Systemic Lupus Erythematosus – presentation and diagnosis in children and adolescents

American Academy of Pediatrics New Jersey Chapter

RUTGERS Robert Wood Johnson Medical School

Systemic Lupus Erythematosus – presentation and diagnosis in children and adolescents

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•Shoreline, By Moorthy LN

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Disclosures

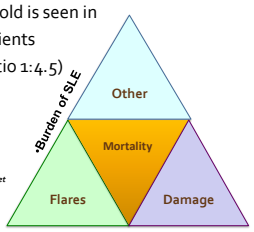
- Site PI An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis- BMS
- Site – PI A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)- GSK

SLE

- Multisystem, episodic, chronic fluctuating autoimmune disease
- Extensive inflammation of blood vessels and connective tissues, with variable clinical manifestations, morbidity and course
- Causes multiple organ involvement and damage
- Requires multiple medications with unpleasant short-/long-term side-effects
- SLE-associated responsibilities significantly disrupt lifestyle

Childhood onset SLE (cSLE)

- Incidence: 0.5 -0.6 case per 100,000 persons (Klein-Gitelman Nov 2015 (Medscape)
- Prevalence 4-250 cases per 100,000 persons
- Onset of disease before 18 years old is seen in approximately 15% of SLE patients
- More in females (male:female ratio 1:4.5)
- Uncommon in <8 yr olds



•Tucker et al Lupus 2008, Stichweh et al Curr Opin Rheum 2004, Gonzalez et al Lupus 2005, Ardoin et al Nat Clin Pract Rheumatol 2005, Borchers 2004, Ippolito 2008, Trager 2003, Uramoto 1999; Brunner et al; Klein Gitelman, Medscape 2015

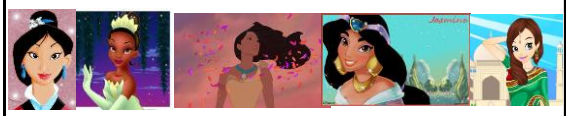
Ethnic differences in cSLE

•*Boats at dawn*
•*By Moorthy LN*

cSLE prevalence

- Greater prevalence in Native Americans, Asian Americans, Latin Americans and African Americans.
- African American children may represent up to 60% patients younger than than 20 years with lupus.
- Asians have the highest prevalence of SLE and SLE nephritis and have most severe disease (Hiraki et al, Levy et al)

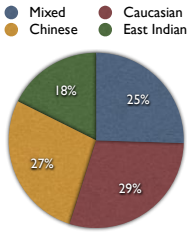
(Hiraki et al, Pluchinotta et al, M Klein Gitelman)



Associations of gender and ethnic origin with longterm outcome in childhood-onset systemic lupus erythematosus (SLE)

Cohort from Vancouver
n=51 (13 males; 38 females); Follow up=7 years
No African-Americans/Hispanics
5-year survival 100%; 10-year survival 86%
Median SDI =2 (0-9)

SDI scores, mortality and need for intensive immunosuppressive therapy were not influenced by either gender or ethnic origin
Miettunen et al, J Rheumatol 2004



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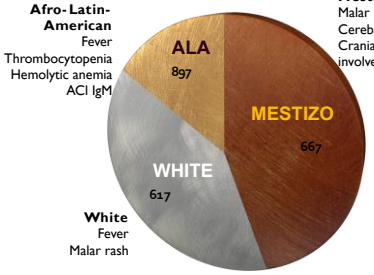


•*LA Ramírez Gómez et al, Lupus 2008 (Childhood SLE in Latin America)*

Most affected groups were ALA and Mestizo

Ethnic differences in pediatric SLE

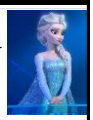
Non-Caucasians were younger at diagnosis (12.6 vs 14.6 yrs; p = 0.007

Non-Caucasians had more renal disease (62% vs 45%; p = 0.01)

Blacks - increased prevalence of CNS disease vs. Asians (p = 0.108).

•*Hiraki et al 2009*
•*Asians and S. Americans seemed to have a younger age of onset (Moorthy et al, 2012)*

Ethnic variations in cSLE



- Children of European/White ethnicity/race have a lower incidence and prevalence of
  - SLE
  - lupus nephritis
  - have milder disease
  - may sustain less damage than other ethnicities/races

(Review by Silverman et al; Levy et al, Watson et al, Hiraki et al, Hersh et al)

•*Dancing while playing chess,*
•*By Moorthy LN*

Childhood onset versus adult onset SLE

Adult onset SLE vs. Childhood onset SLE

- Malar rash, lymphadenopathy, cytopenias, and nephritis have a greater prevalence in cSLE.

(Brunner et al, Mina et al Papdimitraki et al, Livingston et al) The Rheumatologist

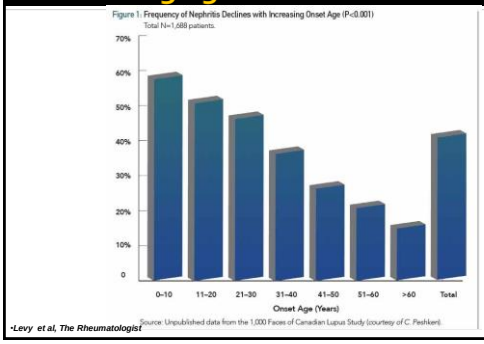
Table 1: Cumulative Incidence of Common SLE Manifestations

	CSLE (%)	ASLE (%)
CONSTITUTIONAL – FEVER*	37–100	42–57
MALAR RASH	65–92	50–61
ORAL OR NASAL ULCERS*	14–49	14–42
PHOTOSENSITIVITY	35–50	41–56
ARTHRITIS	60–90	83–93
RENAL DISEASE*	50–80	31–65
NEUROPSYCHIATRIC SLE (ANY MANIFESTATION)	6–39	9–22
SEIZURES*	11–14	6–12
PSYCHOSIS	5–10	4–12
SEROSITIS	20–30	17–28
HEMOLYTIC ANEMIA	16–39	11–22
THROMBOCYTOPENIA*	15–37	14–38

*Manifestation has significantly greater prevalence in cSLE (odds ratio > 1 by meta-analysis)

