reported 28 SLE patients associated with TTP. Dubois et al reported that TTP can follow SLE by several years or occur concurrently with SLE and rarely antedate the onset of SLE.

Tzioufas AG et al 1997 found 15.2% patients to have antibody to erythropoietin and it was associated with anaemia and active disease. AL-Shahi R et al 1997, discovered platelet CD36 glycoprotein antibody which produced severe thrombocytopenia and microangiopathic haemolytic anaemia (MAHA).

Splenomegaly is seen in nearly 30% of childhood SLE and about 20% in adult onset. Lymphadenopathy is seen in 60% at the onset and usually subsides with treatment[6].

Anti Phospholipid Antibody Syndrome and SLE

Secondary APL in SLE is characterised by the presence of APL antibody (+ve ELISA for IgG/IGM ACL antibody / +ve LAC/BFP test for syphilis), recurrent arterial / venous thrombosis, fetal loss and thrombocytopenia. Association has been seen with livedoreticularis, cerebral disease (CVA, TIA, chorea, amaurosis fugax) and pulmonary hypertension. Persistent false positive VDRL is seen in various SLE studies as 10-20%. LAC can be detected by diluted russel viper venom test, kaolin clotting time and complete activated partial thromboplastin test with three steps procedure. In SLE, ACL is positive in 50% of LAC positive cases but LAC is positive only in 20% of ACL positive cases. In catastrophic APLS, the ACL antibodies may be negative because it is used up in the consumption[25].

Pathogenesis

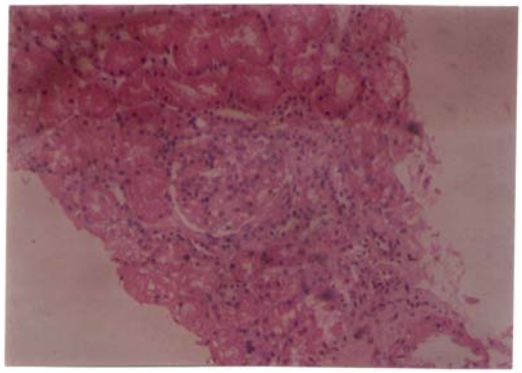
Endothelial injury precedes non-inflammatory vascular occlusion. Antibody are directed against a co-factor. β2 glycoprotein-I sushi domain, which on binding to phospholipid template undergoes a conformational change and triggers off the coagulation cascade. The

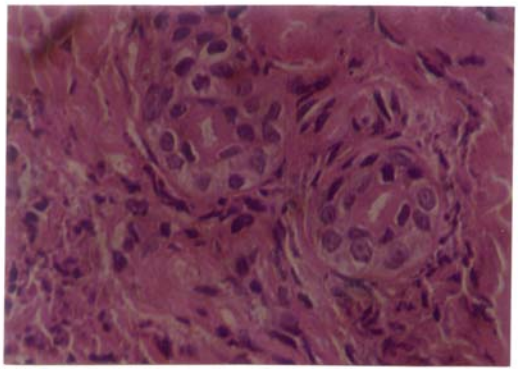
antibodies are directed against phospholipids , prothrombin, protein C, protein S and thrombomodulin[29,30,31,32,33].

8. Renal lupus: Cameroon while analyzing 365 renal biopsies found Type 1 in 6%, Type 2 in 19%, Type 3 in 23%, Type 4 in 43%, Type5 in 9% and Type6 in 1%. Bhuyan et al 15 observed among 85 SLE Indian patients, 65% had renal involvement, with hypocomplementemia and high dsDNA activity. Chandrasekharan et al [16] reported 37% renal involvement among 170 patients. Renal lupus is found in 50-70% of patients during the disease course[6,8,10]. WHO classification of lupus nephritis Plate 3.

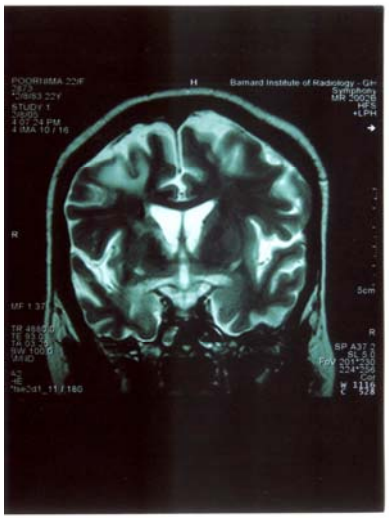
Type of lesion	***Microscopic findings***
0 - Normal glomeruli	A- Nil B - Deposit in EM/IFT
1 - Pure mesangial	A - Mesangial widening & mild hypercellularity B – Moderate hyper cellularity
2 - FSGN	A - Active necrotizing B - Active and sclerosing lesions
3 - FPGN	A - Active necrotizing B - Active and sclerosing lesions
4 - Diffuse GN	A - Without segmental lesion B - With activenecrotising lesion C - With active and sclerosing lesion D - Sclerosing lesions
5 - Diffuse membranous GN	A - Pure membranous B - Class II + membranous C - Class III+ membranous D - Class IV+ membranous
6 - Advanced sclerosing GN	Sclerosing Glomeruli

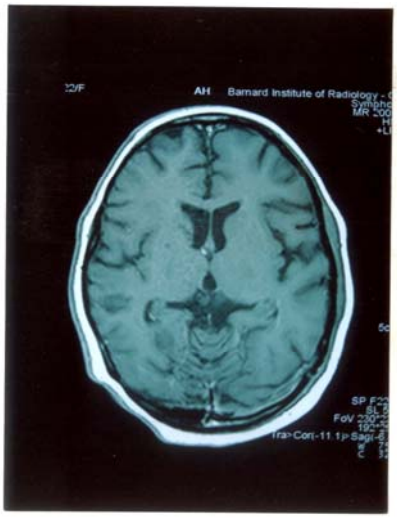
LUPUS NEPHRITIS





MRI BRAIN





Immunopathogenesis in renal lupus is due to antidsDNA and antihistones antibodies, which get complexed with the polyanionic glycoprotein in the glomerular ground substance. Along with the antigen antibody complex, IgG, IgM, IgA, C1, C3 and fibrinogen get deposited. The renal activity scoring is used by the NIH from the work of Austin et al. Activity is scored as 4 grades (glomerular proliferation, necrosis-karyorrhexis, hyaline thrombi, cellular crescents, leukocytic exudation, monocytic infiltration in the tubules) a total of 24 and chronicity is scored as (sclerosing glomeruli, fibrous crescents, tubular atrophy and interstitial fibrosis) as 3 grades with a total of 12. Renal involvement is nearly 100% in the course of the illness and hence renal biopsy is mandatory[13,26,29].

Many studies on SLE, have reported that hydroureteronephrosis, mega ureters, sterile cystitis and bladder dysfunction were seen[9,15].

9. Neuropsychiatric: Twenty six percent (Dubois et al) of SLE patients manifest NP features[29]. The 1999 ACR Nomenclature Committee identified 19 different NP conditions that are part of the lupus complex 12 with CNS and 7 with PNS. They are headache, cognitive dysfunction, mood disorder, acute confusion state, psychosis, seizures, aseptic meningitis, demyelinating syndrome, movement disorder, stroke syndromes, transverse myelitis, GullianBarre like inflammatory demyelination, myasthenia gravis, autonomic neuropathy, cranial and peripheral neuropathy. Anti sm antibody is with neurosis and anti RNP is seen with psychosis. The other antibodies seen are anti neuronal, anti lymphocyotoxic, anti myelin, antibodies to the neurotransmitter and receptors. CT scan and MRI scan will enable to delineate the exact area involved, but for neuronal function PET studies are helpful[30,31] Plate 4.

Eye manifestation are conjunctivitis, iritis, choroidal and retinal vasculitis, glaucoma, cataract, opticneuropathy, papilloedema, cytoidbodies (pathologically they represent fibrinoid degeneration of the nerve terminals), macular degeneration, orbital myositis and ophthalmoplegia. SLE can present at the onset with the retinal vasculitis in 3-4% of the cases[32].

SLE can involve the external ear in sec. APLS, vasculitis involving the tympanum, middle ear, semicircular canals and as sensorimotor or conduction deafness.

PREMATURE ATHEROSCLEROSIS IN SLE

Atherosclerosis is an active inflammatory and immune mediated disease[32,33,34,35]. Immune complex formation, complement activation, upregulation of CD 40-40L interaction (between B and T cells), C reactive protein and APLS cause endothelial injury and local inflammation and LDL uptake by endothelial cells. Hyper triglceridemia, hypertension and renal disease adds on to the atherosclerosis burden. Among Asians there is higher insulin resistance producing hypertriglyceridemia and low density lipoproteinemia, lowered HDL, procoagulant tendency, increased proinflammatory cytokines and endothelial dysfunction which lead on to early atherosclerosis. This has been observed in other studies [37,38,39].

DEVELOPMENT OF THE PLAQUE

The stages through which plaque evolves are 1) Leukocyte recruitment, adhesion molecule upregulation along with increased homocysteine levels resulting in endothelial injury. 2) The smooth muscle cell and the fibroblast transform into foam cell by taking up the

LDL components. This phenomenon is favoured by impaired lipoprotein lipase, ↑ apolipoprotein B, ↓HDL3, ↑HDL 2 and ↑ serum lipoprotein (a) levels. The latter component is increased in lupus nephrotic syndrome. Complement fixing antibody inhibit 27 (OH) cholesterol which down regulates LDL receptors. β2glycoprotein-1, oxidized LDL, M-CSF, MCP-1, TNF-α, help in the proliferation of macrophage and elaboration of tissue factor enabling increase plaque formation 3) Finally the plaque ruptures[40,41,42].

Joanne McDonald et al. in his study reported that coronary artery involvement depends on SLE duration, usage of steroids and atherosclerosis at other sites.

The assessment of vascular disease can be done by Duplex Doppler of the carotids looking for plaque as a marker and measurement of intimo medial thickness as a surrogate marker of diffuse atherosclerotic process. One can measure IMT, peak systolic velocity, end diastolic velocity, waveform, plaque, compliance, dispensability, stiffness index, stenosis and elastic incremental modulus[43].

Theodoridu A et al[58] measured ankle branchial index by using 12 cm cuff and 8MHz Doppler probe and found that if the ratio is <1 then there is vascular compromise in the peripheral vessel. This is picked up in the late stage of atherosclerotic disease.

Pigouli et al[44] demonstrated in 1980's that Doppler U/S can be used for carotid measurement. The double line pattern correlated with the intimo medial thickness seen in histopathology. The positive predictive value and negative predictive value for categorization of

stenosis >50%diameter reduction was seen more accurate by B mode ultrasound.

IMT is the distance between lumen –media interface and media-adventitia interface.

Cholesterol lowering and atherosclerosis study (CLAS) study showed that the relative risk for MI and coronary death was 3.1 for each 0.03 mm /yr (1 SD) ↑ in mean CCA IMT[25].

Cardiovascular health study (CHS) showed in 5888 non smoking males aged 40-59yrs who had undergone previous CABG, were observed to have an increased risk of stroke and MI for each 0.2mm/yr(1SD) of intimo medial thickness[34]. Thus in several studies it was highlightened that Duplex Doppler measurement provide valuable information about the genesis and progression and atherosclerosis.

The morphology appreciated in Doppler U/S is as follows,

Stage I-normal wall,

Stage II- wall thickening (stenosis with out plaque),

Stage III- non stenosing plaque,

Stave IV- stenosing plaque. Death occurs in stage III&IV events.

The other type of classification of stages of plaque along with scoring is from A to F which was devised Backero G et al. in 1995.

Class A: Normal, 3 US layers clearly separated. No disruption of lumen-intimal interface for at least 0.5 cm - Score (0).

Class B: Interface disruption: lumen-intimal interface disruption at intervals < 0.5 cm - Score (2).

Class C: Intima-media granulation: granular echogenicity of deep, normally unechoic intimal-medial layer - Score (4).

Class D: Plaque without hemodynamic disturbance: wall thickening and increased density involving all US layers. No hemodynamic disturbance on duplex - Score (6).

Class E: Stenotic plaque: as in D but with hemodynamic disturbance on duplex - Score (8).

Class F: Stenotic plaque and presence of symptoms - Score (10).

Studies in SLE

Among 229 SLE patients, in 1992 **Petri et al.**[44] studied the frequency and risk factors of CAD. He found that a 0.2mm increment of IMT in CCA and 0.5mm in ICA IMT, increases the risk of CAD.

Mansi et al.[45] in 1999studied the prevalence and risk factors of carotid plaques in females with SLE and saw that mean IMT was 0.71$\pm$0.14, for plaques.

Rahman et al.[46] in 2000 studied vascular events in SLE with hypertension. The factors that contributed were hypertension , azotemia, corticosteroid usage and hypercholestrolemia[50].

Fallaschie et al.[47] in 2000, studied atherosclerotic events in the carotids and the risk factors in 26 childhood SLE patients. He found that below 16 yrs mean IMT is 0.5mm$\pm$0.05mm. IMT did not correlate with

age, disease duration, SLEDAI but did correlate with nephrotic range of proteinuria >3.5gm / 24 hrs and lipid profile[63].

Doria et al.[50] study in 2003, of SLE patients showed that IMT reading of 0.9mm for thickened intima and of >1.3mm for atherosclerotic plaque was present as significant cut off limits.

Duplex Doppler of carotid can be studied in comparison with other peripheral arteries also. **Talia Wolak et al**. in 2004 studied 51 patients with SLE along with age and sex matched controls. High risk factors like hypertension was found in 30% smoking in 23% and dyslipidemia in 17%. A 3.17 fold of atherosclerotic plaque was found in the patients.

Duplex Doppler can be used as a early diagnostic tool for detecting premature atherosclerosis.

CERTAIN SPECIAL SITUATIONS

Drug induced SLE is seen in Procainamide, isoniazid and hydralazine commonly. CNS, renal disease, leukopenia, mucocutaneous ulcers and anemia are rare. Antihistone Ab's are positive in 100% of drug induced SLE patients Recently usage of TNF α blockers show ANA positivity of 10-15%, and is reversible with drug withdrawal[9,31].

LUPUS IN MALES

World wide reports on male SLE patients reveal that the onset is with fever, and milder skin manifestation. Chellapandian et al[60] in a SI study observed renal involvement, recurrent infections and coronary artery disease were seen more and malarrash, serositis, neuropsychiatric, leukopenia and thrombocytopenia were seen with lesser frequency.

Prognosis is worse. Fifty percent of patients in one study series had elevated plasma estrogen levels **(Miller et al, 1980)**, hence individuals with Klinefelter's syndrome are more susceptible to develop SLE[15,16].

Late onset LUPUS

Chandrasekharan et al[8,9] had observed in his study that, there was less female preponderance and musculoskeletal and haematological manifestations were more than renal, serositis and CNS involvement.

Lupus beyond 50 years represents 10% of study population. There is a lesser frequency of anti dsDNA Ab & decreased C 3/C4. Overlap between lupus and Sjogren's is common. Polymyalgia rheumatica like presentation can occur[16].

Pregnancy and Lupus

Fertility is normal in SLE patients (exception - renal failure is associated with decreased fertility). Dysmenorrhea, amenorrhoea or oligomenorrhea is common in active disease. 28-40% of pregnancy wastage is seen as spontaneous abortion, still birth and perinatal deaths. Fetal loss is due to active disease, APLS or active lupus nephritis. APLS is associated with IUGR, PET and preterm delivery[51].

Neonatal lupus syndrome is associated with 20% maternal anti Ro/La antibodies, thrombocytopenia, rash and congenital heart block. Indicators of activity are elevated anti ds DNA levels, alternative pathway hypo complementemia, true arthritis, rash, mucosal ulcers and lymphadenopathy[6,52].

Johns KR et al in 1998 studied pregnancy outcome in 54 cases and found mean gestational age for live births to be 36 weeks and mean birth weight to be 2.4 - 3 kg. He found that renal flares had a worse outcome.

LUPUS AND MALIGNANCY

According to studies by John H. Klippel et al; in 1995, documented an increased risk for lymphoma and soft tissue sarcoma. Malignant lymphoma and macroglobulinemia is due to prolonged antigenic stimulation of B-lymphocytes.

ANA NEGATIVE LUPUS

True ANA negative cases comprise less than 2%. Several reports have stated the delayed appearance of ANA. A negative ANA can become positive by merely using another substrate, e. g. with HEp-2cell line shows that 98% are ANA positive because non DNA containing antigens Ro/SS-A are better represented when these cell lines are studied (Reischllin et al) The causes for ANA negativity are pro zone phenomena, invivo binding of ANA by tissues, ANA hidden within circulating immune complexes, variations in microscope quality, substrate specificity, use of monospecific antisera, technical inaccuracy and low cut off dilutions. ANA negativity is seen in Primary APL antibody syndrome, early disease, previously positive ANA made negative by steroids, cytotoxic drugs or uremia.

Childhood onset SLE: In children the sex ratio is nearly F:M 2:1 (<12 yrs) and 6-7:1 (> 12 yrs). Tucker et al[10] compared childhood SLE to adult SLE and he observed that the onset was more severe and the hematological, renal complications were frequent while cardiopulmonary diseases were more common in adult onset group. Anti

ds DNA, anti Sm, anti RNP and decreased C3 were more frequently observed in childhood SLE.

The treatment have to be individualized and depends on organ involvement and disease flares. Steroid is still mainstay of treatment.

Morbidity and mortality in SLE depends on the systems involved (renal, neuropsychiatric, cardiovascular, ILD, PHT), age of the onset of the disease and infections. It has been seen that in 1955, 5 yr survival was 50%, in 1990 10 yr survival has risen to >90% and 20 yr to 70% and mortality 3-5 times greater than general population.

Joshi et al[55] in his boot's oration 1994, reported that SLE in pediatric age group is severe and infections still form a considerable cause (next to renal and CNS) for the mortality in developing countries.

Lupus activity can be periodically assessed by indices like SLEDAI, (appendix 2). It is scored by events which has occurred 10 days prior. Twenty four items involving 9 systems are scored from 1 to 8 (Appendix 3).

Mex-SLEDAI was devised for the developing countries wherein the investigation (immunology and complement assay) have been removed and scoring involves only clinical assessment and simple tests. BILAG is a grading system from a to d. SLAM measures 32 items of 11 organs where the degree of severity is recorded as 0-3.

SLICC / ACR DI is a damage assessment index wherein damage that has occurred in the last 6 months is scored (Appendix 4).

MATERIALS AND METHODS

One hundred consecutive patients who attended the Rheumatic care center, Government General Hospital, Madras Medical College, Chennai and satisfied the revised 1982 ACR criteria for SLE, during 2003 January to 2004 December were selected out of 12,786 adult and 2282 childhood Rheumatic cases. 68 were adults and 32 were children. A detailed history was documented and after clinical examination (Appendix 2) they were subjected to laboratory investigations which included complete blood count, erythrocyte sedimentation rate, (Westegren method) serum creatine, blood urea, urine analysis, muscle enzymes and 24 hrs urine analysis. Immunological tests include tests for ANA by IIF on rat liver substrate, RF & CRP by latex agglutination method by using commercial kits provided by Vital Diagnostics, Chennai. Antibodies to dsDNA, Sm, Ro, La, U1RNP, ACL was done by ELISA using commercial Bindazme company kits. LAC was done by Activated partial thromboplastin method complete test with three step procedure, using commercially obtained APTT substrate. The significant cutoff values for the positivity of the various antinuclear antibodies had already been determined in our lab with respect to healthy controls. C3, C4 were quantitated by single radial immunodiffusion (SRID) using Diffusa plates from Bioscientifica. The cut of values taken were (C_3-70 mg/L, C_4-20 mg/L). Serological test for syphilis were performed by the VDRL test in the Institute of Sexually transmitted diseases, M.M.C.

All patients underwent a 12 lead ECG, skiagram of the chest and relevant areas. Patients were subjected for 2D echocardiogram and doppler study by cardiologist. Laboratory evidence of renal involvement was noted and renal biopsy was done. Renal biopsy was subjected to light and immunofluorescent microscopy. Special tests like EEG, EMG,

CT scan, MRI, EMNCS, Bone marrow, CSF analysis were done in relevant situations. The clinical, immunological profile of childhood and adult patients were analysed and compared with previous studies in India.

The study population for Duplex Doppler evaluation was drawn from the previous sample. Patients who were non compliant to the instruction were not included. The sample contained 20 children and 30 adults who were evaluated for subclinical atherosclerosis.

A information on the age, disease duration, smoking, family history of atherosclerosis disease previous diabetic state, steroid usage and presence of hypertension was noted. SLEDAI scoring was done at the point when patients were subjected to Doppler ultrasound.

BP in adults above 140/90mmHg, in children 120/80mmHg was taken as cut off value. The laboratory variables like the haemoglobin (Hb) Total count (TC), platelet (Pt), blood glucose, chest X-ray (CXR), LAC, ACL, anti dsDNA, C_3, C_4 were noted. Estimation of lipid profile was done on fasting serum sample in these patients.