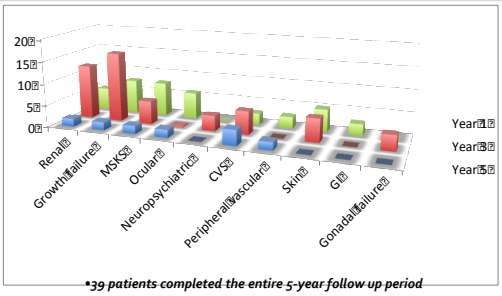
•*Levy et al, The Rheumatologist*

Frequency of nephritis declines with increasing age of onset



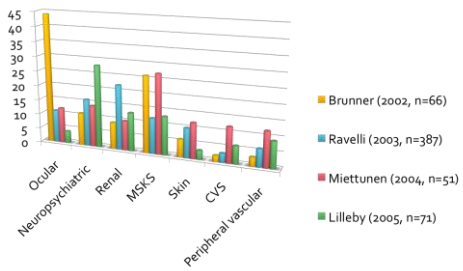
•*Levy et al, The Rheumatologist*

New damage in each organ system at years 1, 3 and 5 after diagnosis (n=57)



•*39 patients completed the entire 5-year follow up period*
•*Bandeira et al, Lupus 2006*

Percentage of patients with damage in the particular organ system



•Similar data from our cohort also, Moorthy et al, PRYSM 2011

Childhood –onset SLE versus adult onset SLE

Higher disease activity at onset and during the disease course (1)

Significant and early damage
Increased exposure to steroids, Longer disease duration
Higher frequency of organ involvement cSLE (1-4)

Cataracts, avascular necrosis, fractures, osteoporosis, low BMD (longer disease vs. steroids), premature atherosclerosis, persistent cognitive dysfunction in cSLE (1,2)

Incurable, potentially devastating disease during a vulnerable period of psychosocial development in cSLE

Increased and unique psychosocial stressors

•(1) Brunner et al (2) Kamphius et al (3) Watson et al (4) Mok et al

Mortality in childhood-onset SLE

Young adults with SLE: SMR 20 times higher than general population (vs. 2-5 fold in adults)

Accumulate disease damage more quickly

More aggressive course → increased exposure to immunosuppressive medications over a longer disease duration •19.5 vs. 16.5 years (p<0.0001)

More likely to meet ACR criteria for renal disease and have ESRD •56%vs.24% and 21% vs. 8% (p<0.0001)

•(Brunner 2008, Tucker 1995, Tucker 2008, Hersh 2009, Hersh 2010)

Predictors for early mortality

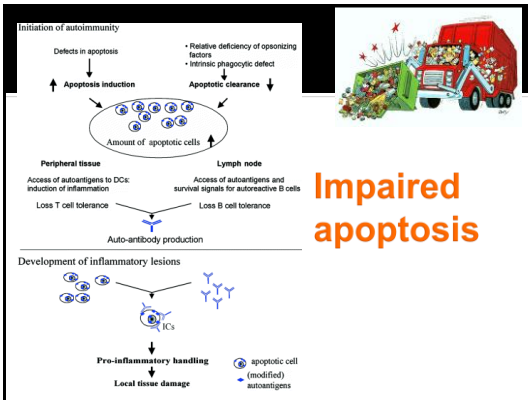
Mean age at death 33 (childhood-onset; n=98) versus 52 years (n=859)

Childhood-onset SLE	Male sex
Education	Cardiovascular disease
ESRD	Medicare or Medicaid insurance

•Hersh 2010

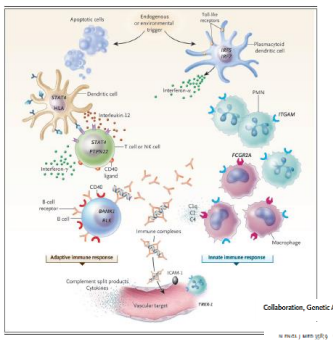
What is the difference?

SLE- Pathogenesis

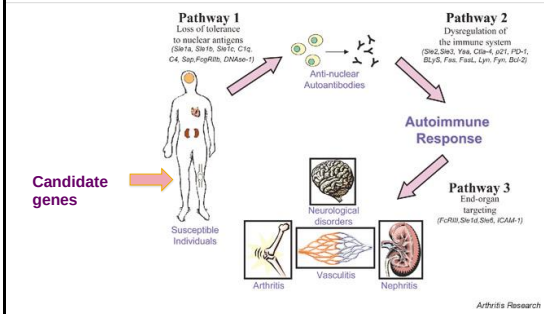


Impaired apoptosis

SLE- Pathogenesis



SLE- Pathogenesis



•*Sunflowers*
•*With acrylic, By Moorthy LN*

Clinical presentation and diagnosis

The girl with fevers and weight loss

11 year old girl is feeling very tired and has a malar rash that is worsening. It is maculopapular erythematous with brownish plaques. She also has some photosensitivity and alopecia. For the last 2 months she has had intermittent fevers, fatigue, weight loss, and irritability

- CBC and diff, CMP, UA NL
- ESR 30 mm/hr
- ANA positive
- Anti-DS-DNA ab+, Anti-Smith ab +ve;
- -ve anti-Ro, La and RNP ab

Constitutional symptoms in SLE

- Fever
- Fatigue
- Wt Loss
- Alopecia
- Arthralgias
- Diffuse generalized inflammation
- Lymphadenopathy
- Hepatosplenomegaly

Common Clinical Features of cSLE

Clinical Feature	Prevalence of Involvement
Constitutional and generalized symptoms	
Fever	37 – 100%
Lymphadenopathy	13 – 45%
Weight loss	21 – 32%
Mucocutaneous	60 – 90%
Musculoskeletal	60 – 90%
Nephritis	48 – 78%
Neuropsychiatric disease (NPSLE)	15 – 95%
Gastrointestinal	24 – 40%
Hematologic	50 – 100%
Cardiovascular	25 – 60%
Pulmonary	18 – 81%