Colour Doppler interrogation of the carotid arteries at the level of CCA, carotid bulb, ECA, ICA using a 8.5 MHz probe by a experienced Radiologist.

The parameters like intimomedial thickness (IMT), stenosis, peak systolic velocity, end diastolic velocity, wave form and presence of plaque were studied. Presence of the parameters was taken as 1 and absence of the parameter was taken as 0.

The cut off values for the laboratory variables was taken as follows:

1. Haemoglobin-children 12mg%, adults 10gm%
2. Total count - 4000/ mm^3
3. Platelet - 1lakh / mm^3
4. Total cholesterol <200 mg%,
5. LDL cholesterol < 100 mg%,
6. HDL cholesterol 40 mg%,
7. Triglycerides <150 mg%
8. Lupus pneumonitis in CXR-presence as 1, absence as 0
9. Complements -C_3 or C_4 normal as O, reduced levels as 1

The LDL was calculated by Friedwald equation:

LDL cholesterol=Total cholesterol-(HDL cholesterol+1/5 Triglycerides).

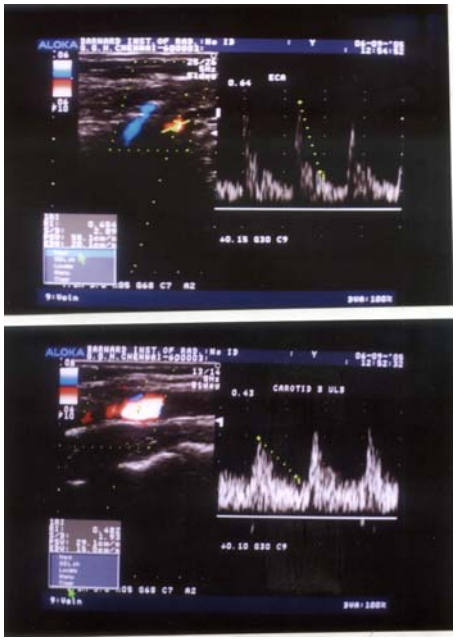
TC/HDL, LDL/HDL ratios were calculated.

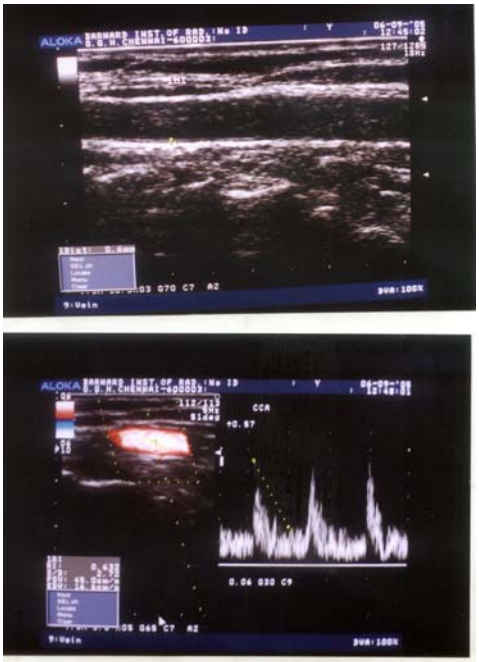
The doppler parameters given below were analysed with variables like LAC, ACL, anti ds DNA, C3, C4, CXR, haemoglobin (Hb), total count (TC), platelets, (pl), lipid components (TCl, HDL, LDL, TGL) and TCl/HDL, LDL/HDL ratios.

(I) 1. IMT
2. Plaque formation
3. Spectral widening
4. Stenosis for laboratory variables.

(II)1. IMT
2. Plaque for risk factors (Traditional and related to SLE disease).

COLOUR DUPLEX DOPPLER OF CAROTIDS





STATISTICAL ANALYSIS

The clinical profile of the patients were analysed using descriptive statistics like mean, median, percentages for the different characteristics.

Analysis of the lipid profile and the Duplex Doppler of the carotids was done. Descriptive statistics like mean, standard deviation were calculated for continuous variables, while percentages were calculated for categorical variables. Chi-square test was done to determine association between two categorical variables. Student's t test was used to test for significant difference between two means. Pearson's correlation was calculated to determine association between two continuous variables. Renal involvement was analysed with Mann-whitney U test and Kruskal-Wallis test. Significance was determined at 5%. Statistical analysis was done using SPSS Ver. 11.0. Graphs were produced using Microsoft Excel.

RESULTS

Among 32 children there were 4 male and 28 female children, M: F 1:7. The mean age in childhood onset SLE was 12.6 years (range 6.5-16 yrs) and mean disease duration 1.2 years (1 month - 2.6 years). There was no child below 5 years in the study group. The observed sex ratio below 10 years was M:F = 1:4.2 and between 10 to 16 years was 1:10.

Among adults there were 4 males and the sex ratio was M:F=1:17. In the adult onset SLE the mean ages was 28 years (17-42 yrs) and the disease duration was 1.18 years (3 months - 3.6 years).

The results have been tabulated as initial manifestation and cumulative.

Table 1: INITIAL MANIFESTATION

Clinical features	Child n= 32	Adult n=68
Fever	65%	10%
Cutaneous	48%	70%
Arthritis	45%	51%
Renal	9.3%	7.3%
Haemolytic anaemia	12.5%	3.2%
Thrombocytopenia	12%	6.2%
Seizures	6.2%	2.9%
Pleural effusion	3%	17.6%
Pericardial effusion	3.1%	20%
Ascites	3%	20.5%
Lymphadenopathy	62%	36.6%

In children among the initial manifestations, fever was a prominent feature in 65%, followed by arthritis and cutaneous involvement. Adults had cutaneous more pronounced along with photosensitivity and alopecia.

CUMULATIVE MANIFESTATION:

1. Muco-cutaneous

	Child	Adult
Cutaneous	52%	75%
ACLE	65%	62%
SCLE	1%	28%
DLE	1%	5.8%
Oral ulcer	44%	68%
Photo sensitivity	54%	72%
Raynauds	6.25%	13.2%
Digital gangrene	2.9%	7.3%
Urticaria	2.9%	5.8%
Dyschromia	22%	65%
Alopecia	48%	57%
Fever	82%	65%

2. Musculoskeletal

	Child	Adult
Arthralgia	76%	82%
Arthritis	52%	58%
AVN	12.5%	4.4%
Jaccouds	12.5%	13.2%

3. Reticuloendothelial

	Child	Adult
Hepatomegaly	55%	9%
Splenomegaly	25%	20%
Lymphadenopathy	55%	25%

4. Cardiovascular

	Child	Adult
MVPS	6.2%	4%
MR	3%	2.9%
Pericardial effusion	18.7%	14.7%
Myocarditis	3%	2.9%
Libman-sach's	Nil	Nil
IHD	Nil	1.4%
PHT	Nil	5.8%

5. Pulmonary

	Child	Adult
Pleural effusion	31.2%	17. 64%
Pneumonitis	9.3%	5. 8%
Pulmonary-haemarrhage	3%	Nil
ILD	Nil	2. 9%
Shrinking lung	Nil	1. 4%

6. Gastrointestinal

	Child	Adult
Ascites	6.5%	7.2%
Pancreatitis	nil	4%
Enteritis	6%	12%

7. Renal Biopsy

WHO Classification	Child Total 18.6%	Adult Total 16.2%
Class I	-	-
Class II	3.1	4.4%
Class III	3.1%	2.9%
Class IV	6.2%	7.3%
Class V	6.2%	1.4%

8. Renal manifestation

	Child Total 65%	Adult Total 44%
Proteinuria	46%	60%
Haematuria	21%	26%
Casturia	9.3%	26%

9. Neuropsychiatry

CNS manifestations	Child Total 37.5%	Adult Total 36%
Seizures	30%	5.2%
EEG	12.5%	8.8%
CVA	Nil	2.9%
PNS	2.9%	4.4%
Chorea	Nil	Nil
Spinalcord	Nil	1%
Eye	9.3%	7.3%
Psychiatry	31.2%	36.7%

10. Muscular system

	Child	Adult
Myositis	6%	8%
Muscle enzyme	21%	17. 8%
EMG	15%	22%

11. Investigation

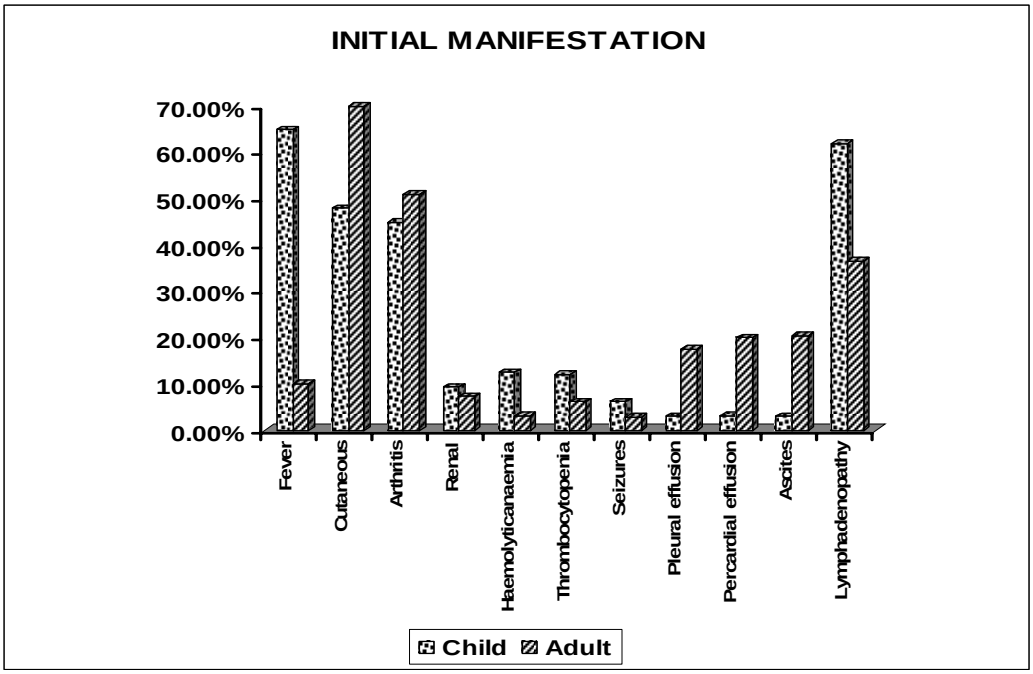
Laboratory	Child	Adult
Anaemia-haemoglobin	56%	51.4%
Coombs	12.5%	11.7%
Thrombocytopenia7	18.7%	22%
TTP	Nil	Nil
Leukopenia	15%	8.8%
Lymphopenia	3%	2.9%
MRI	3%	1. 4%
CT scan	3%	5.8%
ANA (negative)	2.9%	4.4%
ANA (positive)	97.1%	95.6%
ds DNA	65.6%	51.4%
ACL	16%	13%
LAC	9.3%	8.8%
C3	18.75%	13-20%
C4	3.75%	3.5%

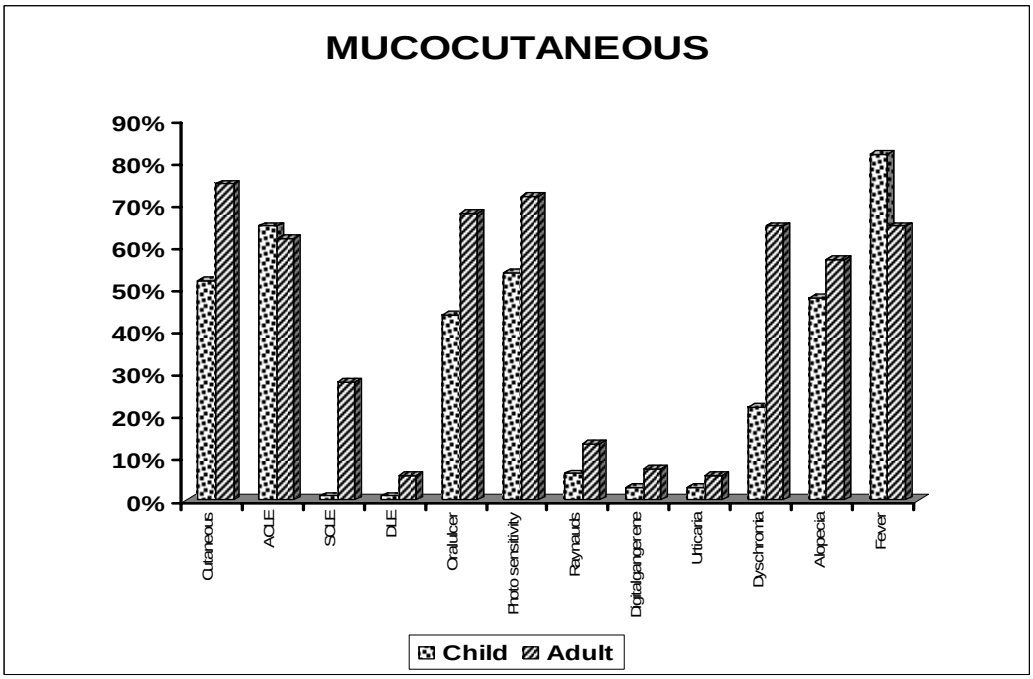
12. Muscular system

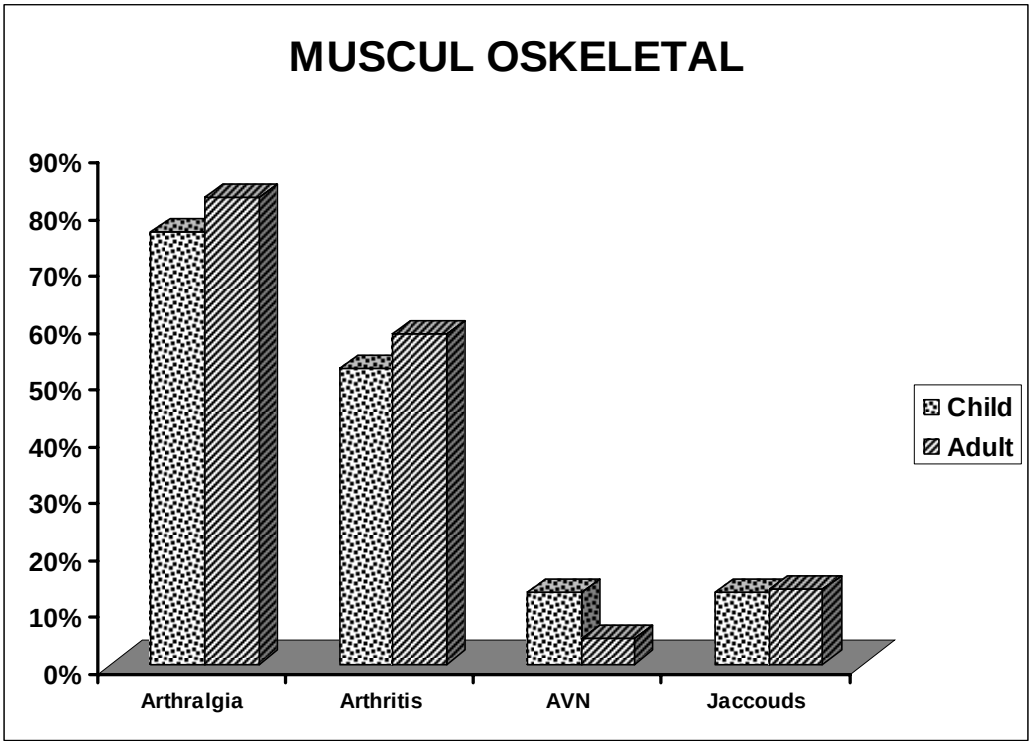
Lipidlevels	*Child n= 25*	*Adult n=60*
↓HDL	3 N 22	12 N 48
↑LDL	5 N 20	10 N 50
↑Total Cholesterol	5 N 20	16 N 44
↑Triglycerides	8 N 17	28 N 32

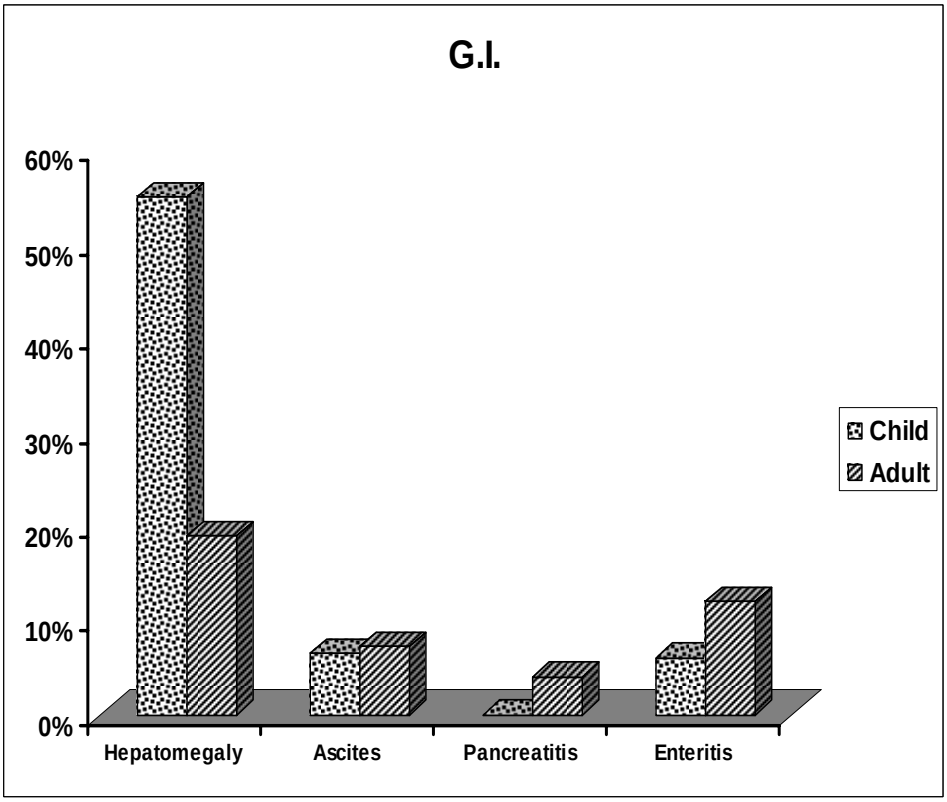
N= normal

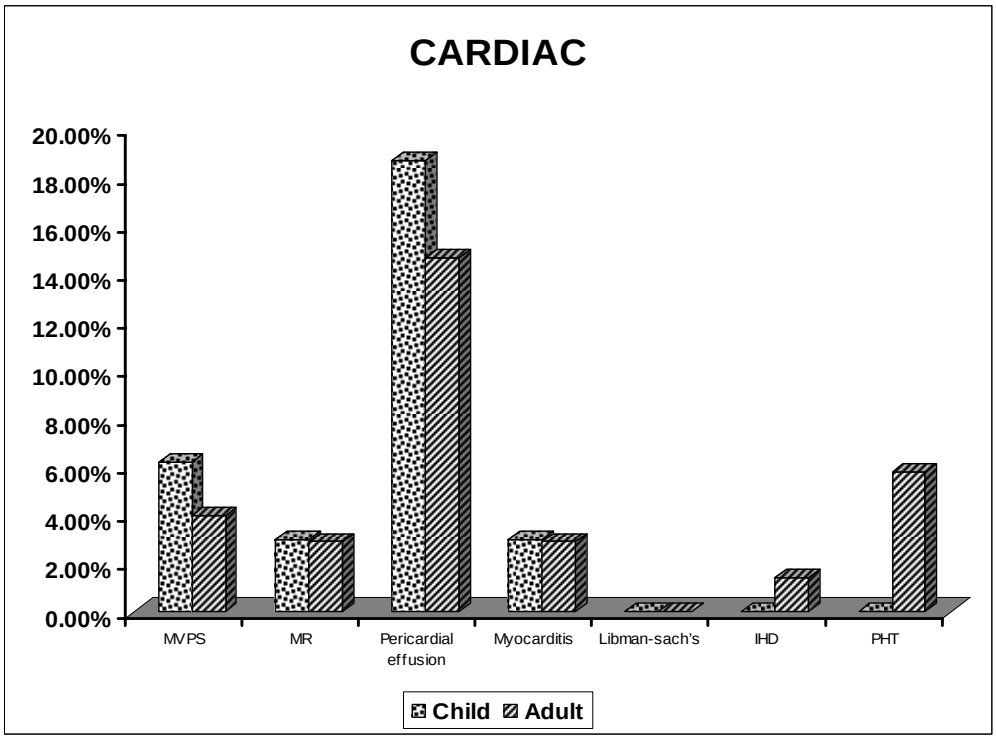
Treatment	Child	Adult
Methylprednisolone	21%	30%
Oral Prednisone Low dose High dose	46% 53%	47% 52%
Chloroquine	> 10 years 25%	91%
Azathioprine	12.5%	16%
Cyclophosphamide	18.75%	22%
Methotrexate	1.4%	2.9%
Anticonvulsants	15.6%	16.1%
Acitrom	9.3%	15.2%
Antihypertensives	15.6%	22.05%
Antidepressants	1%	36%
Aspirin	9.3%	36%
Atorvastatin	1%	7.3%
ATT	Nil	2.9%
Antianginal	Nil	4.4%