Data from 7, 12, 17,13,14-16

•**Review by Levy et al**

Clinical Characteristics of Patients Who Have SLE

Organ System Involvement	At Diagnosis (%) (n = 256)	Within 1 Year After Diagnosis (%) (n = 256)	Ever (%) (n = 256)
Diffuse lymphadenopathy	48 (19)	50 (20)	51 (20)
Other			
Raynaud phenomenon	35 (14)	45 (18)	49 (19)
Thrombotic thrombocytopenic purpura	2 (0.8)	2 (0.8)	2 (0.8)
Constitutional symptoms			
Fatigue	129 (50)	136 (53)	142 (55)
Fever	101 (39)	104 (41)	106 (41)
Weight loss	74 (29)	79 (31)	82 (32)
Anorexia	51 (20)	72 (28)	72 (28)
Headache[b]	34 (13)	39 (15)	46 (18)

- Dry eyes and mouth (Sjogrens)
- Stomach, liver, pancreas
- Thyroid, diabetes
- Irregular or absent periods

Pediatric Systemic Lupus Erythematosus : More Than a Positive Antinuclear Antibody
Jennifer E. Weiss
Pediatrics in Review 2012;33;62
DOI: 10.1542/pir.33-2-62

Systemic lupus erythematosus: ACR classification criteria --4/11

- Malar rash
- Discoid rash
- Photosensitivity
- Naso-oral ulcers
- Arthritis
- Pleuritis/Pericarditis
- Proteinuria (>500 mg/d) or evidence of nephritis in urinalysis
- Hemolytic anemia, thrombocytopenia, leukopenia, or lymphopenia
- Seizure or psychosis
- Positive ANA finding
- Positive anti–double-stranded DNA, anti-Smith, or antiphospholipid antibody/lupus anticoagulant

Systemic lupus erythematosus: 1982 classification criteria
Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-1277.

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997 Sep. 40(9):1725. [Medline].

SLICC† Classification Criteria for Systemic Lupus Erythematosus

RheumTutor.com

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria	Immunologic Criteria
1. Acute Cutaneous Lupus*	1. ANA
2. Chronic Cutaneous Lupus*	2. Anti-DNA
3. Oral or nasal ulcers *	3. Anti-Sm
4. Non-scarring alopecia	4. Antiphospholipid Ab *
5. Arthritis *	5. Low complement (C3, C4, CH50)
6. Serositis *	6. Direct Coombs' test (do not count in the presence of hemolytic anemia)
7. Renal *	
8. Neurologic *	
9. Hemolytic anemia	
10. Leukopenia *	
11. Thrombocytopenia (<100,000/mm³)	

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

Acute cutaneous lupus including the following:

- Lupus malar rash
- Bullous lupus
- Toxic epidermal necrolysis variant of SLE
- Maculopapular lupus rash
- Photosensitive lupus rash (in the absence of dermatomyositis)

- OR subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias

Bullous lesions

Photosensitive rash

Mucocutaneous manifestations- Malar rash

- Acute cutaneous lupus erythematosus (ACLE) -facial rash or generalized eruption (disseminated ACLE)
- Localized ACLE (Butterfly rash) usually after UV light exposure, mistaken for a sunburn
  - Malar rash-fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds

Mucocutaneous manifestions

Subacute cutaneous lupus erythematosus (SCLE)– erythematous scaly papules or annular plaqunes over neck, upper trunk and arms

Chronic cutaneous lupus including the following:

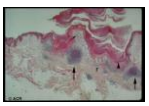
- Classic discoid rash
  - Localized (above the neck)
  - Generalized (above and below the neck)
- Hypertrophic (verrucous) lupus
- Lupus panniculitis (profundus)
- Mucosal lupus
- Lupus erythematosus tumidus
- Chilblains lupus
- Discoid lupus/lichen planus overlap

Discoid – inflammatory plaques evolving into atrophic disfiguring scars

Chronic cutaneous lupus

Discoid lupus erythematosus: Ig deposition, skin (photomicrograph)

Skin Lesion-hyperkeratosis



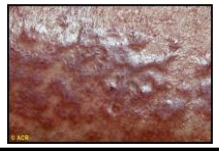
J Clarke, Initial management of discoid lupus and subacute cutaneous lupus, UpToDate updated May 2015

Mucocutaneous manifestations

LE panniculitis (Lupus profundus)

Vascular lesions

- Periungual erythema
- Raynauds
- Telangiectasias
- Livedo reticularis
- Chilblain LE
- Urticaria or purpuric vasculitis



ORAL-NASAL ULCERS

- Ulcers in the absence of other causes such as vasculitis, Behçet disease, herpesviruses, inflammatory bowel disease, reactive arthritis, or acidic foods
  - Palate
  - Buccal
  - Tongue
  - Nasal

ALOPECIA

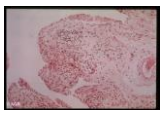
- Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs) in the absence of other causes such as alopecia areata, drugs, iron deficiency, or androgenic alopecia

MSKS manifestations

- Synovitis involving 2 or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness (SLICC criteria)
- Commonly children with SLE have arthralgias and arthritis
- Osteopenia (38% LS spine DEXA)
- Osteoporosis (20%)

(SLE in children, reviewed in UpToDate, 3/2016)

Musculoskeletal manifestations



Nonerosive synovitis in SLE. Note the inflammatory exudate of occasional neutrophils and numerous lymphocytes immediately beneath the surface layer of synoviocytes.

Avascular necrosis of bone is a frequent complication, occurring in about 25% of children with SLE over time.

Boy with a limp

- A 13 year old Asian boy presented with malar rash, fevers and cutaneous vasculitis. He had mild renal involvement (class 2)
- Given steroids and mycophenolate
- He started limping
- He had avascular necrosis of both his knees

"Walking is the best possible exercise. Habituate yourself to walk very far."- Jefferson

Mucocutaneous and musculoskeletal manifestations

Table 2. Clinical Characteristics of Patients Who Have SLE

Organ System Involvement	At Diagnosis (%) (n = 256)	Within 1 Year After Diagnosis (%) (n = 256)	Ever (%) (n = 256)
Arthritis	157 (61)	159 (62)	171 (67)
Mucocutaneous involvement			
Malar rash	155 (61)	161 (63)	169 (66)
Other rash	96 (38)	106 (41)	111 (43)
Oral ulcers	55 (21)	59 (23)	76 (30)
Alopecia	56 (22)	62 (24)	73 (29)
Photosensitivity	44 (17)	45 (18)	52 (20)
Nasal ulcers	21 (8)	25 (10)	26 (10)
Digital ulcers	9 (4)	10 (4)	13 (5)

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SEROSITIS

- Serositis in the absence of other causes such as infection, uremia, and Dressler pericarditis
  - Typical pleurisy for more than 1 day
  - OR pleural effusions
  - OR pleural rub
  - Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
  - OR pericardial effusions
  - OR pericardial rub
  - OR pericarditis by electrocardiography (SLICC criteria)

Pulmonary abnormalities

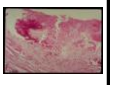
- Subclinical lung disease (restrictive lung disease)
- Pleuritis -often present with chest pain
- Pulmonary hemorrhage- acute and chronic (rare in children)
- Pulmonary hypertension (due to small multiple pulmonary emboli- dyspnea on exertion, fatigue, lethargy, chest pain and hemoptysis and hoarseness – rare but severe (suspect it if worsening TI on ECHO)
- Acute and chronic pneumonitis – often confused with pneumonia- CT usually helps with diagnosis

Beresford et al Lupus 2005, Samad et al South Med J 2003, Mok et al, Lehman, SLE in children, UpToDate, 2016)

Cardiovascular manifestations

- Pericardial disease
  - Common in children esp in 1st 6 months of diagnosis
  - Acute, sharp anterior chest pain with dyspnea
  - Pain is exacerbated by inspiration and alleviated by upright forward leaning position
  - Low grade fever, tachycardial and tachypnea are present.
  - Pericardial rub may be heard
  - ECG and ECHO
  - Severe cases may result in cardiac tamponade and failure
- Clinically significant myocarditis is rare
- Valvular heart disease is rare (Libman Sacks Endocarditis)
- Coronary heart disease
  - ***Increased risk for atherosclerosis***

Beresford et al Lupus 2005, Samad et al South Med J 2003, Mok et al, Lehman UpToDate 2016)



Fibrinoid and Histiocytes

Neurologic

- Seizures
- Psychosis
- Mononeuritis multiplex in the absence of other known causes such as primary vasculitis
- Myelitis
- Peripheral or cranial neuropathy in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus
- Acute confusional state in the absence of other causes, including toxic/metabolic/uremia/drugs (SLICC)

Neurocognitive functioning in childhood SLE

•*E Muscal et al, Lupus 2010*

•Scores >1.5 SD below age-matched norms in tests of:

•Executive functioning
•Visual memory
•Visual–spatial planning

•Memory

Cognitive domain	*•Prospective cohort (n=24)* *score >1.5 SD below norms*	*•Retrospective cohort (n=15)* *score >1.5 SD below norms*
Intelligence		
Full scale IQ	12.5	None
Attention		
Trails A	13.6	13.3
CCPT [b]		
Omissions	9.1	
Commissions	4.4	
Executive functioning		
Trails B	31.8	20.0
Verbal fluency	28.6	53.3
WCST[b]	NONE	
Visuo–spatial functioning		
RCFT copy[c]	25	20
VMI	38.1	53.3
Psychomotor speed		
Grooved pegboard		
Dominant	40.9	20.0
Non-dominant	34.8	13.3
Finger tapping[b]		
Dominant	16.7	
Non-dominant	16.7	
Memory		
RCFT recall		
Immediate	61.1	26.7
Delayed	64.7	26.7
TOMAL[b]		
Word reminding		
Immediate	9.5	
Delayed	9.5	

Neurocognitive involvement in childhood SLE

- Predominantly African-American and Hispanic adolescent girls of average intelligence.
- Deficits were seen at times of wellness, without previous neuropsychiatric lupus, and early in disease courses.
- aPL positivity and aspirin use was prevalent.

Prospective (15)

- Neurocognitive impairment in 47%
- Volume loss in 73% (cerebral) and 68% (cerebellar)
- White matter hyperintensities in 47%

Retrospective (24)

- Neurocognitive impairment in 71%
- Depression in 33%
- White matter hyperintensities in 37%

Neuropsychiatric Syndromes observed in SLE (NPSLE)

CENTRAL NERVOUS SYSTEM	PERIPHERAL NERVOUS SYSTEM
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)
Cerebrovascular disease	
Demyelinating syndrome	
Headache	Autonomic disorder
Movement disorder (chorea)	Mononeuropathy, single/multiplex
Myelopathy	Myasthenia gravis
Seizure disorder	Neuropathy, cranial
Acute confusional state	Plexopathy
Anxiety disorder	Polyneuropathy
Cognitive dysfunction	
Mood disorder	
Psychosis	

Adapted from American College of Rheumatology : Nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum.* 1999; 42:599-608.

Case: Girl with eye pain

21 year old girl with SLE is complaining of blurry vision and eye pain

C3 70

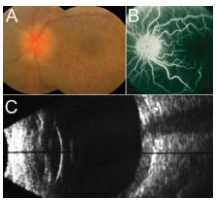
C4 14

CBC, CMP and ESR nl

UA – nl

She sees opthalmology- has loss of vision

She says now that she has severe pain at 6 o' clock position in the L eye.



Posterior scleritis in a patient with systemic lupus erythematosus. Optic disc hyperemia and retinal striae were evident clinically (A, B). B-scan ultrasonography showed posterior eye wall thickening with retrobulbar fluid producing the so-called "T-sign" (C).