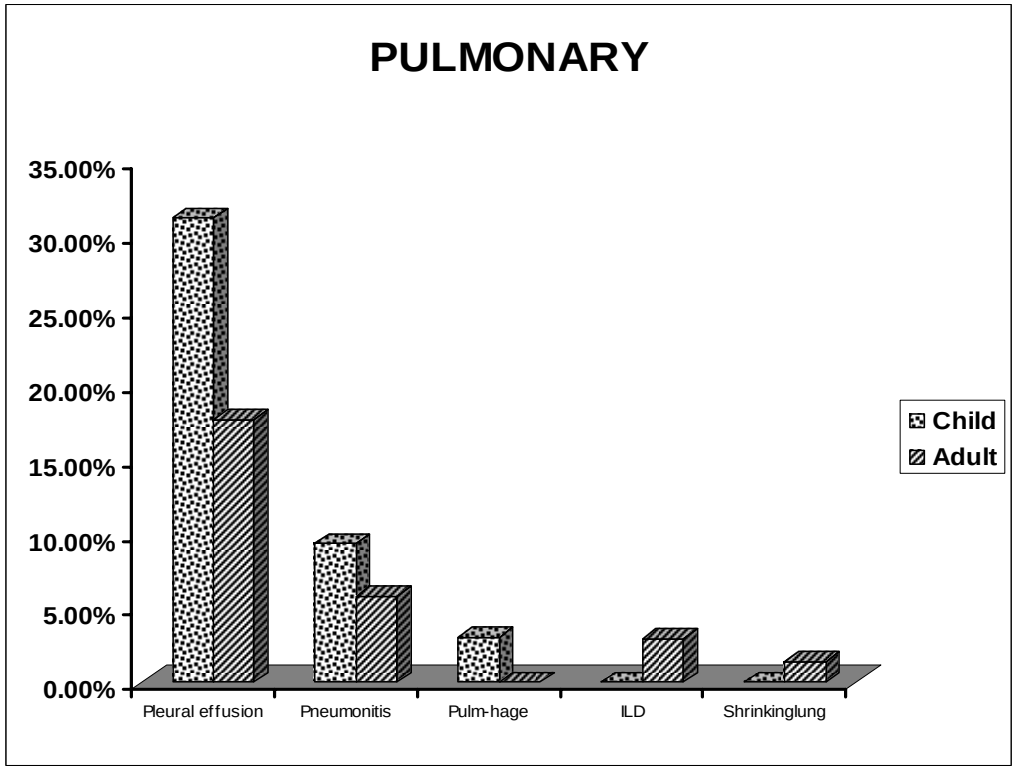

INITIAL MANIFESTATION
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
Fever
Cutaneous
Arthritis
Renal
Haemolyticanaemia
Thrombocytopenia
Seizures
Pleural effusion
Percardial effusion
Ascites
Lymphadenopathy
Child
Adult

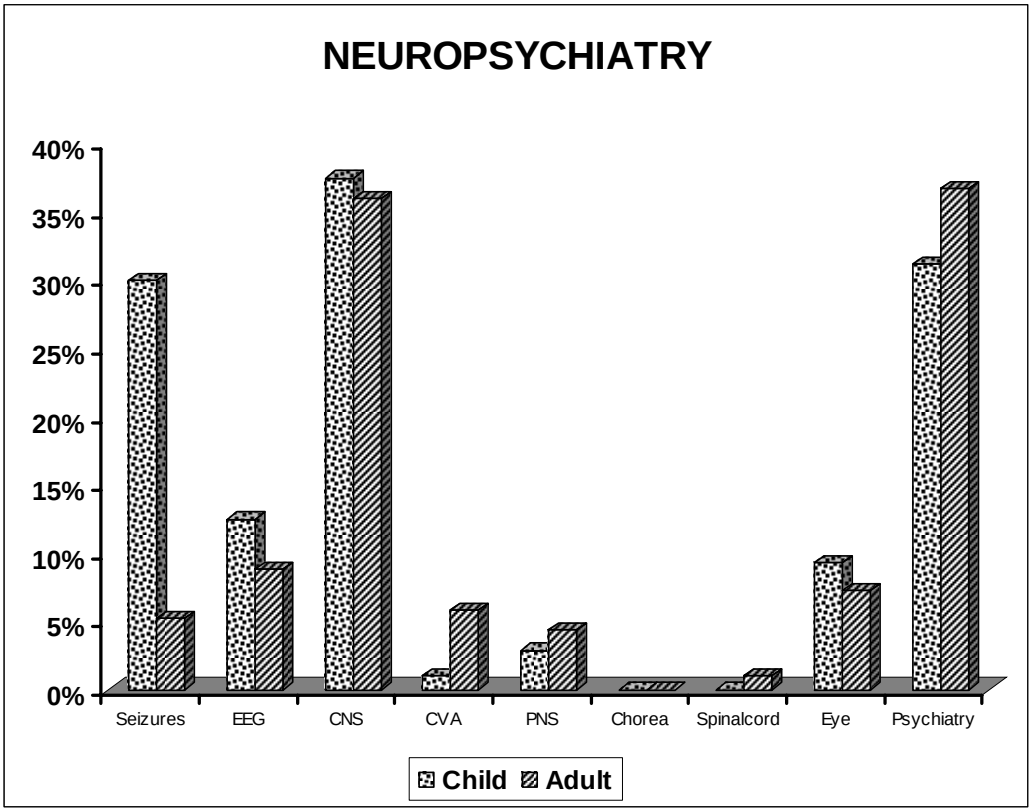

MUCOCUTANEOUS
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cutaneous
ACLE
SCLE
DLE
Oral ulcer
Photo sensitivity
Raynauds
Digital gangrene
Uticaria
Dyschromia
Alopecia
Fever
Child
Adult

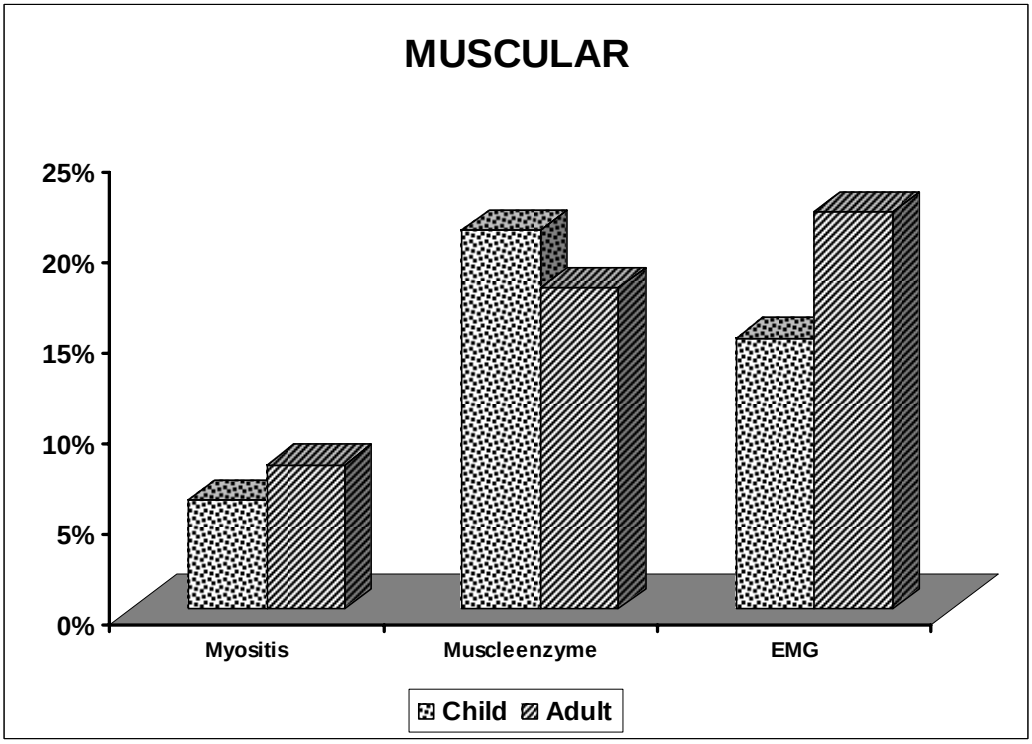

MUSCUL OSKELETAL
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Arthralgia
Arthritis
AVN
Jaccouds
Child
Adult

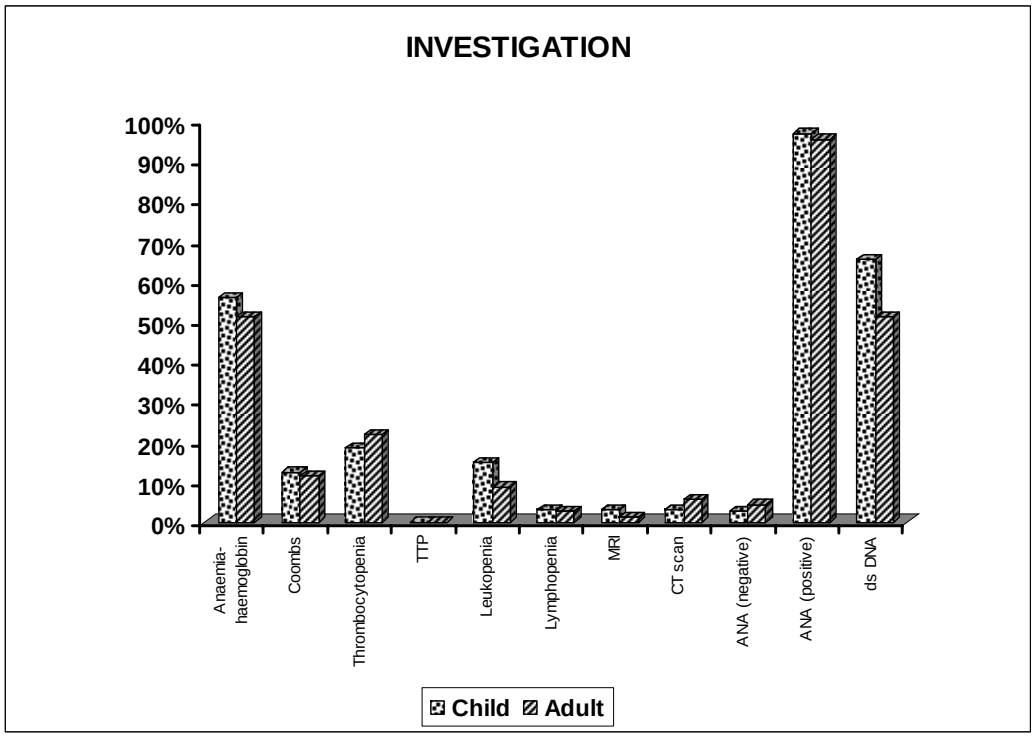

G.I.
60%
50%
40%
30%
20%
10%
0%
Hepatomegaly
Ascites
Pancreatitis
Enteritis
Child
Adult

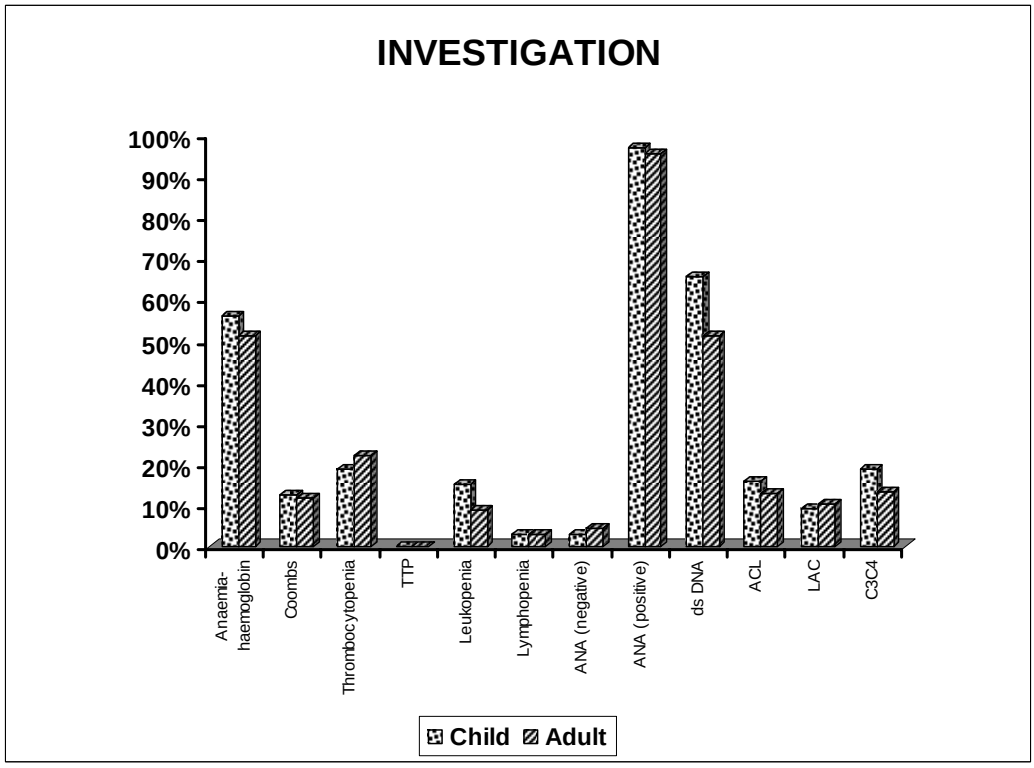

CARDIAC
20.00%
18.00%
16.00%
14.00%
12.00%
10.00%
8.00%
6.00%
4.00%
2.00%
0.00%
MVPS
MR
Pericardial effusion
Myocarditis
Libman-sach's
IHD
PHT
Child
Adult

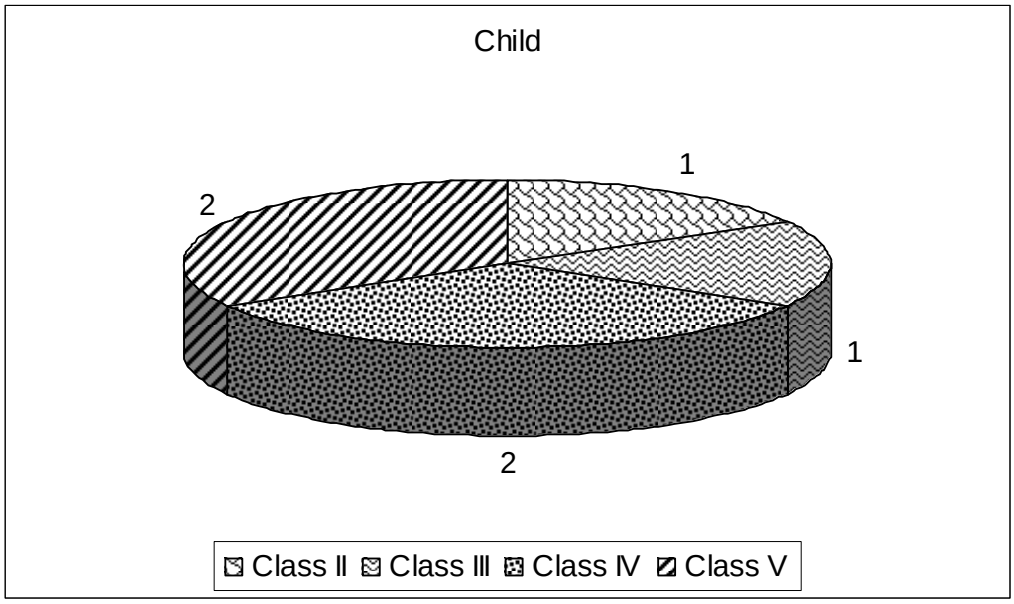

PULMONARY
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
Pleural effusion
Pneumonitis
Pulm-hage
ILD
Shrinkinglung
Child
Adult

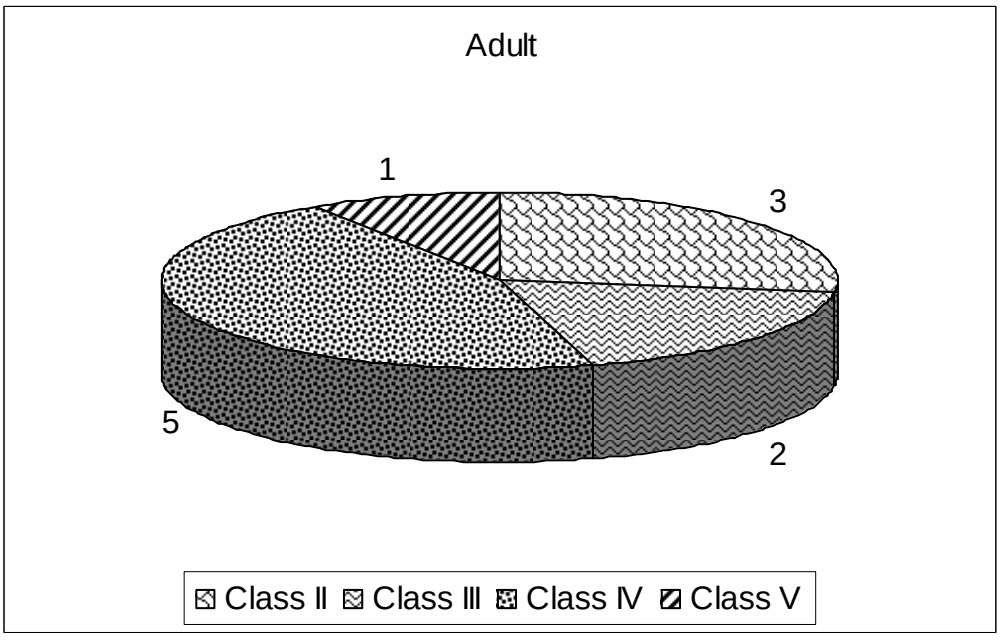

NEUROPSYCHIATRY
40%
35%
30%
25%
20%
15%
10%
5%
0%
Seizures
EEG
CNS
CVA
PNS
Chorea
Spinalcord
Eye
Psychiatry
Child
Adult


MUSCULAR
25%
20%
15%
10%
5%
0%
Myositis
Muscleenzyme
EMG
Child
Adult


INVESTIGATION
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Anaemia-haemoglobin
Coombs
Thrombocytopenia
TTP
Leukopenia
Lymphopenia
MRI
CT scan
ANA (negative)
ANA (positive)
ds DNA
Child
Adult


INVESTIGATION
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Anaemia-haemoglobin
Coombs
Thrombocytopenia
TTP
Leukopenia
Lymphopenia
ANA (negative)
ANA (positive)
ds DNA
ACL
LAC
C3C4
Child
Adult


Child
1
2
1
2
Class II
Class III
Class IV
Class V


Adult
1
3
5
2
Class II
Class III
Class IV
Class V

One of the complications in SLE is recurrent infection. It was seen in 12.5% in children and 7.3% in adults.

The statistical observations between parameters of Duplex Doppler and components of lipid profile (TCl, HDL, LDL, TGL), haemoglobin, complements, anti dsDNA, LAC and ACL and the risk factors are given in the tables below.