Causes of red eye in SLE

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

Sivraj et al, 2007

Causes of loss of vision in SLE

Anterior segment-- Severe kerato-conjunctivitis sicca
Lens--Cataract (secondary to inflammation and/or corticosteroids)

Vitreous--Vitreous haemorrhage (secondary to proliferative retinopathy)
Retina

Severe vaso-occlusive retinopathy
Central retinal vein occlusion (CRVO)
Branch retinal vein occlusion (BRVO)
Central retinal arteriole occlusion (CRAO)
Branch retinal arteriole occlusion (BRAO)
Exudative retinal detachment
Toxic maculopathy (secondary to anti-malarial treatment)

Sivraj et al, 2007

Causes of loss of vision in SLE

Choroid

- Lupus choroidopathy
- Choroidal effusion
- Choroidal infarction
- Choroidal neovascular membranes

Neuro-ophthalmic

- Optic neuritis
- Anterior ischaemic optic neuropathy
- Posterior ischaemic optic neuropathy
- Optic chiasmopathy
- Cortical infarcts

Sivraj et al, 2007

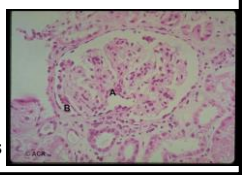
The girl with tea colored urine

- 14 yo girl has tea-colored urine, low grade fever and edema over face and feet in the past 2 weeks.
- UA 3+ protein
- CBC and diff – NL
- CMP- low albumin 2.5
- ESR 50mm/hr
- C3= 50, C4 = 7, ANA 1:1280, DS-DNA 1:160

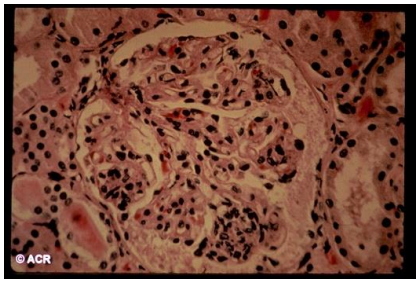
Renal involvement

- Urine-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours
- OR red blood cell casts
- Clinical nephritis in 75% of children
- Creatinine in <10 year olds is 0.5mg/dl; 1.1 is abnl in that age group!

Mesangial nephritis



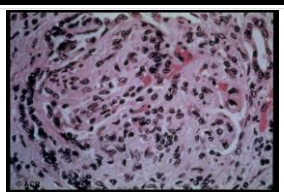
Focal Proliferative Glomerulonephritis

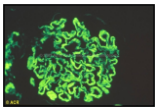


In one glomerular tuft there is marked hypercellularity and obliteration of capillary lumina; another tuft shows similar but less pronounced changes. The remainder of the glomerulus is normal or minimally altered. (hematoxylin-eosin, high power)

Diffuse Proliferative GN

- "Wire loop" lesions
- Enlarged glomerulus with increased cellularity
- Characteristic GBM thickening and bright red staining of the GBM of peripheral capillary loops ("wire loop" lesion)

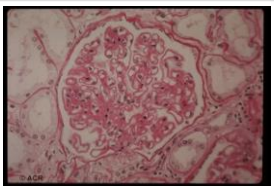




Immunofluorescence micrograph of glomerulus stained for human IgG--- Note the fine and coarsely granular deposits of IgG along the GBM of peripheral capillary loops.

Note the granular and massive "lumpy-bumpy" deposits of IGs along the GBM of peripheral capillary loops.

Membranous GN

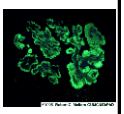


Widespread, uniform thickening of capillary basement membranes is particularly striking because the section is very thin (2 mm). (periodic acid-Schiff, high power)

In most areas of this glomerulus, the capillary walls are thickened by pink-staining deposits (corresponding to immune complexes) on the outer (epithelial) surface of the black-staining basement membrane. Between deposits are protrusions of black basement membrane material (arrows, S). Mesangium also stains black (single arrow). (periodic acid-silver methenamine stain, high power)

Table 3. **International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis**

Class I	Minimal mesangial lupus nephritis Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	Mesangial proliferative lupus nephritis Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	Focal lupus nephritis[a] Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	Diffuse lupus nephritis[b] Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	Membranous lupus nephritis Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
	Class V lupus nephritis show advanced sclerosis
Class VI	Advanced sclerosis lupus nephritis ≥90% of glomeruli globally sclerosed without residual activity



Clinical Characteristics of Patients Who Have SLE

Organ System Involvement	At Diagnosis (%) (*n* = 256)	Within 1 Year After Diagnosis (%) (*n* = 256)	Ever (%) (*n* = 256)
Nephritis[a]	95 (37)	117 (46)	141 (55)
Mesangial (class II)	14 (15)	21 (18)	25 (18)
Focal proliferative (class III)	27 (28)	36 (31)	41 (29)
Diffuse proliferative (class IV)	45 (47)	50 (43)	65 (46)
Membranous (class V)	15 (16)	20 (17)	29 (21)
Nephrotic syndrome	20 (22)	22 (19)	25 (18)
Central nervous system	40 (16)	53 (21)	68 (27)
Lupus headache	23 (58)	31 (58)	42 (62)
Psychosis	14 (35)	21 (40)	25 (37)
Cerebrovascular disease	13 (33)	14 (26)	20 (29)
Cognitive dysfunction	9 (23)	13 (25)	15 (22)
Cardiac			
Pericarditis	30 (12)	33 (13)	39 (15)
Myocarditis	3 (1)	5 (2)	6 (2)
Endocarditis	0	0	1 (0.4)
Pulmonary			
Pleuritis	30 (12)	32 (13)	37 (14)
Pneumonitis	1 (0.4)	1 (0.8)	2 (0.8)

Pediatric Systemic Lupus Erythematosus : More Than a Positive Antinuclear Antibody
Jennifer E. Weiss
Pediatrics in Review 2012;33;62
DOI: 10.1542/pir.33-2-62

Hematological manifestations

- Leukopenia- nearly 2/3rds of the children
  - Leukopenia (< 4,000/µL at least once) in the absence of other known causes such as Felty syndrome, drugs, or portal hypertension
  - OR lymphopenia (< 1,000/µL at least once) in the absence of other known causes such as corticosteroids, drugs, or infection

(Euler et al 1997, McDougall et al 2000, Ahn et al 1985, Majer et al 1988, Von Keyserlingk et al 1987, Gomard-Mennenson 2006 et al, Rivero 1979et al; Lehman, SLE in children, UpToDate, 2016)

Hematological manifestations

- Anemia in 50-75% of affected children (2SD below the mean for age and gender) typically occurs due to
  - Anemia of chronic disease- normocytic normochromic typically; may be hypochromic and microcytic
  - Autoimmune Hemolytic Anemia - typically mild to moderate
  - Iron deficiency- especially in adolescent females with SLE due to:
    - Increase in body mass, but no parallel increase in iron stores
    - Menstruation losses
    - Dietary choices decrease iron intake.