PARAMETERS OF DUPLEX DOPPLER AGAINST VARIABLES

CHILDREN

Table1: Plaque Vs variables

Variables	0 (n = 18)		1 (n = 2)		p value*
	n	%	n	%	
LAC	1	33.3	2	66.7	**0.02**
ACL	1	50.0	1	50.0	0.19
ANA	18	90.0	2	10.0	-
Ds_dna	9	81.8	2	18.2	0.48
C3_C4	4	66.7	2	33.3	0.08
CXR	2	100.0	-	-	1.00

* Chi-square test

Table 2:Plaque

Variables	0 (n = 18)		1 (n = 2)		p value*
	Mean	SD	Mean	SD	
Hb	8.9	1.9	8.7	2.1	0.88
TC	7622.2	3771.8	6700.0	707.1	0.74
Pt	1.9	0.8	1.6	0.3	0.64
TCL	161.7	31.1	162.0	36.8	0.99
HDL	40.4	8.2	38.0	8.5	0.69
LDL	101.5	31.6	101.0	18.4	0.98
TGL	155.2	75.0	167.0	60.8	0.83

* Independent t-test

Table 3: Stenosis

Variables	0(n = 10)		1(n = 10)		p value*
	n	%	n	%	
LAC	-	-	3	100.0	0.21
ACL	-	-	2	100.0	0.47
ANA	10	50.0	10	50.0	-
dsDNA	-	-	7	63.6	0.37
C_3 C_4	1	16.7	5	83.3	0.14
CXR	2	100.0	-	-	0.47

* Chi-square test

Table 4: Stenosis

Variables	0(n = 18)		1 (n = 2)		p value*
	Mean	SD	Mean	SD	
Hb	8.9	1.9	8.7	2.1	0.88
TC	7622.2	3771.8	6700.0	707.1	0.74
Pt	1.9	0.8	1.6	0.3	0.64
TCL	161.7	31.1	162.0	36.8	0.99
HDL	40.4	8.2	38.0	8.5	0.69
LDL	101.5	31.6	101.0	18.4	0.98
TGL	155.2	75.0	167.0	60.8	0.83

* Independent t-test

Table 5: Spectralwidening

Variables	0 (n = 18)		1(n = 2)		p value*
	n	%	n	%	
LAC	1	33.3	2	66.7	**0.02**
ACL	1	50.0	1	50.0	0.19
ANA	18	90.0	2	10.0	-
ds DNA	9	81.8	2	18.2	0.48
C_3C_4	4	66.7	2	33.3	0.08
CXR	2	100.0	-	-	1.00

* Chi-square test

Table 6: Spectralwidening

Variables	0 (n = 10)		1 (n = 10)		p value*
	Mean	SD	Mean	SD	
Hb	9.7	2.0	8.1	1.5	0.06
TC	8010.0	4263.1	7050.0	2900.3	0.56
Pt	1.8	0.8	1.9	0.9	0.54
TCL	149.7	23.9	173.8	32.8	0.08
HDL	39.4	5.8	41.0	9.9	0.67
LDL	89.0	22.3	113.9	32.8	0.06
TGL	109.6	56.5	203.2	54.9	0.001

* Independent t-test

Table 7: IMT

Variables	n	Mean	Standard Deviation	p value*
LAC				
0	17	0.43	0.11	0.30
1	3	0.50	0.16	
ACL				
0	18	0.43	0.11	0.75
1	2	0.49	0.22	
ds DNA				
0	9	0.42	0.09	0.57
1	11	0.45	0.13	
C_3 C_4				
0	14	0.41	0.11	0.06
1	6	0.51	0.10	
CXR				
0	18	0.44	0.12	0.74
1	2	0.47	0.01	

* Independent t-test

Table 8: Correlation with IMT

Variables	Correlation Coefficient	P value
Hb	-0.40	0.08
TC	-0.26	0.27
PT	-0.08	0.73
TCL	0.29	0.21
HDL	-0.08	0.73
LDL	0.27	0.25
TGL	0.51	**0.02**
TCL:LDL	0.395	0.09
LDL:HDL	0.384	0.10

ADULTS

Table 1: Plaque

Variables	0 (n = 27)		1(n = 3)		p value
	N	%	n	%	
LAC	7	70.0	3	30.0	**0.03**
ACL	-	-	1	100.0	**0.002**
ANA	27	90.0	3	10.0	-
ds DNA	7	87.5	1	12.5	1.00
C_3 C_4	9	90.0	1	10.0	1.00
CXR	4	100.0	-	-	1.00

Table 2: Plaque

Variables	0 (n = 27)		1 (n = 3)		p value
	Mean	SD	Mean	SD	
Hb	8.8	1.9	7.3	1.8	0.22
TC	7103.7	1754.0	6900.0	2805.4	0.86
Pt	1.8	0.8	1.9	0.9	0.82
TCL	178.2	40.2	211.0	13.0	0.18
HDL	41.7	4.8	42.7	6.4	0.76
LDL	109.9	32.0	139.0	21.4	0.14
TGL	132.1	73.6	187.7	25.1	0.21

Table 3: Stenosis

Variables	0(n = 10)		1 (n = 20)		p value
	n	%	n	%	
LAC	2	20.0	8	80.0	0.42
ACL	-	-	1	100.0	1.00
ANA	10	33.3	20	66.7	-
ds DNA	3	37.5	5	62.5	1.00
C_3C_4	5	50.0	5	50.0	0.23
CXR	2	50.0	2	50.0	0.58

Table 4: Stenosis

Variables	0 (n = 22)		1 (n = 8)		p value
	Mean	SD	Mean	SD	
Hb	8.8	2.0	8.1	1.7	0.41
TC	7072.7	1742.5	7112.5	2150.4	0.96
Pt	1.9	0.8	1.6	0.6	0.35
TCL	168.9	36.9	216.0	22.8	**0.002**
HDL	41.5	4.8	42.8	5.5	0.55
LDL	103.8	28.3	137.6	30.1	**0.008**
TGL	116.1	55.1	197.1	83.0	**0.004**

Table 5: Spectral widening

Variables	0 (n = 22)		1 (n = 8)		p value
	n	%	N	%	
LAC	6	60.0	4	40.0	0.38
ACL	-	-	1	100.0	0.27
ANA	22	73.3	8	26.7	-
dsDNA	5	62.5	3	37.5	0.64
C_3C_4	9	90.0	1	10.0	0.21
CXR	4	100.0	-	-	0.55

Table 6: Spectral widening

Variables	0 (n = 10)		1 (n = 20)		p value
	Mean	SD	Mean	SD	
Hb	8.7	2.0	8.5	1.9	0.79
TC	7370.0	1606.3	6940.0	1938.4	0.55
Pt	1.9	1.1	1.7	0.6	0.59
TCL	154.4	23.8	195.0	39.2	**0.006**
HDL	42.8	5.2	41.4	4.8	0.45
LDL	89.2	17.5	124.7	31.4	**0.003**
TGL	114.8	63.7	149.1	74.8	0.23

Table: 7 IMT

Variables	n	Mean	Standard Deviation	p value
LAC				0.91
0	19	0.42	0.08	
1	9	0.42	0.11	
ACL				0.24
0	27	0.41	0.09	
1	1	0.52	-	
ds DNA				0.16
0	21	0.43	0.09	
1	7	0.38	0.08	
C_3C_4				**0.02**
0	19	0.44	0.09	
1	9	0.36	0.07	
CXR				0.14
0	24	0.43	0.09	
1	4	0.36	0.07	

Table 8: Correlation with IMT

Variables	Correlation Coefficient	P value
Hb	-0.04	0.83
TC	-0.11	0.58
PT	0.15	0.43
TCL	0.48	**0.01**
HDL	-0.21	0.29
LDL	0.55	**0.003**
TGL	0.24	0.21
LDL:HDL	0.56	**0.002**
TCL:HDL	0.52	**0.005**

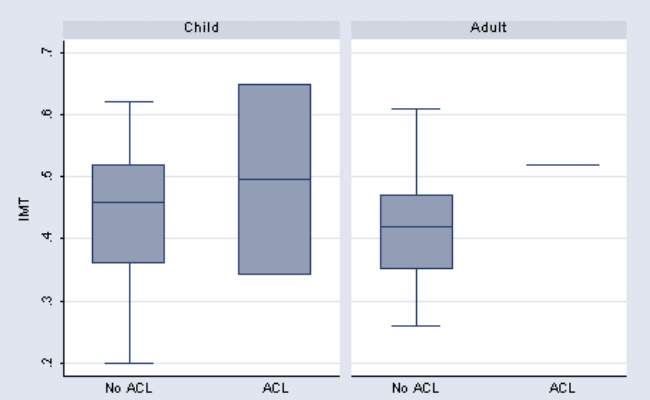
In children IMT was found to have positive correlation with TGL (P=0.02). Plaque was identified in 2 children and was found to significantly associate with LAC (p=0.02). Spectral widening positively associated with TGL (p=0.001). Stenosis was found to be associated with presence of LAC (p=0.02).

In adults IMT was found to positively correlates with TCl(p=0.01), LDL(p=0.003) and TCl/ HDL, LDL/ HDL ratios (p<0.05) Plaques identified in 3 adults were found to correlate with LAC(p 0.03) and ACL(0.002). Stenosis was found to correlate with TCl(p 0.002), LDL(p 0.008) and TGL (p 0.004). Spectral widening was found to correlate with TCl (p=0.006) and LDL (p 0.003).

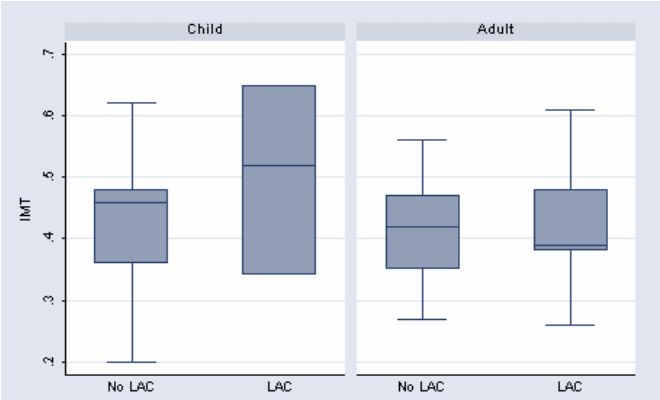
The scatter diagram and the box graphs pictorially represents the above results, where in the box graphs depict the mean and standard deviation.

Comparison between Child and Adult

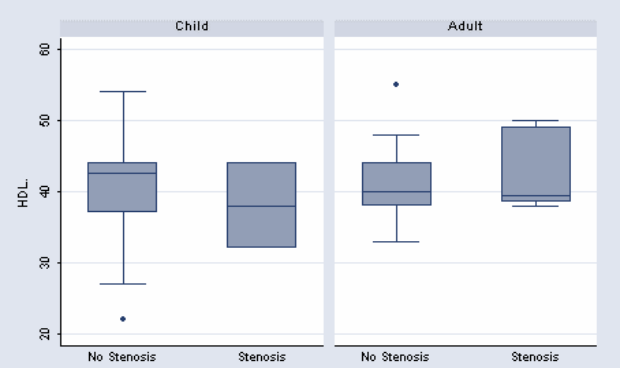
ACL Vs IMT



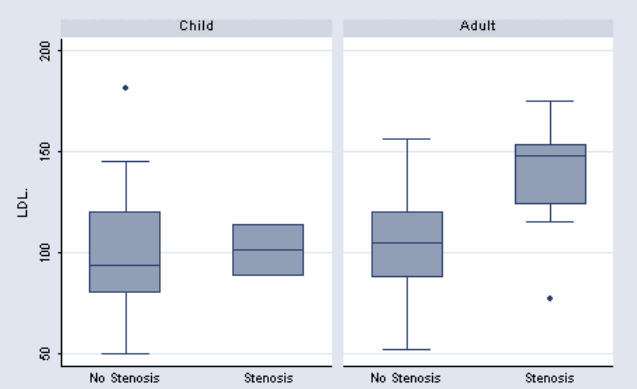
LAC Vs IMT



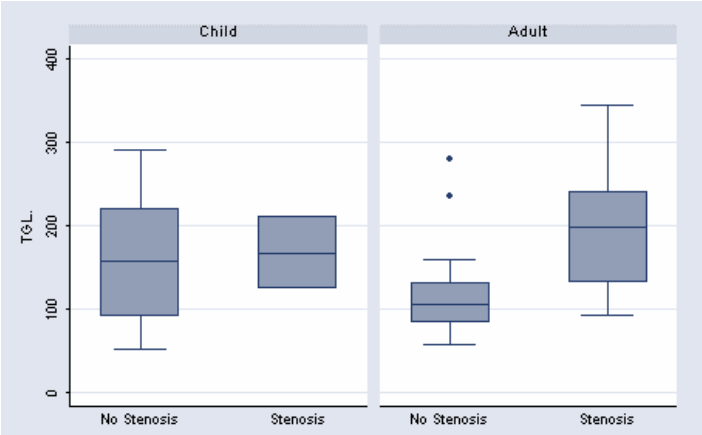
HDL Vs Stenosis



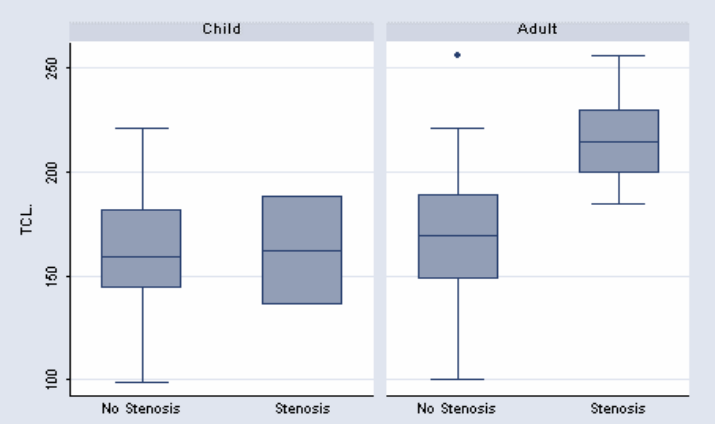
LDL Vs Stenosis



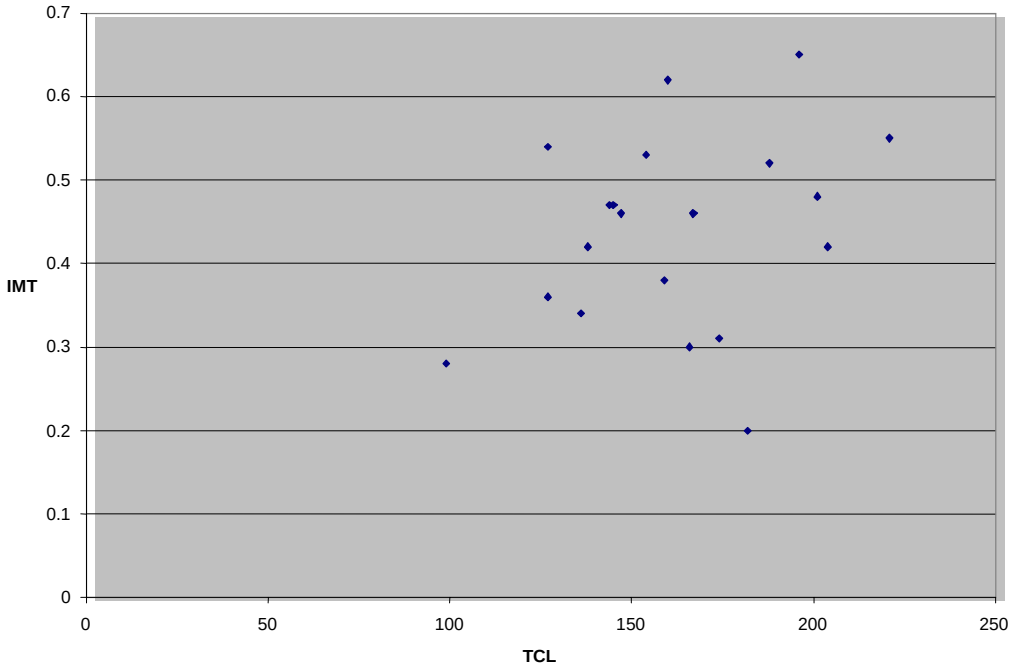
TGL Vs Stenosis



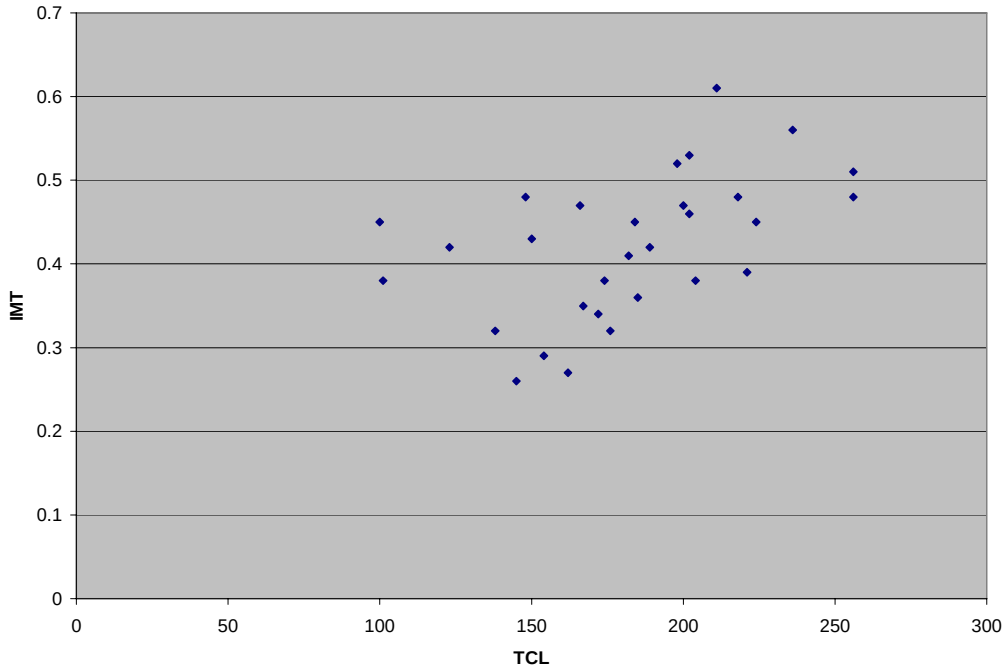
TCL Vs Stenosis



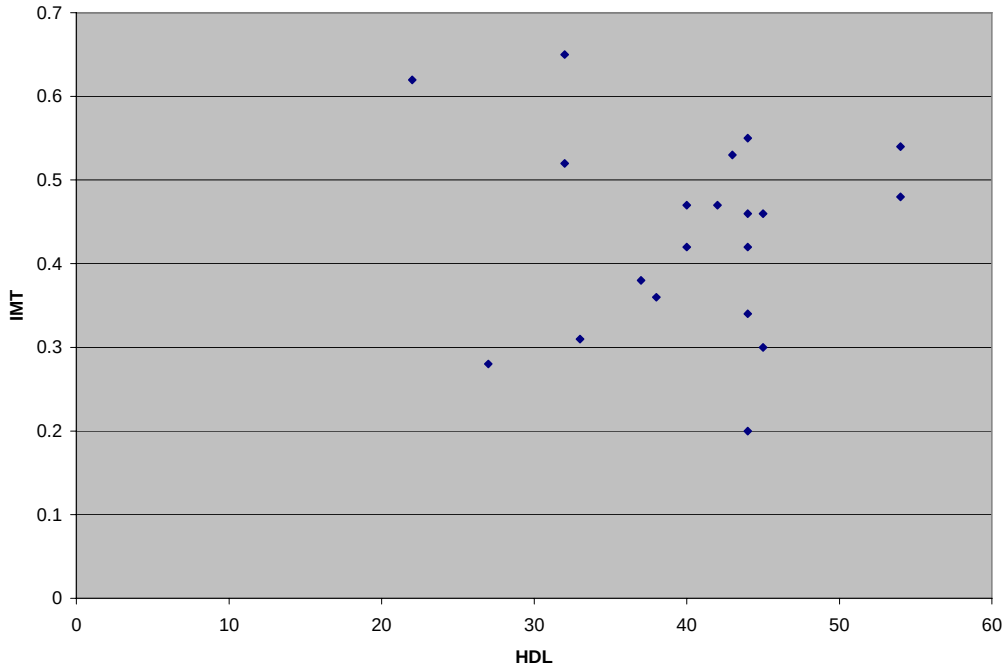
Adults



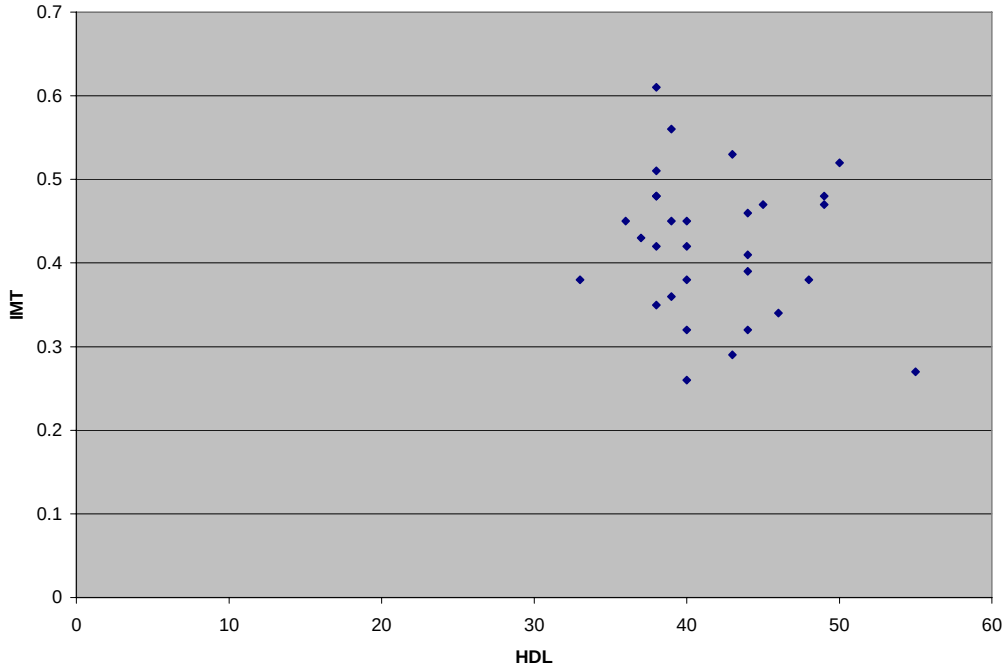
Children



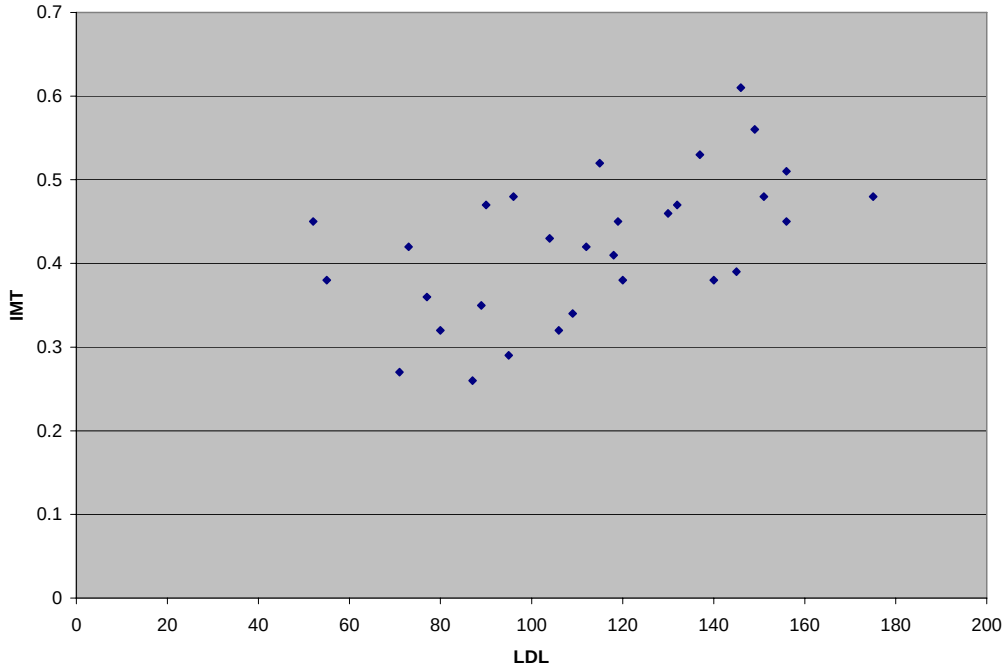
Adults



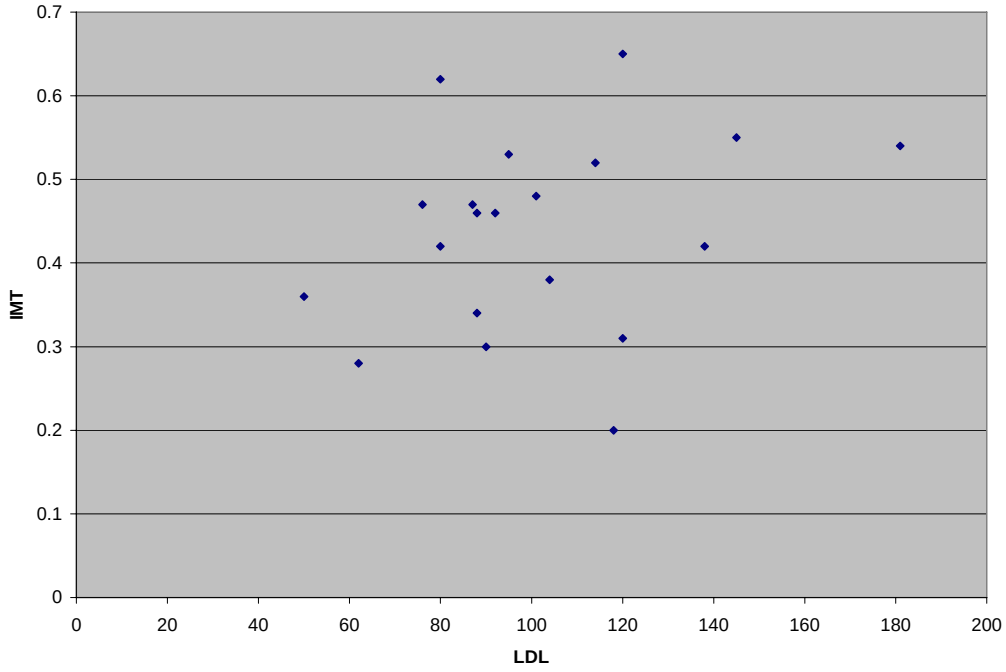
Children



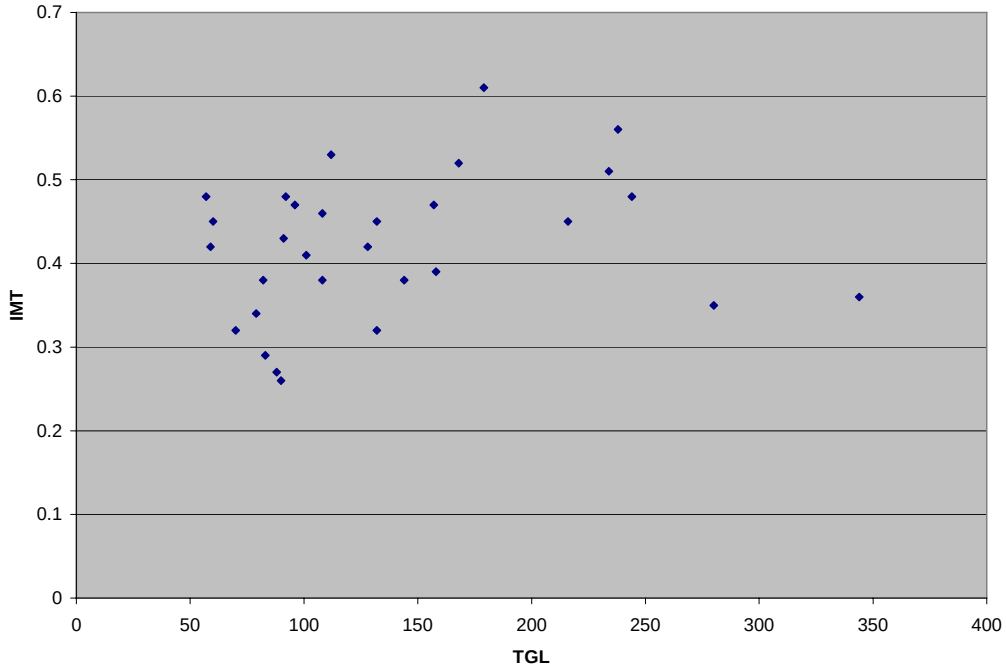
Adult



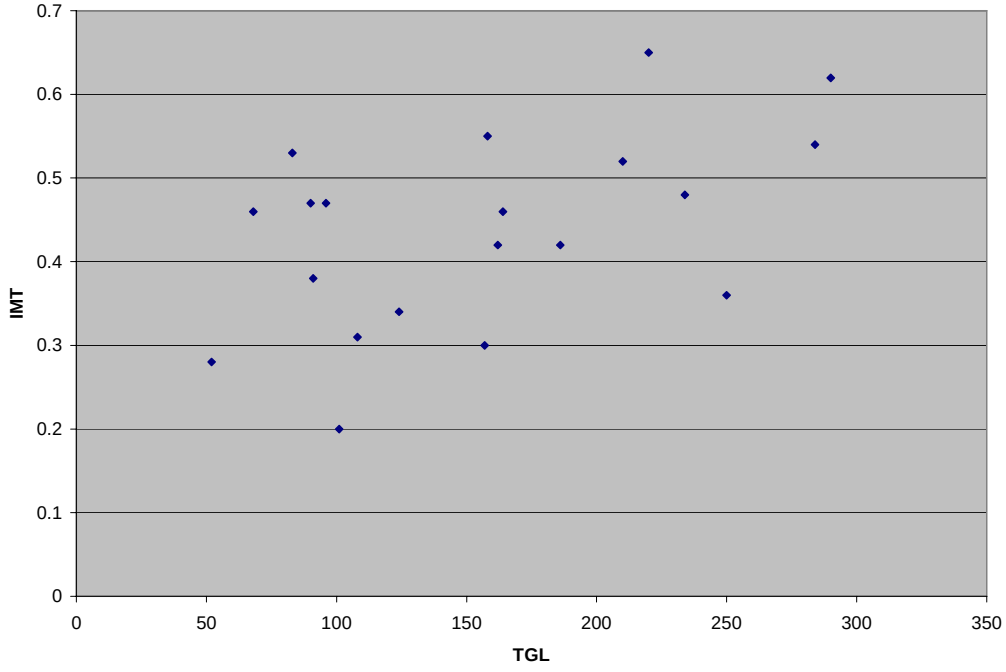
Children



Adult



Children



Correlation of risk factors in SLE with plaque and IMT

Table 1: Steroid usage

	Children		Adult	
	Mean ± SD	**p value**	**Mean ± SD**	**p value**
No plaque	19.7 ± 7.4	**0.01**	16.5 ± 10.4	**0.04**
Plaque	35.0 ± 7.1		31.7 ± 20.2	

	Children		Adult	
	Correlation (r)	**p value**	**Correlation (r)**	**p value**
IMT	0.05	0.85	0.04	0.83

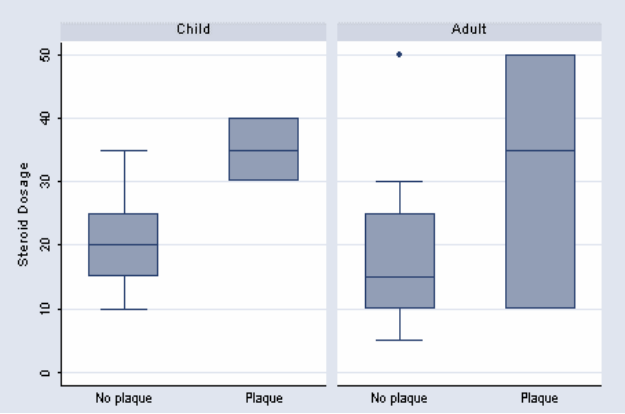


Table 2: Age

	Children		Adult	
	Mean ± SD	**p value**	**Mean ± SD**	**p value**
No plaque	14.2 ± 2.8	0.39	29.3 ± 7.1	0.88
Plaque	16.0 ± 2.8		28.7 ± 10.0	

	Children		Adult	
	Correlation (r)	**p value**	**Correlation (r)**	**p value**
IMT	0.51	**0.02**	-0.31	0.11

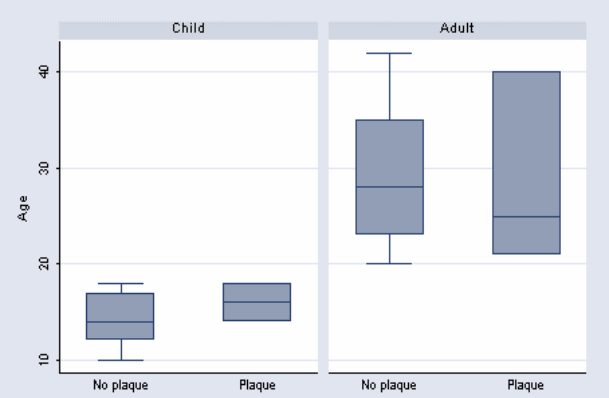


Table 3: Disease duration

	Children		Adult	
	Mean ± SD	**P value**	**Mean ± SD**	**p value**
No plaque	18.3 ± 7.0	0.99	14.6 ± 9.4	0.38
Plaque	18.5 ± 24.7		20.0 ± 15.1	

	Children		Adult	
	Correlation (r)	**p value**	**Correlation (r)**	**p value**
7IMT	0.16	0.49	-0.38	**0.05**

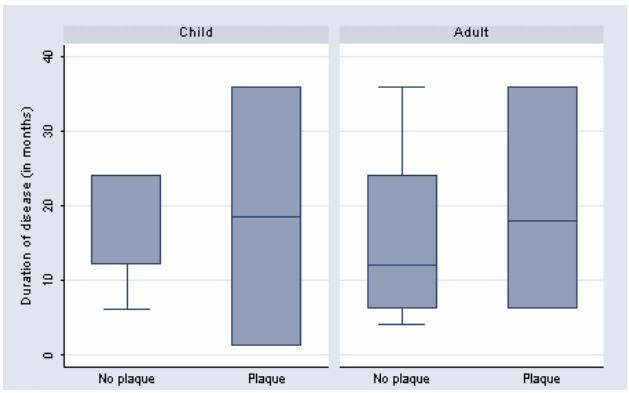


Table 4: SLEDAI

	Children		Adult	
	Mean ± SD	**p value**	**Mean ± SD**	**p value**
No plaque	18.8 ± 8.1	0.25	19.4 ± 12.1	0.72
Plaque	26.0 ± 5.7		16.7 ± 11.4	

	Children		Adult	
	Correlation (r)	p value	Correlation (r)	p value
IMT	0.29	0.21	-0.28	0.15

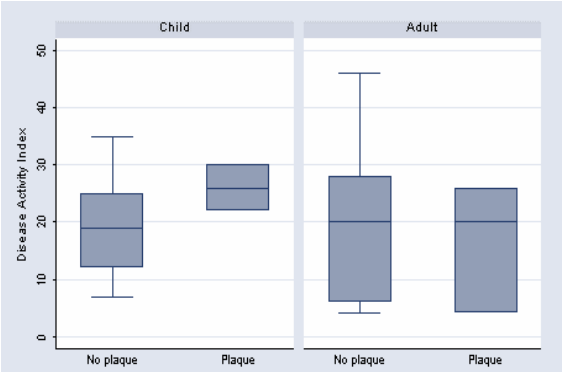


Table 5: Smoking and hypertension

Variables	Children					Adult				
	No Plaque (n = 18)		Plaque (n = 2)		P value	No Plaque (n = 27)		Plaque (n = 3)		p value
	n	%	n	%		n	%	n	%	
Smoking	-	-	-	-	-	2	100.0	-	-	1.00
Hyperten-sion	5	83.3	1	16.7	0.52	9	75.0	3	25.0	**0.05**

**Children

Variables	n	IMT		
		Mean	Standard Deviation	p value
Smoking 0 1	 20 -	 0.44 -	 0.12 -	-
Hypertension 0 1	 14 6	 0.42 0.48	 0.12 0.11	0.37

** Adult

Variables	n	IMT		
		Mean	Standard Deviation	p value
Smoking				
0	26	0.42	0.09	0.83
1	2	0.41	0.09	
Hypertension				
0	17	0.41	0.08	0.73
1	11	0.43	0.1	

Table 6: Renal

	Children			Adult		
	N	Median (Range)	p value*	N	Median (Range)	p value*
No plaque	18	0 (0, 5)	0.35	27	0 (0, 5)	0.32
Plaque	2	2.5 (0, 5)		3	2 (0, 5)	

* Mann-Whitney U test

Renal	Children			Adult		
	N	Mean ± SD	p value*	N	Mean ± SD	p value*
0	14	0.42 ± 0.09	0.09	11	0.43 ± 0.09	0.29
2	1	0.42 ± .		1	0.47 ± .	
3	1	0.20 ± .		1	0.53 ± .	
4	2	0.57 ± 0.12		4	0.33 ± 0.06	
5	2	0.57 ± 0.07		5	0.41 ± 0.09	

* Kruskal – Wallis Test

IMT

Child	N_{20}	Mean	Std.
Adult	30	0.4213	0.0854
Total	50	0.4280	0.0982

DISCUSSION

SLE is a well differentiated autoimmune connective tissue disease which affects all cell constituents during the progression of illness. Due to the advent of more effective treatment modalities there has been prolongation of life expectancy in these patients. 5 years survival is 90% and 10year survival is 70% in the developed world. They are prone for peripheral vascular disease also. This will further deteriorate the quality of life.

Atherosclerosis is a diffuse process involving the coronary and the peripheral vessels including the carotids.

There is a need to measure the atherosclerotic burden of the arteries in SLE patients.

Although vasculitis and intra luminal thrombosis contribute significantly, the major component of long term changes in vessel wall is due to premature atherosclerosis.

6-10% of the patients have clinical recognized premature atherosclerosis, when screening methods are used the prevalence rate may be even greater40% [(42)].

Very few studies have been done on sub clinical atherosclerosis with vascular manifestation in SLE.

Duplex Doppler is a cost effective non invasive procedure used to identify high risk atherosclerotic events. Intimo medial thickness and plaque detection are important parameters taken in various studies. In this study an attempt is made to correlate traditional and disease related risk factors with the Duplex Doppler parameters.

The clinical profile of the patients were compared to the Binoy J. Paul et al study (N K) [56] and Chandrasekharan et al (SI) [8], pertinent to the development of vessel wall disease.

In this study, there was a preponderance of F: M ratio of 17:1 as compared to NK with 22:1. The mean age at onset was 28.4 and in NK, it was 26.2. The mean duration is 1. 4yrs in the NK and in this it was 1. 2 years. This showed that SLE predominantly affects younger age group. Late onset SLE was not seen in this study.

The clinical features at the initial onset were compared to the NK, and SI studies noted in the table below.

Initial manifestation	**A.N.Chandrasekharan et al S I Study n=80 1993**	**Binoy. J. Paul et al *N. Kerala Study n=75 2003***
Arthritis	70%	66.7%
Cutaneous	51%	14.7%
Renal	16%	6.7%
Fever	52. 5%	4.0%
Haemolytic anaemia	NA	1.3%
Thrombocytopenia	1. 2%	1.3%
Chorea	NA	1.3%
Seizure	NA	1.3%
Pericardial effusion	NA	2.7%

Fout J.,Cerevera R. et al in 1998 compared childhood and adult onset SLE among 34 patients. He found that fever, lymphadenopathy and nephropathy more common in the children and on evolution of the disease malar rash, chorea and ACL positivity was seen.

At the initial onset, fever was a common presentation. Fever at the onset was commoner in children 65% than seen in adults (10%). In children there is always a presentation of prolonged fever with hepato splenomegaly which was seen in this present study also. Haemolytic anaemia presented as autoimmune haemolysis in 12.5% of children which was more common than adults (3.2%). Similarly the thrombocytopenic purpura, was seen in 12% of children again commoner than adults who had 6.2%. Serositis was seen in (58%) in adults which was more compared to children (9.1%).

Seizures was seen more in children (30%) compared to (6.2%) in adults. The initial presentation of renal involvement was seen in 9.3% in children compared to 7.3% in adults.

Children present as idiopathic thrombocytopenia (ITP) and haemolytic anaemia (AIHA) initially for few months to years and some of them gradually progress to have others features of SLE[36].

In this study there were 2 adults and 2 children with ITP and 2 children with AIHA who evolved into SLE.

Perez et al found in 1985 6 out of 18 patients with ITP had ANA positivity and 4 out of 18 evolved into SLE.

Dubois et al reported AIHA (2-6%) in childhood onset of SLE.

5 out of 10 AIHA patients studied by Viedeback et al in 1962 evolved into SLE.

During cumulative disease there was involvement of internal organs like the kidney, heart, lung, brain, bonemarrow and vessels.

Clinical Manifestation	*Dubois (1971)*	*Malaviya (1985)*	*Vaidya (1997)*	*Binoy (2003)*
Arthritis	92%	66%	70. 9%	89. 3%
Dermatological	71. 5%	85%	-	64%
Malar rash	-	-	53. 18%	40%
Discoid	-	-	-	5. 3%
Photo	43%	-	9. 55%	33%
Oralulcer	9. 1%	64%	-	64%
Alopecia	21%	82%	-	60%
Raynaud's	18. 4%	32%	15. 5%	2. 7%
Renal	46. 1%	73%	35%	33. 3%
Pulmonary	45%	17%	15. 5%	8%
Cardiovascular	30. 5%	5%	11. 8%	5. 3%
Neuropsychiatric	25. 5%	15%	25. 5%	13. 3%

Certain features like fever, anaemia, lymphadenopathy, cutaneous lesions and transient metabolic parameters showed abnormalities during disease flare.

In this study, the arthritis was seen in 52% of children and 58% in adults as compared to 89% in NK study. The deformable arthritis Jaccoud's was seen in 12.5 % in children and 13.2% in adults in this study. The component of ligament laxity and periarticular capsular fibrosis is the cause of this deformity.

Avascular necrosis was seen in 12.5% in children more than in adults (4.4%). In this present study one child had LAC positivity with avascular necrosis.

A cross sectional study by Bergstein J. et al in 1974, of 35 children with SLE found evidence of AVN in 40%. This may probably due to steroid effects, APLS.

Dermatological manifestation was seen in 52% of children, 75% in adults and was comparable to NK of 64% and NI (Malaviya A.N. etal 37) of 85%.

SCLE Lesions 28% were seen in adults compared to 1% in Children This may be because of influence of sun light exposure and sex hormones triggering auto immune presses in skin. DLE lesions was seen 5.8% in adults and 1% in children comparable to NK study.

Alopecia was seen in 48%of children and 57% adults, which was lower than NK with 60% and NI with 82%. Oral ulcers was seen in 44% and 68% in children and adults respectively which was comparable to NK of 64% and NI 64%.

Dyschromia was seen in 22% in children and 65% in adults in the present study as compared to the previous studies, which quote about 20%. This may be due to a chronic nail bed micro circulatory disturbance.

Kozolav L.K et al described various microcirculatory disorders in SLE disease where in chronic inflammation, hypoxia affected tissue nutrition which may be a factor.