(Euler et al 1997, McDougall et al 2000, Ahn et al 1985, Majer et al 1988, Von Keyserlingk et al 1987, Gomard-Mennenson 2006 et al, Rivero 1979et al; Lehman, SLE in children, UpToDate, 2016)

Hematological manifestations

- Thrombocytopenia 10-50%
  - Thrombocytopenia (< 100,000/µL) at least once in the absence of other known causes such as drugs, portal hypertension, or thrombotic thrombocytopenic purpura
  - Usually the thrombocytopenia is mild and hemorrhage is rare.
  - Correlation between number of platelets and the likelihood of bleeding is poor
  - Common manifestations of thrombocytopenia are petechiae, purpura, and ecchymoses over lower arms and legs.
  - Gum bleeding, epistaxis, heavy menstrual flow and intracranial hemorrhage can occur.

(Euler et al 1997, McDougall et al 2000, Ahn et al 1985, Majer et al 1988, Von Keyserlingk et al 1987, Gomard-Mennenson 2006 et al, Rivero 1979et al; Lehman, SLE in children, UpToDate, 2016)

Thrombocytopenia

- Idiopathic thrombocytopenic purpura may be the first manifestation of SLE
- Thrombotic thrombocytopenic purpura - rare in children

Gastrointestinal manifestations

- 25-40% of SLE patients
- Abdominal pain
- Pancreatitis
- Hepatitis
- Protein-losing enteropathy
- Mesenteric vasculitis and infarction

Massarotiand Schur, Gastrointestinal manifestations of SLE, UpToDate, Last updated Jan 2014

Clinical Characteristics of Patients Who Have SLE

Organ System Involvement	At Diagnosis (%) (n = 256)	Within 1 Year After Diagnosis (%) (n = 256)	Ever (%) (n = 256)
Autoantibody (%)			
Anti-dsDNA	184 (72)		214 (84)
Anti-Smith antibody	88 (34)		124 (48)
Anti-ribonucleoprotein antibody	68 (27)		95 (37)
Anti-Ro	69 (27)		84 (33)
Anti-La	34 (13)		37 (15)
Antiphospholipid (any)	82 (32)		115 (45)
ACLA[c]	67 (26)		102 (40)
LAC	22 (9)		32 (13)
Rheumatoid factor	28 (11)		35 (14)
Hematologic (any)	141 (55)		161 (63)
Thrombocytopenia	75 (29)		80 (31)
Lymphopenia	73 (29)		93 (36)
Coombs positive hemolytic anemia	58 (23)		63 (25)

Pediatric Systemic Lupus Erythematosus : More Than a Positive Antinuclear Antibody
Jennifer E. Weiss
Pediatrics in Review 2012;33;62
DOI: 10.1542/pir.33-2-62

Mild SLE

- No renal or life threatening organ involvement
- NSAIDS for musculoskeletal manifestations
- Hydroxychloroquine up to 200mg/day (400mg/ day for adults)
- Avoid Sulfa drugs (such as Sulindac)- Sulfa antibiotic allergy more common in SLE (Pope et al, Aceves et al)
- Dapsone in some dermatological manifestations (David et al)
- Low dose glucocorticoids (< 0.35mg/kg/day of prednisone
- Dose above 0.2mg/kg/dose may impact longitudinal growth (David et al)
- Add 2nd line agent, Mycophenolate mofetil if glucocorticoid dose is >0.35/kg/day

Reviewed in UpToDate, TJA Lehman, last updated April 2015

Moderate SLE

- Clinically significant but not life threatening organ involvement of kidneys or other vital organs/systems
- Daily higher dose glucocorticoids (or alternate day/intermittent IV therapy) (Guiducci et al) with hydroxychloroquine
- Steroid sparing agent:
  - Mycophenolate mofetil
  - Azathioprine
  - Methotrexate (aware of renal toxicity, toxic levels if renal function deteriorates)
  - Cyclophosphamide and Rituximab as steroid sparing agent

(Buratti et al, Ravelli et al)

Reviewed in UpToDate, TJA Lehman, last updated April 2015

Severe SLE

- Substantial Renal (worst DPGN) and CNS involvement
- Glucocorticoids (often high dose IV)
- Cyclophosphamide (IV monthly/ po)
- Rituximab with Cyclophosphamide regimen
- Mycophenolate mofetil
- Azathioprine
- Length may vary with organ involvement (longer for renal vs. 1 year for extra-renal manifestations)

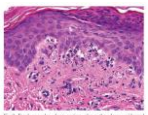
(Guiducci et al, Ravelli et al, Buratti et al, Lehman et al) (Lehman et al 1991, Lehman et al 1989, Lehman et al 2000, Ginzler 20045, Austin et al, Lehman et al 2014)

Neonatal Lupus Erythematosus

- **1 to 2% percent of babies born to mothers with autoimmune disease**, primarily SLE, Sjögren's syndrome, and antibodies to SSA/Ro and/or SSB/L
- A considerable proportion of mothers of affected infants are asymptomatic (40%).
-
- If a anti-Ro (SS-A)-positive mother has one child with NLE, risk of recurrence is close to 20%

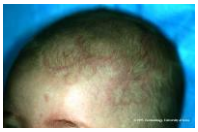
NLE

- Skin lesions are transient, lasting weeks to months
- Usually resolve without scarring—mild epidermal atrophy
- Hypopigmentation
- Rarely, remnant telangiectasias can occur at previously affected sites. Cutaneous telangiectasia 6-12 mo (10% of cases)—temples near hairline
- ~ to Subaculte cutaneous LE (SCLE)
- Treatment
  - Reassurance
  - Sun avoidance
  - Usually heal w/o scarring
  - Low potency topical mild steroid (increased risk of telangiectasia), Pulse dye laser



DIFFERENTIAL DIAGNOSIS

- Neonatal lupus erythematosus has a very characteristic appearance but the following are in the differential diagnosis-
  - For Polycyclic lesions: Urticaria, E marginatum, tinea, seborrheic dermatitis
  - For Annular erythema: E multiforme, Pityroisporum, Annular erythema of infancy
  - A photodistributed drug eruption