Hepatomegly, was seen in 55% in children 9% in adults . Lymphadenopathy was seen in 55% in children and 25% in adults. Reticuloendothelial system response is exaggerated physiologically in children compared to adults with SLE.

Pericardial effusion was found to be 18.7% in children and 14.7% in adult and valvular abnormalities disease was seen in 9% children and 5% in adults.

Migajo et al described 1997 in his study that pericardial effusion was seen in 12% and valvular abnormalities in 34%, and of Mitral valve was 17%.

1 patient in this study had coronary heart disease.

Homcy et al is 1982 described 6 Ischaemic heart disease patients among 16-29 years age group, in his SLE study.

Doherty et al described 30 patients below 35 years with Ischaemic heart disease. This shows the magnitude of premature athoeroselerosis in SLE.

4 adult cases had developed Pulmonary hypertension and one had shrinking lung syndrome, and two had interstitial lung disease in this present study.

Dubois et al observed 2 symptomatic patients with PHT in his study group.

Perez et al observed 4 patients with PHT among 43 SLE, over a period of 2 years.

Simmonson et al showed 5 patients out of 36 SLE had PHT by using 2D ECHO.

Severe pulmonary upper airway obstruction was seen in 1 patient in this present study who had severe laryngeal edema, immobile left vocoal cord, which was reversed with intralesional steroids.

Anita Karim et al in 2002 described a patient with similar presentation but did not reverse with steroids but under went tracheostomy[68].

One had shrinking lung syndrome (1.4%) in adults in this study. It is an uncommon pulmonary manifestation[11].

Acute lupus pneumonitis occurred in 9.3% in children compared to 5.8% in adults. Dubois et al reported pneumonitis up to 14% in his study.

Two adults had ILD (2.9%) of 3 years disease duration. Eisenberg et al reported 18 patients with SLE and ILD with mean age 45.7 years and disease duration of 10.7 years. This showed that ILD occurs in late stage of the disease. In this study disease duration for the development of ILD was three years.

In 2004 **Cefti E et al** noticed rarity of ILD in his study population who were followed up for 10 years[65].

Renal manifestation was seen in 65% in children and 44% in adults comparable to the NI of 73% and (NI) 33.3%. Only 6 children and 11 adults were subjected to biopsy. This was because we took cases for biopsy if they showed persistent urinary findings. Hence the asymptomatic patients were not subjected to biopsy. 4 children and 5 adults had nephrotic range of proteinuria.

Among 6 children who underwent biopsy Class II-1, class III-1, class IV –2, Class V –2 and in adults class II- 1,class III-1, Class IV 5,ClassV-4. Patients with renal involvement and also who had nephrotic range of proteinuria were taken for Doppler evaluation of carotids.

Among Neuro psychiatric manifestations, two cases of adults had CVA, also complicated by hypertension. Two adults had LAC positivity. In this study the above two patients manifested with intractable seizures, intracranial tension

and their MRI showed hyper intense lesions on T2 weighted images one of the marker for CNS involvement. (Plate 4).

Among CNS manifestation seizures noticed in 30% of children compared to adult. It was found to be increased in **Tucker et al** study of childhood SLE.

Chorea which had been reported in 2-3% in previous study was not seen in this present study among children and adult. 2 adult patients had CVA without associated systemic hypertension. One child developed catastrophic APLS[40].

Among laboratory parameters, ANA positivity was seen in 97. 1% in children and 95. 6% in adults. Complements were seen to be decreased C3 in 18. 75% and 13. 2% of C4 in children, 3. 75% and 3. 5% in adults respectively. LAC positivity was seen in 9.3% in children and 10.2% in adults. Among three cases of LAC +ve children,2 had renal lupus and one had catastrophic APL. Among 6 adults who were LAC+ve, 2 had PHT, 1 had renal lupus, 1 digital gangrene and 2 had NP lupus.

ACL was seen in 16% in children and 13% in adult in this study.

Two children who had manifested with ANA negative and ACL positivity, progressed to develop SLE. This has also been reported by Gatterne M et al in 2003 that out of 10 children who present with primary APLS, but two of them developed SLE[62].

MRI in this study was used to pick up lesions in CNS lupus.

Tom W.J. et al described different imaging modalities in CNS SLE can used to differentiate patients of active CNS SLE, from those cost by residual disease. (Symptoms being similar).

Thus the clinical and laboratory profile showed the burden of the disease among the study population and various manifestation of vascular involvement.

In the study group, none had a family history of atherosclerotic event. None were found to be diabetic.

In this study the mean **IMT in children was 0.421** and the mean **IMT in adults was found to be 0.428**.

On analysis of the risk factors, it was found that smoking habit was seen in 3 adult males.

Smoking did not correlate with IMT and plaque in adults and children. This factor was low in this part among women who formed the major group.

Age was found to correlate with IMT in children and not in adults.

Selzer et al in his study observed that atheroclerosis was found in older age groups. In this study adults were seen predominantly of younger age compared to Western study patients.

Disease duration was found to correlate with IMT in adults p=0.04, but not in children. **Petri et al** in his study had seen that disease duration influenced the IMT and plaque. The longer the duration the more was the correlation.

Hypertension correlated in adults with plaque p=0.05 but not with IMT. **Bruce et al** in 2003 observed that hypertension and diabetic states in a study of 2500 SLE patients associate with higher risk of coronary artery disease.

SLEDAI scoring did not correlate with IMT and Plaque in both children and adults.

Mansi et al in his study observed that along with the traditional risk factors SLEDAI also influence the Doppler parameters. In this study SLEDAI was done at the point of evaluation of Doppler alone. Serial SLEDAI would be more helpful in the interpretation.

Renal involvement did not influence the IMT and plaque in children and adults. **Fallaschie et al** in his study among childhood SLE had shown that renal involvement with nephrotic range of proteinuria contributed more to plaque formation.

Steroid usage was found to correlate well with the development of plaque in children (p=0.001) and adults (p=0.04). Doria et al in his study showed that the steroid dose, (cumulative, duration) affected the plaque formation.

On analysis of the lipid profiles from table 12,

The total cholesterol was high in 5 children and in 16 adults.

This showed that this component affected adults more than children.

The LDL fraction was raised in 5 children and 10 adults.

Triglycerides was raised in 8 children and 28 adults. This may be due to steroid and also because of the disease per se. Similar findings were noticed in other studies also[34,43,49,57].

HDL is a component which is helpful to prevent the atherosclerosis and plaque formation.

HDL was found in normal amounts in 22 of children and in 48 of the adults showing that in this part of the country in spite of the disease, majority of patients are having HDL in normal range. It is reduced in 12 adults as compared to 3 children.

In children IMT was well associated with triglycerides, but in the adults both total cholesterol and LDL cholesterol were significantly associated. Dyslipidemia has been noted in several studies[43].

The scatter diagram shows that significant values follow an upward trend between IMT and the variables.

Many Western studies showed SLE activity of 7-10 yrs to influence the plaque, but in this study, patients less than 3 yrs had developed plaques[40,32].

Swengsson et al in 2001, studied prevalence of traditional and nontraditional factors with or without CVS disease. In a cohort of 26 patients, he found that IMT thickness (0.66±0.15) compared to controls (0.59±0.12). SLE patients had plaques (17/26) compared to SLE controls (10/26).

Sonia Jimenez et al in 2005 had studied preclinical atherosclerosis in three groups. The groups were SLE, Primary APL and controls. He found that hypertension, hyper triglceridemias, persistent

disease activity, renal disease and chronicity of the disease influence the IMT more than APL and control groups. Only when the LAC positivity was taken into account the formation of plaque correlated.

In this present study two patients with plaque among children ,both had renal lupus. Among 3 adults who had plaques one had coronary heart disease, one had neuropsychiatric manifestation and another had pulmonary hypertension.

Plaque was found to depend on LAC positivity in adults and children. This has been reported in various studies.

Stenosis was found to be associated with presence of LAC ($p=0.02$) in children and lipid profiles (TCL, LDL,TGL) in adults ($p=0.05$).

Spectral widening was associated with lipid components in adults only.

The ratios of LDL/HDL and TCL/HDL are used as one of the markers in calculating high risk in atherosclersis[44,48]. In this study the above ratios were found to increase significantly the risk of developing intimomedial thickness in adults.

SUMMARY AND CONCLUSIONS

This was a descriptive study of 32 children and 68 adults with SLE. The clinical profile had been discussed in both age groups. The highlighting feature was the association of lipid profile and the duplex Doppler.

The female to male ratio in children was 7:1 and in adults 17:1. The mean age at diagnosis was 12. 6 yrs in children and 28 yrs in adults. The mean disease duration was 1. 2 yrs in children and 1. 18 in adults.

The commonest initial manifestation in children were fever and arthritis whereas in adults cutaneous lesion and arthritis was observed.

Dyschromia was found more in adults with SLE .

ITP and AIHA were found to be commoner in children compared to adults. Pulmonary hypertension, Ischaemic heart disease, shrinking lung syndrome, were seen in lesser percentage in this study compared to other studies. Renal involvement was found to be more in children than adults. Hypertension with renal involvement was seen in 3 children and 10 adults.

MRI is the preferential modality for learning NP Lupus.

The mean IMT in this study was found among children 0.421 and among adults was 0.428.

Duplex Doppler had picked up stenosis and plaque in both children and adults. Plaques were associated with hypertension in children and adults. Older children had greater IMT. Disease duration correlated with the IMT in adults. Smoking did not influence the plaque or the IMT. SLEDAI did not correlate with the plaque and IMT. Renal

involvement did not significantly correlate in children and adults with plaque. Steroid usage influenced the development of plaque in children and in adults.

IMT in adults was found significantly associated with TCL/HDL and LDL/HDL ratios.

Dyslipidemia had affected all components of the lipids and also significantly altered the Total cholesterol /HDL and LDL/HDL. Lipid profile, complement level and presence of antiphospholipid antibody had contributed to some of the development of premature atherosclerosis in this study.

Duplex Doppler can be used as early diagnostic tool for premature atherosclerosis.

Intimomedial thickness can be used as surrogate marker in assessing atheroselerotic events in SLE patients.

The IMT in adults with age related atherosclerosis is 1. 2 mm and above but cutoff values in disease states like SLE has to be standardized to the geographical area, dietary habits and Body mass index.

Notably the LDL/HDL ratio and the Total cholesterol /HDL ratio has to be in the lower range in order to prevent atherosclerosis. The disease activity has to be treated promptly, for prevention of premature atherosclerosis in SLE.

Duplex Doppler study of the carotids must be done serially along with the evaluation of the disease activity during follow up of SLE patients.

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APPENDICES

APPENDIX 1: American College of Rheumatology (ACR) Criteria for Diagnosis of SLE, 1997.

THE 1982 REVISED ACR CRITERIA		
1.	Malar rash	Sparing the nasolabial folds
2.	Discoid rash	Characterised by follicular plugging , atrophic scarring and keratotic scaling
3.	Photo sensitivity	Due to unusual reaction to sunlight
4.	Oral ulcers	Usually painless
5.	Arthritis	**Non erosive involving ≥ 2 peripheral joints**
6.	Serositis	a. Pleuritis b. Pericarditis
7.	Renal disorder	a. Persistent proteinuria > 0.5 g/d or > 3+ b. Cellular casts – red cell, Hb, granular tubular etc.
8.	Neurologic disorder	a. Seizures b. Psychosis
9.	Haematologic disorder	a. Hemolytic anemia b. Leukopenia < 4000 / mm^3 } on more than c. Lymphopenia < 1500 / mm^3 } 2 occasions d. Thrombocytopenia < 1 lakhs / mm^3
10.	Immunologic disorder	a. + ve LE cell b. Anti-ds DNA or c. Anti-Sm, or d. False + ve VDRL for atleast 6 months
11.	Antinuclear antibody	Abnormal titre by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce ANAs.

If four of these criteria are present at any time during the course of disease, a diagnosis of systematic lupus can be made with 98% specificity and 97% sensitivity.

APPENDIX 2: PROFORMA

Name :

Age :

Sex :

Address :

Height : Weight :

History : Skin changes, Constitution,symptoms related to, Musculoskeletal, Respiratory, Cardiovascular, Neurological and Gastro Intestinal Symptoms.

Past History : Gangrene, Pregnancyloss, DVT, CVA, CAD.

Personal History : Smoking, Alchohol.

Drug History : Steroids (Dose and Duration), Chloroquine, OCP, Statins, Supplements.

Examination : General, Pulse, BP, Mucocutaneous lesions, Malar rash, Photo sensitivity, Urticaria, Discoidlesions, Oral/Nasal Ulcers, Alopecia.

Musculoskeletal : Arthralgia/Arthritis, Myalgia, Subcutaneous Nodules.

Cardio Respiratory : Pericarditis/pericardial effusion, Pleurisy/pleural effusion.

Genito Urinary : Proteinuria, Abnormal Sediment, Haematuria, WBCs, Casts.

Haemolymphatic : Adenopathy, Hepatospleenomegaly.

Neural System : CVA, Cranial nerve, Psychological and Peripheral nervous system and motor system assessment.

Ocular Lesions : Retinal changes, Uveitis, Dry Eye Syndrome.

Vascular : Gangrene, Raynaud’s, Ischaemic Ulcers.

Investigations : All investigation which includes haemogram. Biochemistry, relevant to SLE, along with serology – ANA, DSDNA, Complements, LAC, ACL.

Duplex Doppler Study of Carotid A (Intimo-Medial Thickness, Spectral Wave form, Plaque, Stenosis).

APPENDEX 3:SLEDA1

Weight	*Descriptor*	*Weight*	*Descriptor*
8	Seizure	4	Proteinuria (>0.5 g/day)
8	Psychosis	4	Pyuria(>5 WBC/hpf)
8	Organic Brain Syndrome	2	New rash
8	Visual Disturbance	2	Alopecia
8	Cranial N. Disorder	2	Mucosal Ulcers
8	Lupus Headache	2	Pleurisy
8	CVA	2	Pericarditis
8	Vasculitis	2	Low Complement
4	Arthritis	2	↑DNA Binding
4	Myositis	1	Fever(>38°C)
4	Urinary Casts	1	↓Platelets(< 1Lakh/mm^3)
4	Hematuria(>5 RBC/hpf)	1	Leukopenia(<3000/ mm^3)

APPENDEX 4

System Lupus International Collaborating clinics / American College of Rheumatology Damage Index for Systemic Lupus Erythematosus*

Item	Score
Ocular (either eye, by clinical assessment)	1
Any cataract, retinal changes	1
Neuropsychiatric	
Caogntive impairment	1
Seizures	1
CVA	1 (2)
Cranial or peripheral neuropathy	1
Transverse myeilitis	1
Renal	
Estimated or measured GFR, 50%	1
Proteinuria for > 3.5 gm%	1
ESRD	3
Pulmonary	
PHT	1
Pulmonary Fibrosis	1
Shrinking lung syndrome	1
Pleural fibrosis	1
Pulmonary infarction	1
Cardiovascular	
Angina or CBG	1
Myocardial infarction	1(2)

Cardiomyopathy	1
Valvular disease	1
Pericarditis for 6 months	1
Peripheral vascular disease	1
Claudication for 6 months	1
Significant tissue loss	1(2)
Venous thrombosis	1
Gastrointestinal	
Infarctionor resection of bowel below duodenum	1(2)
Mesentric insufficiency	1
Chronic peritonitis	1
Stricture or upper GI tract surgery	1
Musculoskeletal	
Muscle atrophy	1
D forming arthritis	1
Osteoporosiswith fracture	1
Avascular necrosis	1(2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring	1
Skin ulceration	1
Premature gonadal failure	1
Diabetes	1
Malignancy	1(2)

APPENDIX :5

Classification of LDL, Total, HDL Cholesterol(mg/dl) and serum Triglycerides (mg/ dl)

LDL Cholesterol

< 100 optimal

Near optimal

Borderline high

High

Very high

Total Cholesterol

<200 Normal

200-239 Border line high

>240 High

HDL Cholesterol

<40 Low

>60 High

Serum Triglycerides

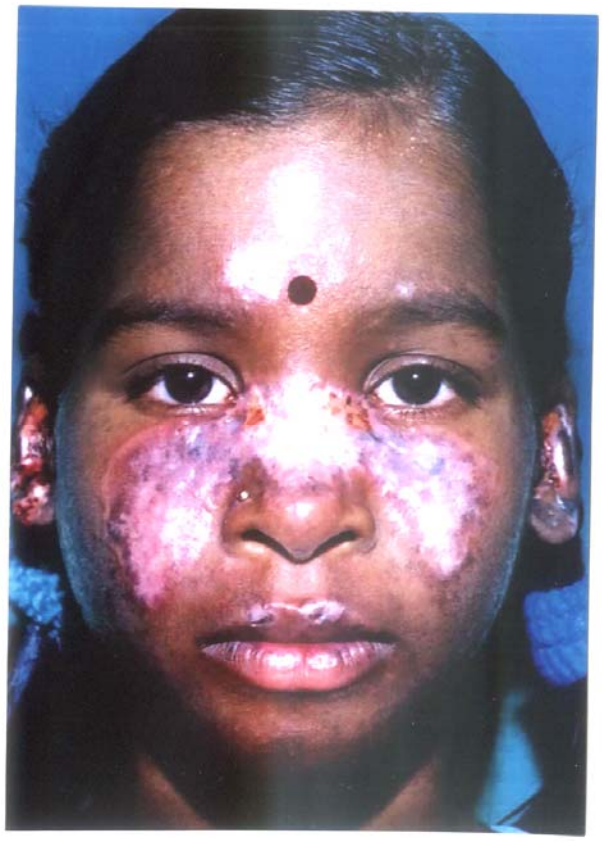
<150 Normal

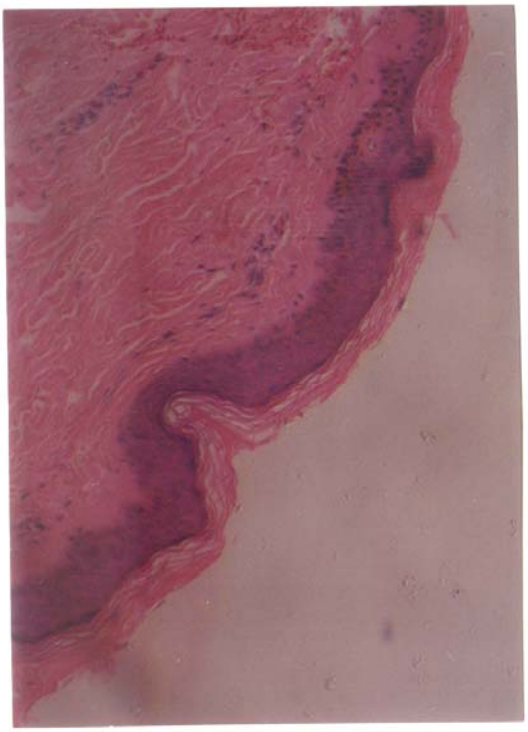
150-199 Border line high

200-499 High

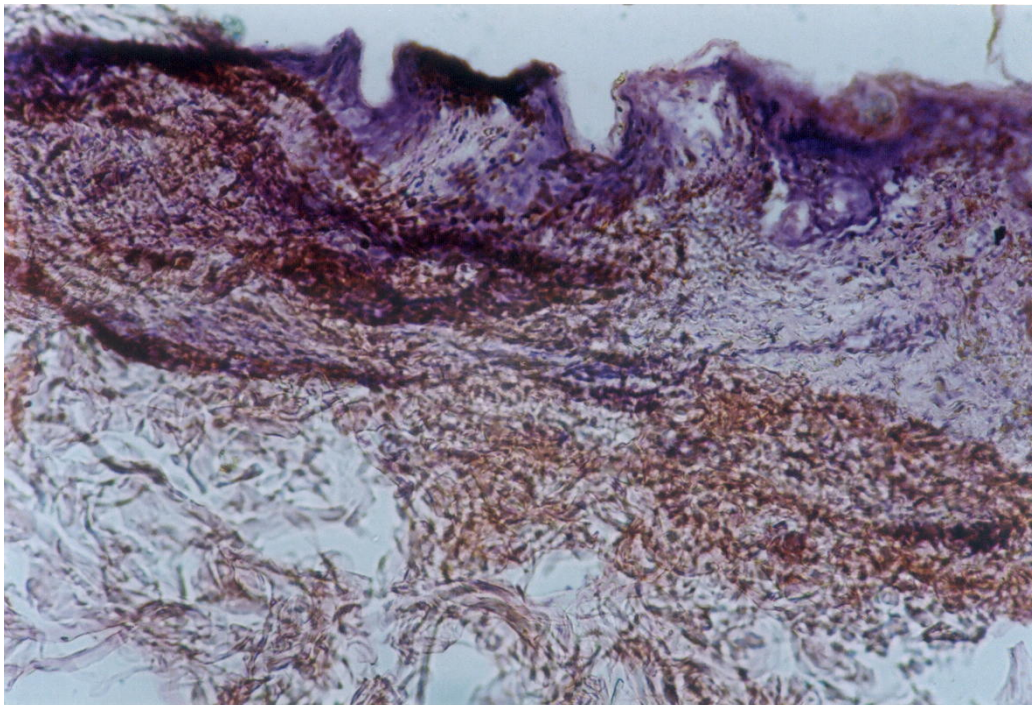
>500 Very high

200-239





ACUTE LE LESION



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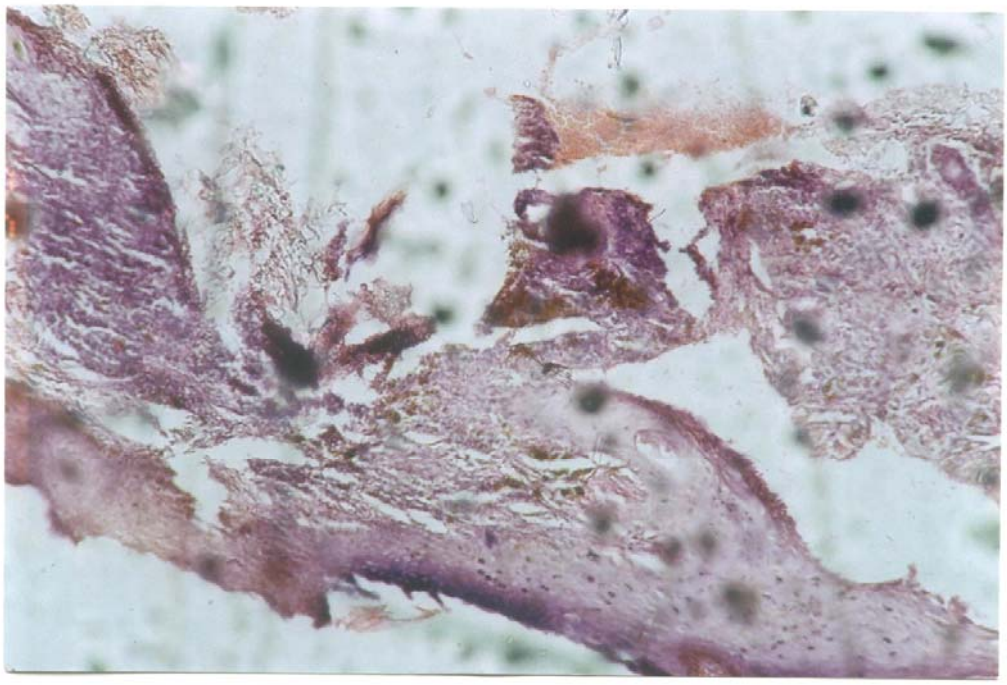

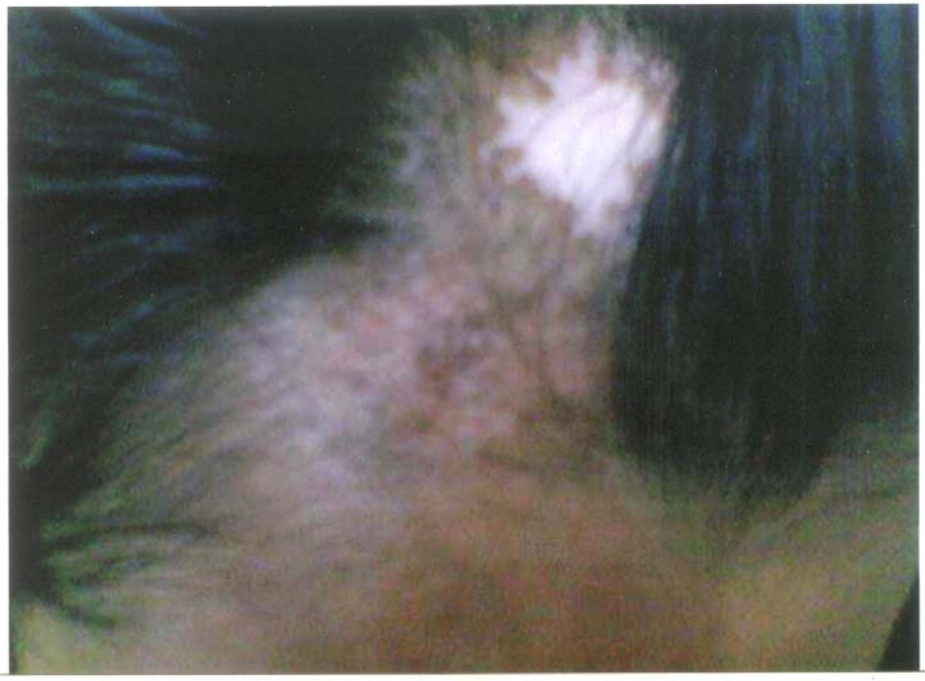

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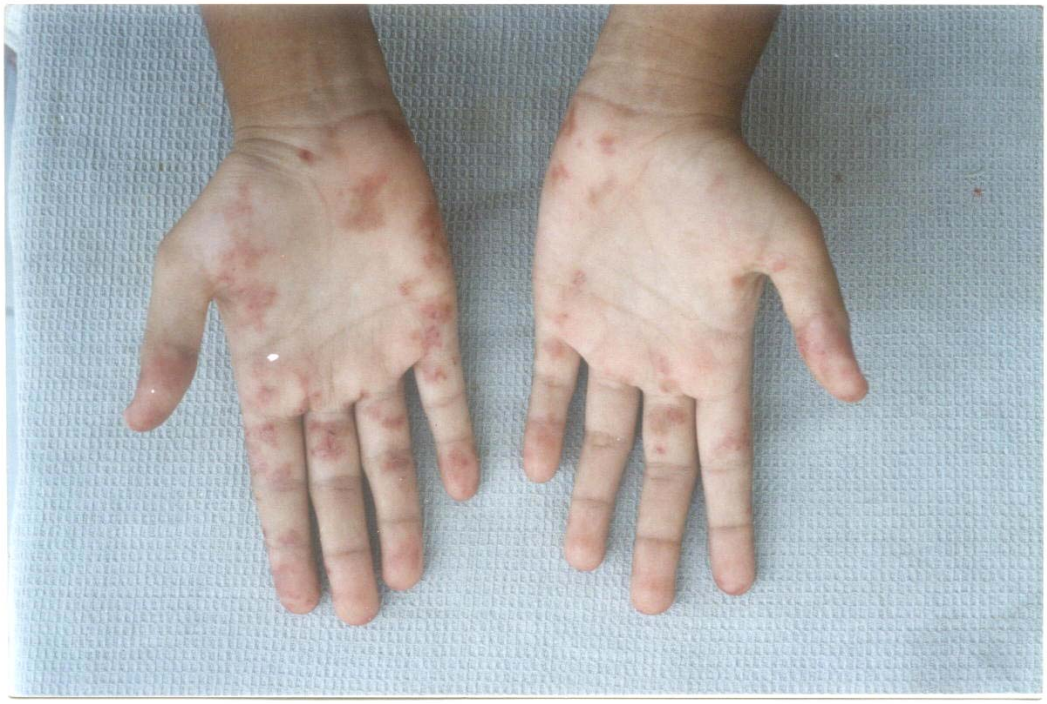
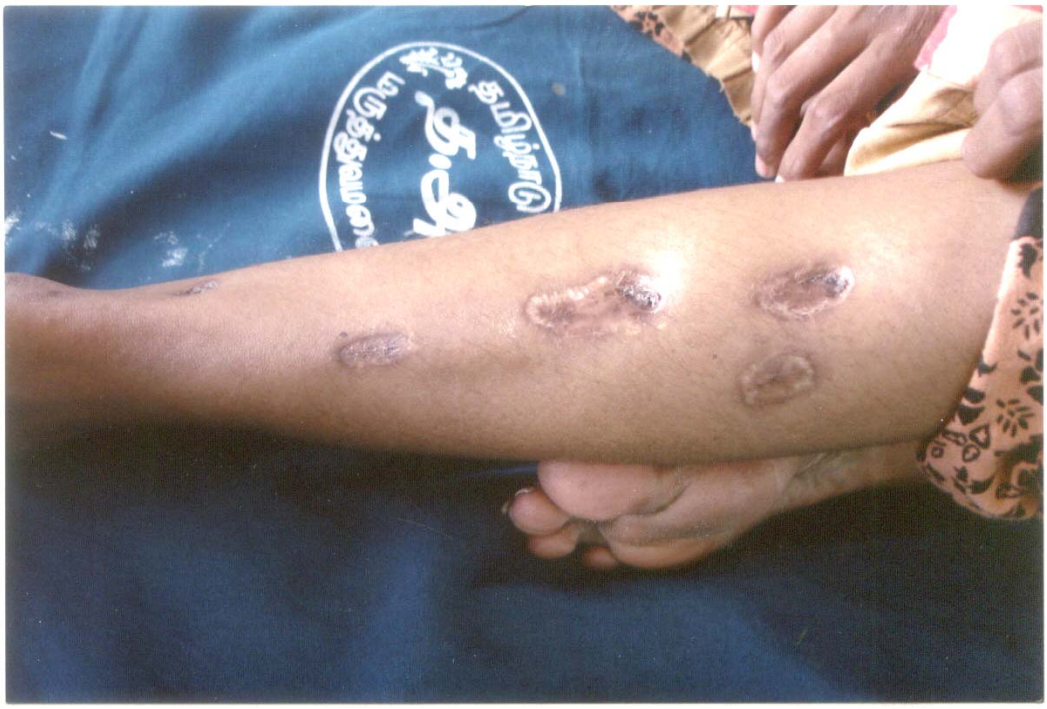
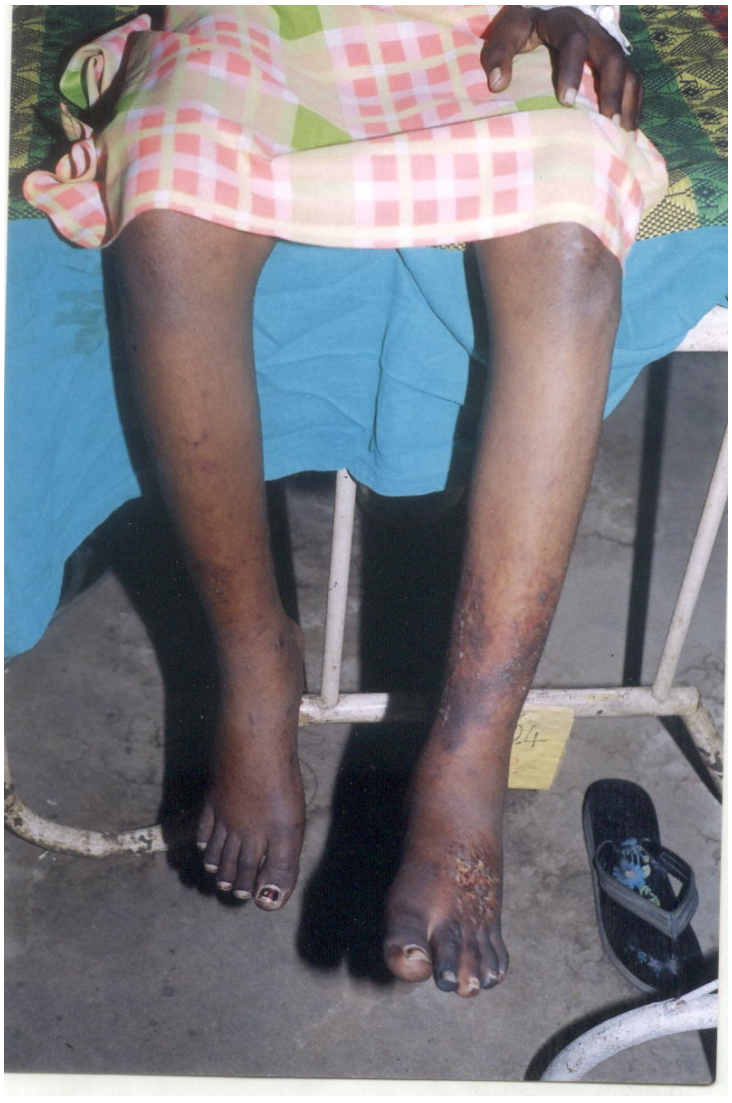
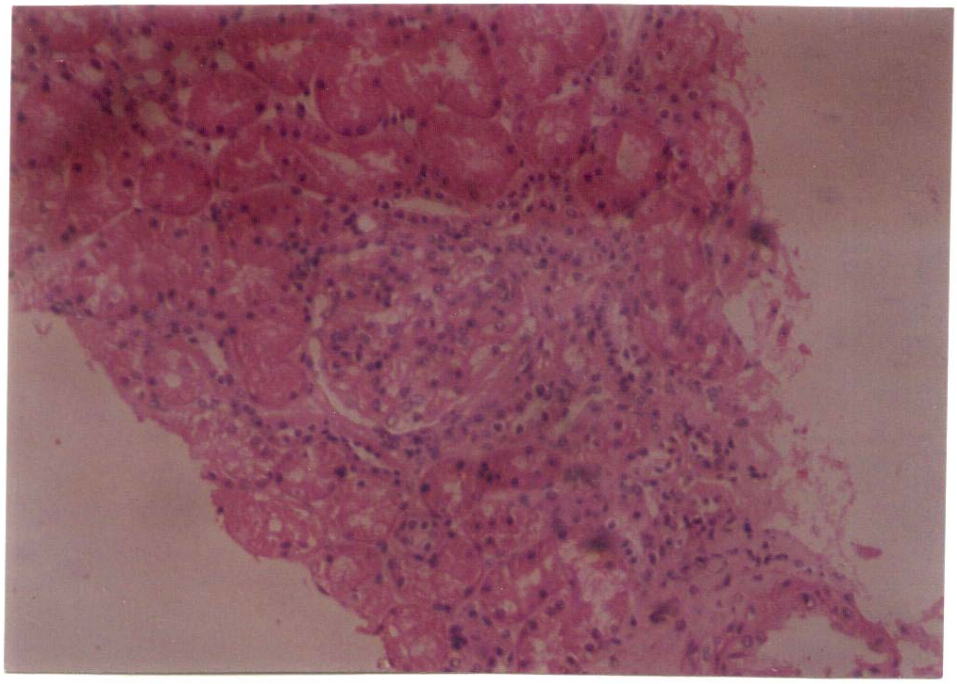