Laboratory exam

General

Hematologic disorder

- Hemolytic anemia
- 10. Leukopenia (< 4,000/µL at least once) in the absence of other known causes such as Felty syndrome, drugs, or portal hypertension
- OR lymphopenia (< 1,000/µL at least once) in the absence of other known causes such as corticosteroids, drugs, or infection
- 11. Thrombocytopenia (< 100,000/µL) at least once in the absence of other known causes such as drugs, portal hypertension, or thrombotic thrombocytopenic purpuraHemolytic anemia--with reticulocytosis OR
- Leukopenia--less than 4,000/mm3 total on 2 or more occasions OR
- Lymphopenia--less than 1,500/mm3 on 2 or more occasions OR
- Thrombocytopenia--less than 100,000/mm3 in the absence of offending drugs

Evidence of immune dysfunction

Bleeding and clotting abnormalities

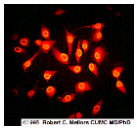
Liver functions

Increased ESR

Urine--Blood and protein in urine

Laboratory abnormalities

Anti-ds-DNA



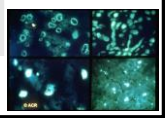
- **Low complements**- C3, C4
- **Autoantibodies -**ANA, Anti-ds-dna, ENA
- **Antiphospholipids**

- *Immunologic disorder*
  - *a) Anti-DNA: antibody to native DNA in abnormal titer OR*
  - *b) Anti-Sm: presence of antibody to Sm nuclear antigen OR*
  - *c) Positive anti-phospholipid antibody*

ANA

- Antinuclear antibody-An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time

Pattern	Disease	Antibodies
Rim (peripheral)	SLE	DsDNA
Homogeneous (diffuse)	Drug induced LE, SLE	Histones, deoxyribonucleopr
Nucleolar	Scleroderma	Nucleolar RNPs
Speckled	Sjogrens MCTD Scleroderma	Nonhistone proteins Nuclear RNP



Sensitivity and specificity of ANA

Table 1: Sensitivity and specificity of ANA and its clinically important subtypes [18,19]

Autoantibodies	Associated CTD	Sensitivity	Specificity
ANA	SLE	93	57
	Sjogren's syndrome	48	52
	SS	85	54
	PM/dermatomyositis	61	63
	Raynaud phenomena	64	41
Specific ANA			
Anti-dsDNA	SLE	57	97
Anti-Sm	SLE	25–30	High*
Anti-SSA/Ro	Sjogren's syndrome, subacute cutaneous SLE, Neonatal lupus syndrome	8–70	87
Anti-SSB/La	Sjogren's syndrome, subacute cutaneous SLE, Neonatal lupus syndrome	16–40	94
Anti-U3-RNP	SS	12	96
Anticentromere	Limited cutaneous SS	65	99.9
Scl-70	SS	20	100
Jo-1	PM	30	95

Diagnostic Pathology 2009, 4:1

Antinuclear antibodies and their detection methods in diagnosis of connective tissue diseases: a journey revisited

Significance of a +ve ANA test

Table 2: Significance of positive ANA test in CTD and some non-autoimmune conditions [36]

Useful for diagnosis	Useful for monitoring or prognosis
1) Lupus erythmatosus (LE) SLE	1) Juvenile chronic oligoarticular arthritis 2) Raynaud phenomenon
Discoid LE	**Not useful for diagnosis**
Subacute cutaneous LE Neonatal LE Overlap of two or more LE subsets	1) Relatives of patients with CTD 2) Other autoimmune diseases (e.g., Rheumatoid arthritis, Idiopathic thrombocytopenia purpura, primary biliary cirrhosis, autoimmune thyroiditis)
Overlap of LE with other CTD 2) SS Cutaneous SS (morphea) Systemic SS a) Limited disease b) Diffuse disease 3) PM/Dermatomyositis 4) Sjögren's syndrome (primary and secondary) 5) Mixed CTD 6) Overlap and undifferentiated CTD	3) Drugs (e.g., procainamide, hydralazine) 4) Silicone breast implant patients 5) Fibromyalgia 6) Chronic infections 7) Neoplasms 8) Elderly persons 9) Pregnant women 10) Healthy persons

Antinuclear antibodies and their detection methods in diagnosis of connective tissue diseases: a journey revisited
Yashwant Kumar*†, Alka Bhatia† and Ranjana Walker Minz†

Diagnostic Pathology 2009, **4**:1

Reproductive Health

•Mother and child, by Moorthy LN

Sexual function and reproductive health in adolescent females with systemic lupus erythematosus

Clovis Artur Almeida da Silva[1], Marília Vieira Febrônio[2], Eloísa Bonfá[3], Rosa Maria Rodrigues Pereira[4], Elsa Aida Gay de Pereira[5], Albertina Duarte Takiuiti[6]

- Age matched controls for 52 SLE patients
- Mean age of menarche higher in JSLE patients (12.82 ± 1.62 versus 11.55 ± 1.45 years, P = 0.0004).
- Frequency of sex activity lower in patients with JSLE (23% versus 60%, P = 0.0003).
- Higher percentage of sexual dysfunction, reduced vaginal lubrication, decreased performance, reduced orgasm, and dissatisfaction with one's sex life in JSLE patents (58% versus 23%, P = 0.03; 50% versus 16%, P = 0.046; 58% versus 23%, P = 0.03; 50% versus 26%, P = 0.046, respectively).
- Demographic data, pubertal changes, abnormalities in menstrual cycle, and cervicovaginal cytology were similar in JSLE patients and the control group

Bras J Rheumatol 2009;49(6):690-702

Tesher *et al. Pediatric Rheumatology* 2010, **8**:10
http://www.ped-rheum.com/content/8/1/10

PEDIATRIC RHEUMATOLOGY

REVIEW **Open Access**

Contraception for adolescents with lupus

Melissa S Tesher[1], Amy Whitaker[2], Melissa Gilliam[2], Linda Wagner-Weiner[1] and Karen B Onel[*1]

- Protect against STI
- Protect against Pregnancy
- GYN maintenance exam
- Antiphospholipid antibodies, history of thrombosis, smoking, BP,
- Male and female condoms (use rare in adolescents <40%; failure rate 15-21%)
- IUD
- Nuvaring (ethinyl estradiol)
- Combined estrogen-progesterone (very effective, low cost)
- Progestin only pill
- Depo-provera (decreased BMD)
- Emergency contraception- oral levonorgestrel – decreased thrombosis risk)

Adverse Pregnancy Outcomes in Adolescents and Young Women with SLE: A National Estimate

- NIS database
- SLE patients =4142
- Hospitalized women with SLE were:
  - Slightly older (mean age 19.4 with range 14-21 vs.19 with range 8-21)
  - More likely to be black (34% v. 21%)
  - More likely to carry a discharge diagnosis of nephritis (11% v. 0.02%) or aPL (2.7% v. 0.1%)
  - More likely to undergo hemodialysis (0.35% v. 0.0%), all p<0.0001.

Allen et al 2014, ACR abstract

Outcome	SLE N = 4,142	Non-SLE N = 9,121,082	*P**	OR (95%CI) +
Maternal Outcomes	*N (%) unless noted*			
Pre-eclampsia and Eclampsia	657 (16)	417,676 (4.6)	<0.0001	3.9 (3.3 4.7)
Death during hospitalization	15 (0.37)	490 (0.005)	<0.0001	69.7 (22.6 214.6)
Fetal Outcomes				
Preterm	843 (20)	736,665 (8.1)	<0.0001	2.9 (2.5 3.4)
Low birth weight or fetal growth retardation	0 (0)	20 (0)	0.97	1 (0.0004 0.0005)
Spontaneous abortion or Intrauterine death	179 (4.3)	99,426 (1.1)	<0.0001	4.1 (2.9 5.8)
Induced abortion	90 (2.2)	11,749 (0.13)	<0.0001	17.2 (10.4 28.3)
Ectopic pregnancy	²10 (²0.24)^	30,293 (0.3)	0.61	0.7 (0.17 2.78)

Allen et al 2014, ACR abstract

Preeclampsia vs SLE nephritis flare

Clinical and laboratory features	Active lupus nephritis	Preeclampsia
Hypertension	Onset before 20 weeks	Onset after 20 weeks
Proteinuria	≥300 mg/day	≥300 mg/dl
Urinary sediment	Active	Inactive
Uric acid	≤5.5 mg/dl	>5.5 mg/dl
DNA antibody levels	Rising	Stable or negative
24 h urine calcium	≥195 mg/day	<195 mg/day
Complement levels	≥25% drop	Normal

Reproduced with permission from [114].

Medscape Source: Expert Rev of Clin Immunol © 2012 Expert Reviews Ltd

Autoimmune Congenital Heart Block Statistics
Friedman and Buyon et al 2003

Incidence in +Ro/La pregnancies	3%
Recurrences after first index case	18%
Mortality	20%
Need for pacemaker	>60%
Late onset cardiomyopathy	10%

Risk assessment

Previous Obstetric history → SGA, preeclampsia, stillbirth, miscarriage, and preterm birth.

SLE activity
APLA(S)
Ro, La Ab → Evidence of active SLE, especially lupus nephritis, should be advised to defer pregnancy until the disease is well controlled for at least six months.

- *Sunflowers*
- *With crayons, By Moorthy LN*

Health related quality of life (HRQOL) in pediatric SLE

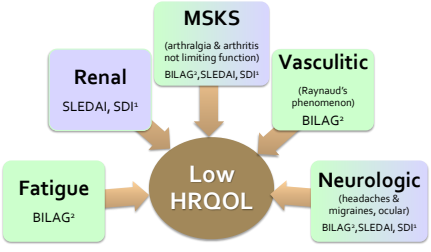
Quotes from my patients with SLE

"I do greatly worry about the future.... passing on this disease to my offspring... Many times I feel I don't have as much time as everyone else."

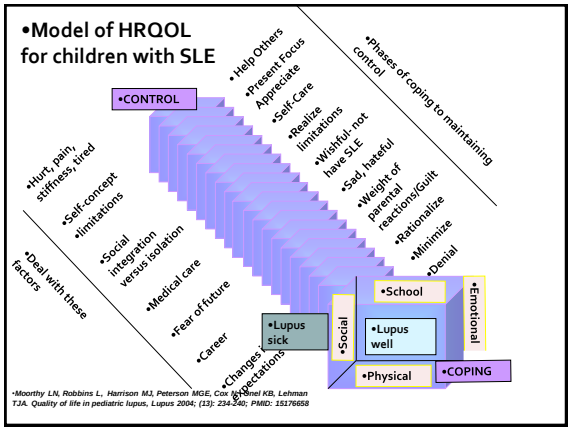
"I can't do the stuff that kids of my age do... Everything in my life has changed."

"I wish I never had lupus in my life."

SLE (activity and damage) involvement of systems and Health Related Quality of Life (HRQOL)



1. Ruperto N, et al, Health-Related Quality of Life in Juvenile-Onset Systemic Lupus Erythematosus and its Relationship to Disease Activity and Damage, Arthritis Rheum 2004; 51 (3) 458-464
2. Brunner et al. Health Related Quality of Life and its Relationship to Patient Disease Course in Childhood-onset Systemic Lupus Erythematosus. J Rheumatol 2009, 36:7 (n=98)


•Model of HRQOL for children with SLE
•Phases of coping to maintaining control
•CONTROL
• Help Others
•Present Focus Appreciate
•Self-Care
•Realize limitations
•Wishful- not have SLE
•Sad, hateful
•Weight of parental reactions/Guilt
•Rationalize
•Minimize
•Denial
•Hurt, pain, stiffness, tired
•Self-concept limitations
•Social integration versus isolation
•Medical care
•Fear of future
•Career
•Changes in expectations
•Deal with these factors
•School
•Emotional
•Lupus sick
•Social
•Lupus well
•Physical
•COPING
•Moorthy LN, Robbins L, Harrison MJ, Peterson MGE, Cox N, Passo MH, Lehman KB, Lehman TJA. Quality of life in pediatric lupus, Lupus 2004; (13): 234-240; PMID: 15176658

Girls going to school
By Moorthy, LN
Thank you