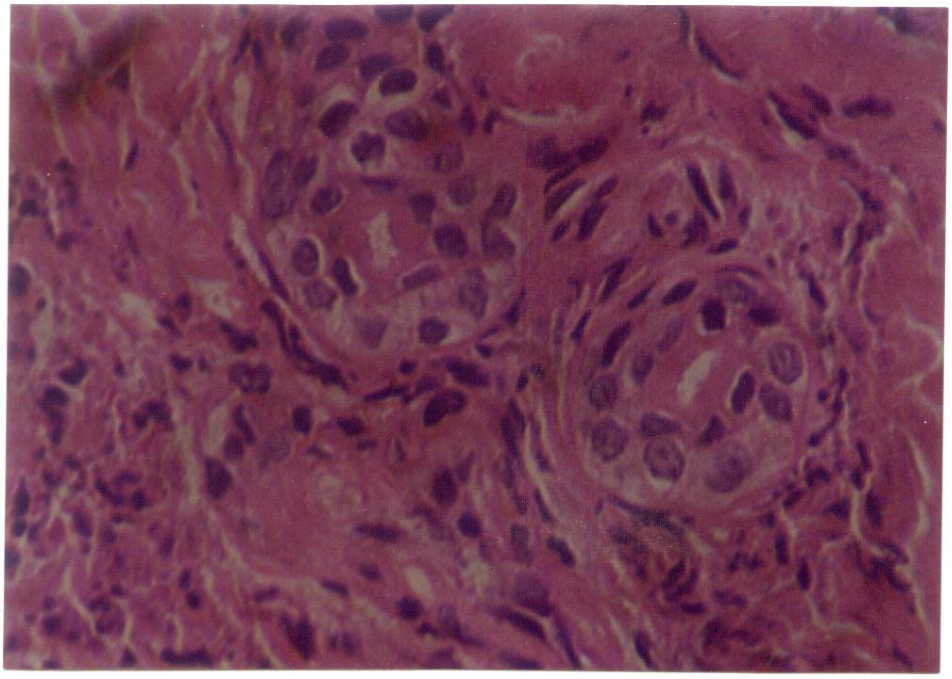


NON SPECIFIC LE LESION

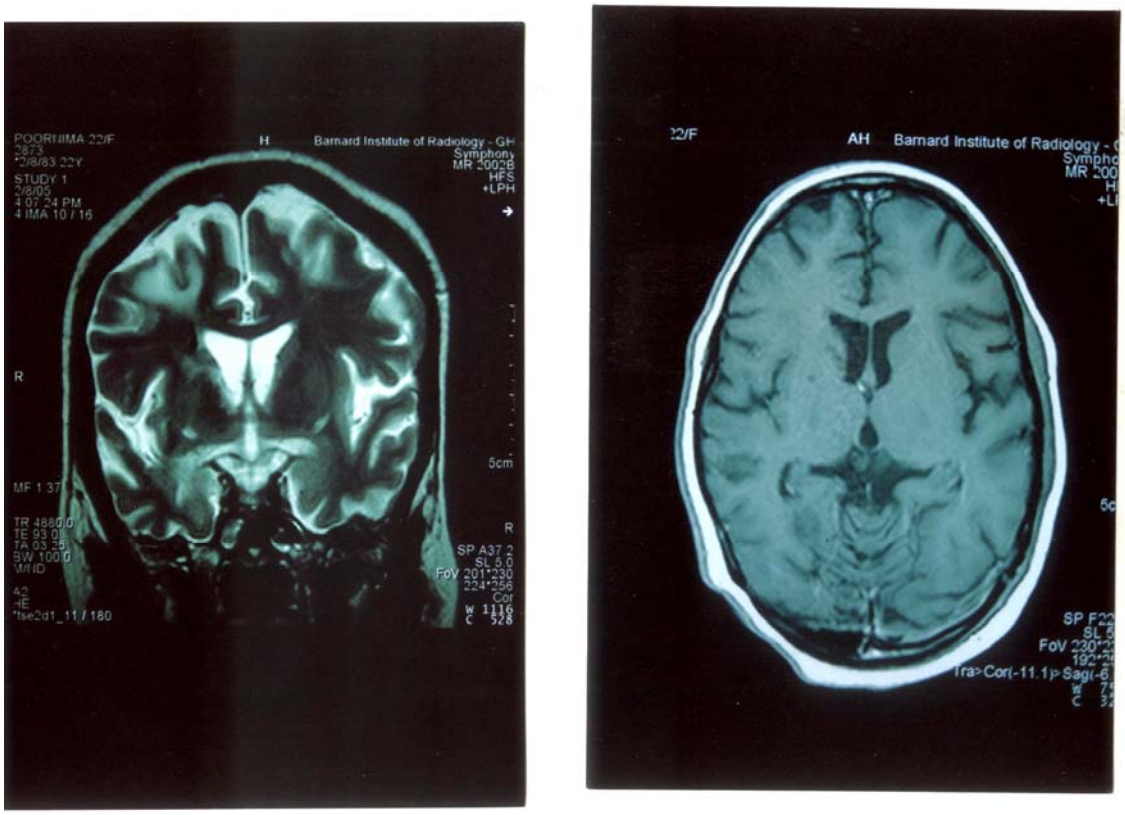


FOOT DROP





LUPUS NE PHRITIS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C 528
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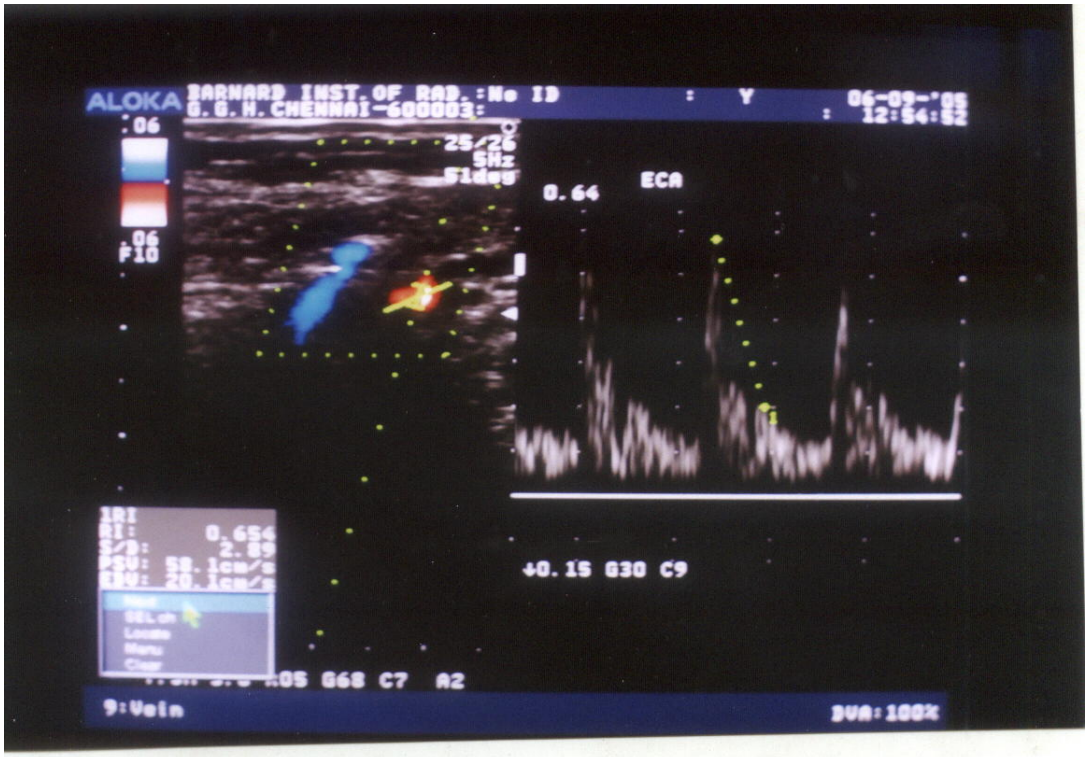
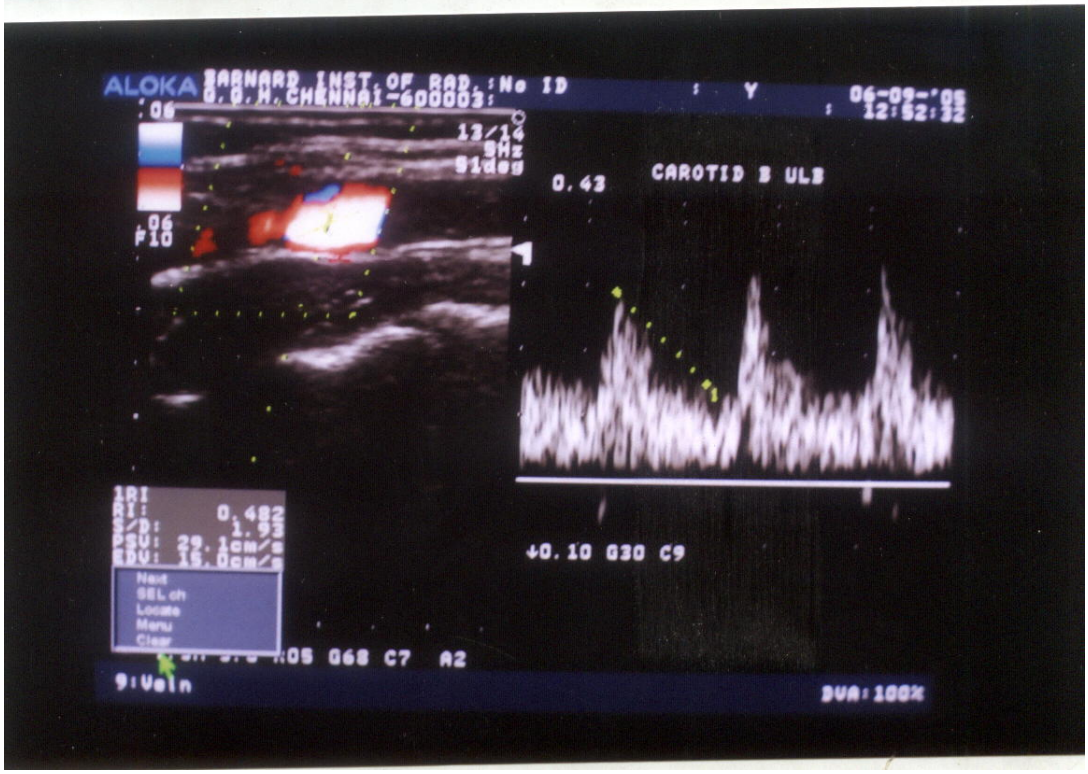
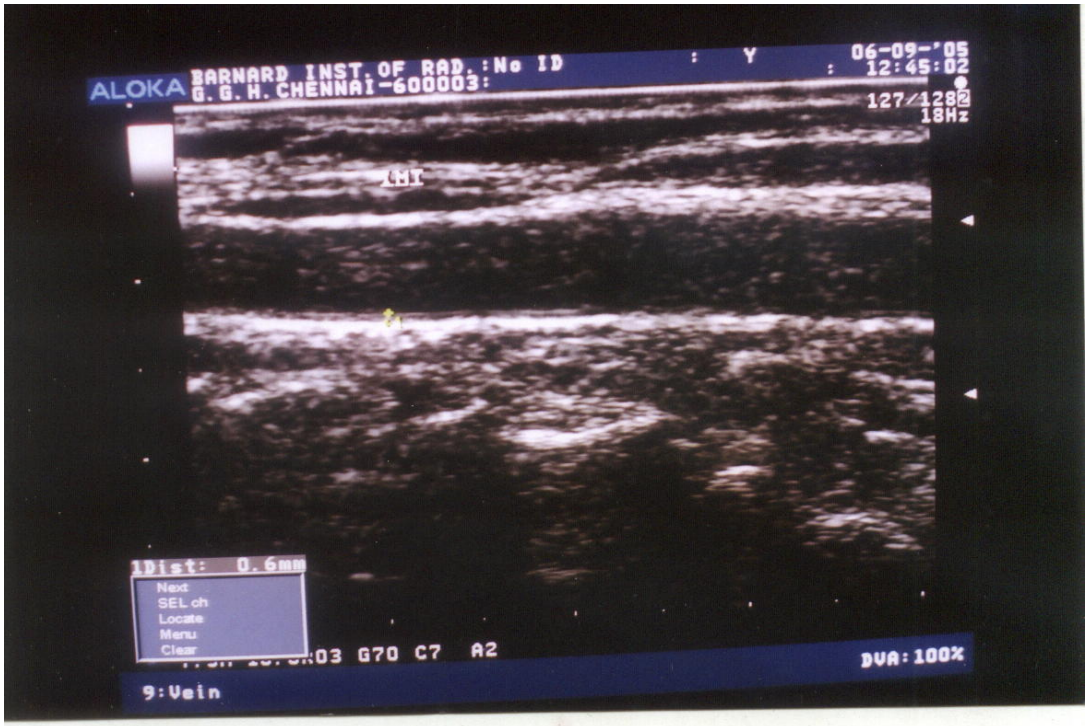
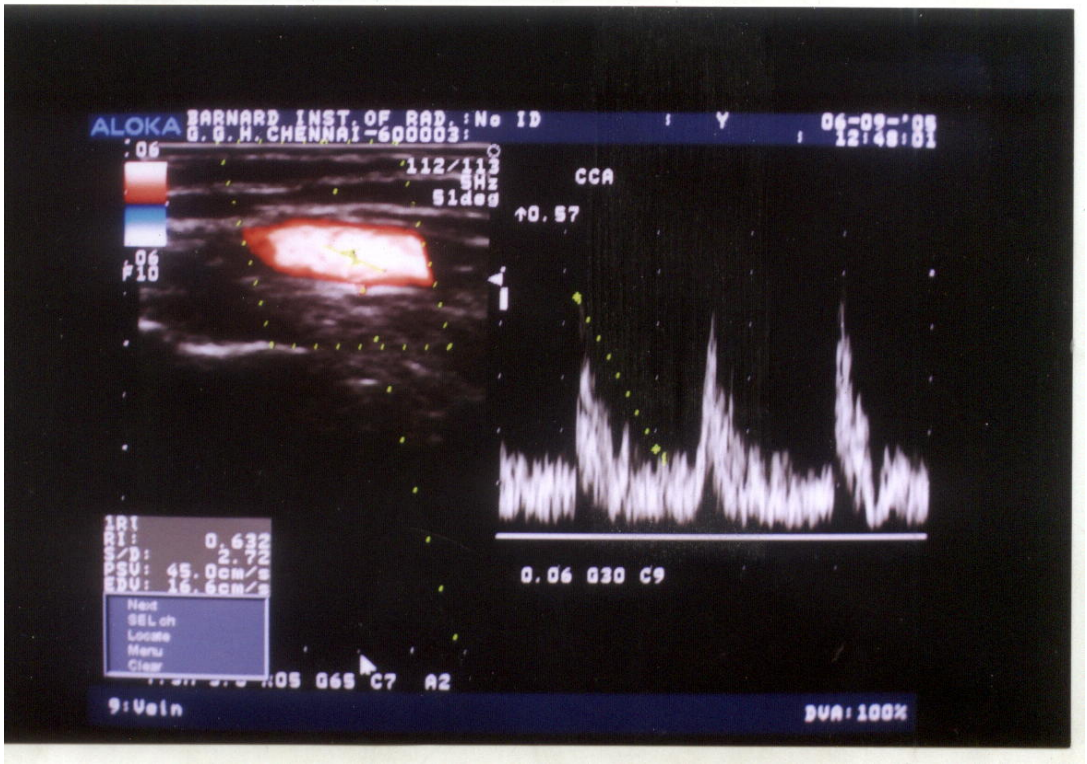
MRI BRAIN





DUPLEX DOPPLER





CAROTID DOPPLER

MASTER CHART

Name	Age	Sex	Duration	Rash	Photo	Oral u.	Ac.Sed	24 Pro	Anemia	Ln.	Hs.	Sero.	Fits	Arth.	Hb.	Tc.	Dc.	Pt.	Lac.	Acl.	Ana.	Ds. Dna	C3-c4	Cxr	Tcl.	Hdl.	Ldl.	Tgl.	Plaque	Stenosis	Imt	Sp. wid	Steroid_dosage	Smoking	Renal	Sledai	Bp.
SUM	17	1	12	1	1	1	0	.8	1	1	1	0	0	1	9.6	18600	51,47,2	1.8	0	0	1	0	0	1	145	40	87	90	0	0	0.47	0	20	0	0	18	0
DHA	16	1	18	1	1	1	1	.7	1	1	0	0	0	1	14.4	5400	58,39,3	1	0	0	1	1	0	1	147	45	88	68	0	0	0.46	0	15	0	0	7	0
SARA	14	1	1	1	1	1	0	1.8	1	1	1	1	1	1	10.2	7200	64,32,4	1.4	1	1	1	1	1	0	136	44	88	124	1	1	0.34	1	30	0	0	22	0
PREM	11	1	6	0	0	1	0	1.6	1	1	1	0	0	1	6.8	4000	58,42	0.35	0	0	1	1	1	0	154	43	95	83	0	0	0.53	0	15	0	0	14	0
KANA	10	1	12	1	1	1	1	2.0	1	0	1	0	1	0	8.8	10000	66,33,2	2	0	0	1	1	0	0	99	27	62	52	0	0	0.28	0	15	0	0	21	0
BHAR	12	1	6	0	1	1	0	1.8	0	0	0	0	0	1	10.5	4600	62,38	1.6	0	0	1	0	0	0	174	33	120	108	0	0	0.31	0	30	0	0	27	1
DWAR	15	0	12	1	1	1	1	1.6	1	0	1	1	0	1	8.2	5300	62,36,2	1.8	1	1	1	1	1	0	196	32	120	220	0	0	0.65	1	30	0	4	30	1
PAD	14	1	24	1	1	1	1	1.5	0	0	0	0	0	1	10.4	7100	71,24,5	1.6	0	0	1	1	0	0	182	44	118	101	0	0	0.2	0	15	0	3	8	0
DEEP	14	1	24	1	1	1	0	0.6	1	0	1	0	0	1	5.2	4600	54,38,18	0.75	0	0	1	1	1	0	221	44	145	158	0	0	0.55	1	20	0	0	20	0
MAHES	12	1	12	1	1	0	0	0.2	0	1	0	0	0	1	10	7400	60,32,8	1.4	0	0	1	0	0	0	166	45	90	157	0	0	0.3	0	35	0	0	24	0
UNBAR	18	1	24	1	1	1	1	1.7	1	0	1	0	0	1	9.8	4200	76,26,2	2.1	0	0	1	0	0	0	160	22	80	290	0	0	0.62	1	25	0	5	35	0
NAGA	18	1	36	1	1	1	1	1.5	1	1	1	1	0	1	7.2	6200	60,37,3	1.8	1	0	1	1	1	0	188	32	114	210	1	1	0.52	1	40	0	5	30	1
PURU	18	0	24	1	1	1	1	1.2	1	0	0	1	0	1	7.6	5200	60,26,14	1.2	0	0	1	1	1	0	201	54	101	234	0	0	0.48	1	10	0	4	11	1
HEMA	12	1	24	1	1	1	0	1.2	0	0	1	0	0	1	9.2	9800	40,22,38	2.1	0	0	1	0	0	0	138	44	80	162	0	0	0.42	1	10	0	0	14	0
RAJK	14	1	12	1	1	0	1	.15	1	0	1	0	0	1	8.1	4800	38,45,17	1.8	0	0	1	1	0	0	127	54	181	284	0	0	0.54	1	10	0	0	9	0
GENO	18	1	24	1	1	1	0	0.1	1	0	1	0	0	1	6.8	12000	80,16,4	3.2	0	0	1	0	0	0	167	44	92	164	0	0	0.46	1	20	0	0	28	0
SUDAR	14	1	24	1	1	1	0	0.5	1	0	0	0	0	1	8.6	11200	89,9,2	3.7	0	0	1	1	0	0	204	40	138	186	0	0	0.42	1	25	0	2	12	1
DURGA	10	1	24	1	1	1	0	.3	0	0	1	0	0	1	9.5	9600	62,36,2	2.5	0	0	1	0	0	0	127	38	50	250	0	0	0.36	0	20	0	0	16	0
VASIF	12	1	24	1	1	1	0	.1	1	0	0	0	0	1	9.2	8400	58,36,6	2.2	0	0	1	0	0	0	159	37	104	91	0	0	0.38	0	15	0	0	20	0
RAMYA	18	1	24	1	1	1	0	.3	1	0	0	0	0	1	7.8	5000	48,46,6	3.1	0	0	1	0	0	0	144	42	76	96	0	0	0.47	0	25	0	0	25	1
JAMUN	35	1	12	1	1	1	1	.2	1	1	1	0	O	0	8.2	4600	62,32,6	2.2	1	0	1	0	0	0	174	33	120	108	0	0	0.38	1	15	0	2	25	1
RAMACH	40	0	6	0	0	1	0	1.5	1	0	1	1	0	1	12	3900	84,2,14	2.1	0	0	1	0	0	0	166	45	90	157	0	0	0.47	0	10	1	0	5	0
ANITH	20	1	6	1	1	1	1	2	0	0	0	0	0	1	10.8	4600	52,38,10	1.2	0	0	1	0	0	0	236	39	149	238	0	1	0.56	1	5	0	0	4	0
SRDE	24	1	24	1	1	1	1	2.5	1	0	0	1	0	1	9.8	7600	56,35,5	1.5	1	0	1	1	1	0	184	39	119	132	0	0	0.45	1	25	0	2	26	1
JAYA	28	1	6	1	1	1	0	1.5	0	0	0	0	0	1	8.8	8200	62,36,2	1.8	0	0	1	0	0	0	218	49	151	92	0	1	0.48	1	10	0	0	4	0

Name	Age	Sex	Duration	Rash	Photo	Oral u.	Ac.Sed	24 Pro	Anemia	Ln.	Hs.	Sero.	Fits	Arth.	Hb.	Tc.	Dc.	Pt.	Lac.	Acl.	Ana.	Ds. Dna	C3-c4	Cxr	Tcl.	Hdl.	Ldl.	Tgl.	Plaque	Stenosis	Imt	Sp. wid	Steroid_dosage	Smoking	Renal	Sledai	Bp.
BAVA	40	1	36	1	1	1	0	2.2	1	0	1	1	0	1	9.1	6700	60,40	1.8	1	0	1	1	1	0	224	40	156	216	1	1	0.45	1	50	0	3	20	1
RAHI	23	1	24	1	1	0	1	.3	1	0	0	0	0	1	6.8	5700	038,36,6	0.8	1	0	1	0	1	0	138	44	80	70	0	0	0.32	0	10	0	0	15	0
VALAR	42	1	4	1	1	1	1	.2	0	0	0	0	0	1	11.6	8000	59,36,5	2.1	0	0	1	0	0	0	162	55	71	88	0	0	0.27	0	5	0	0	4	0
ANJALAI	32	1	7	1	1	1	0	1.5	1	0	0	0	0	0	9.2	7800	60,38,2	2.1	0	0	1	1	1	0	189	40	112	128	0	0	0.42	0	10	0	0	6	0
SUMATHI	28	1	6	1	1	1	1	2.5	1	0	0	0	0	1	8.4	5600	62,28,10	1.9	0	0	1	0	0	0	202	44	130	108	0	0	0.46	1	5	0	0	24	0
SUMATHI	21	1	12	1	1	1	1	2	1	0	0	0	0	1	9.2	9800	44,47,9	1.12	0	0	1	1	0	0	200	49	132	96	0	1	0.47	1	15	0	0	23	0
DANALAX	32	1	24	1	1	1	1	2	1	0	0	1	0	1	8.2	8800	84,12,4	4.6	0	0	1	0	1	0	150	37	104	91	0	0	0.43	0	30	0	0	35	1
RAJALAX	32	1	6	1	1	1	0	.1	1	0	0	1	0	1	9.4	8100	56,36,8	1.6	0	0	1	0	0	0	100	36	52	60	0	0	0.45	1	10	0	0	7	0
VIJAYA	34	1	24	1	1	1	1	2.5	1	0	0	1	0	1	7.6	8400	40,52,8	1.6	1	0	1	1	0	0	221	44	145	158	0	0	0.39	1	15	0	0	25	0
YTHRA	21	1	24	1	1	1	1	.1	1	0	0	0	0	1	6.4	7600	46,38,16	1.4	1	0	1	0	0	0	256	38	175	244	0	1	0.48	1	10	0	0	26	0
PARWIN	23	1	12	1	1	1	1	.2	1	0	0	0	0	1	7.6	7400	76,24	1.2	0	0	1	0	0	1	101	40	55	82	0	0	0.38	0	15	0	4	30	1
PRASA	28	1	6	1	1	0	1	3.5	1	0	0	1	0	1	6.5	9800	60,38,2	1.1	0	0	1	0	1	1	182	44	118	101	0	0	0.41	1	25	0	5	15	0
SAVITH	40	1	24	1	1	0	0	3.5	1	0	0	1	0	1	7.8	6000	55,43,2	1.4	0	0	1	1	0	0	185	39	77	344	0	1	0.36	1	20	0	0	10	0
SELVE	20	0	6	0	0	0	0	1.2	1	0	1	0	0	1	6.2	9600	68,28,4	0.9	0	0	1	0	0	0	172	46	109	79	0	0	0.34	0	15	1	0	20	0
SUVULAX	35	1	24	1	1	1	1	.2	1	0	0	1	0	1	8.2	7000	52,42,4	3.2	1	0	1	0	1	1	204	48	140	144	0	0	0.38	1	30	0	4	36	1
USHA	38	1	6	1	1	1	1	.3	1	0	0	1	1	1	5.6	6800	77,33	1.8	0	0	1	0	0	0	202	43	137	112	0	0	0.53	1	10	0	3	20	1
BALGAS	35	1	36	1	1	1	0	.5	1	0	0	1	0	1	7.4	7100	68,25,2	1.3	1	0	1	1	1	1	145	40	87	90	0	0	0.26	0	15	0	4	28	1
KOKILA	21	1	18	1	1	0	0	.3	0	1	0	0	1	1	7.2	9800	68,28,4	1.1	1	1	1	0	0	0	198	50	115	168	1	1	0.52	1	10	0	0	4	1
GEETHA	24	1	24	1	1	1	0	.6	1	0	0	1	0	1	7.7	8200	40,32,8	1.4	0	0	1	1	1	0	154	43	95	83	0	0	0.29	0	30	0	4	35	0
DAISY	26	1	24	1	1	0	1	.2	1	1	1	0	0	0	10.7	7800	59,37,4	2.6	0	0	1	0	0	0	256	38	156	234	0	0	0.51	1	50	0	0	6	0
VALAR	21	1	12	1	1	1	1	.6	0	0	0	0	0	1	10.7	7200	54,45,1	2.6	0	0	1	0	0	0	167	38	89	280	0	0	0.35	0	20	0	0	10	0
SALSA	24	1	6	1	1	1	1	.7	1	0	0	0	0	1	7.2	3800	71,36,2	1.4	0	0	1	0	0	0	123	38	73	59	0	0	0.42	1	10	0	2	32	1
SHAEELA	40	1	24	1	1	1	0	.1	0	1	1	1	1	1	11.4	4200	80,18,2	1.6	0	0	1	0	1	0	176	40	106	132	0	0	0.32	1	25	0	4	46	1
SHANTHI	25	1	6	1	1	1	1	.8	1	0	0	1	0	1	5.6	4200	58,26,13	2.8	1	0	1	0	0	0	211	38	146	179	1	1	0.61	1	35	0	2	26	1
SELVAM	26	0	6	1	1	1	1	1.1	1	1	0	0	0	1	12.8	8200	56,42,2	1.8	0	0	1	0	0	0	148	38	96	57	0	0	0.48	1	5	0	0	6	0