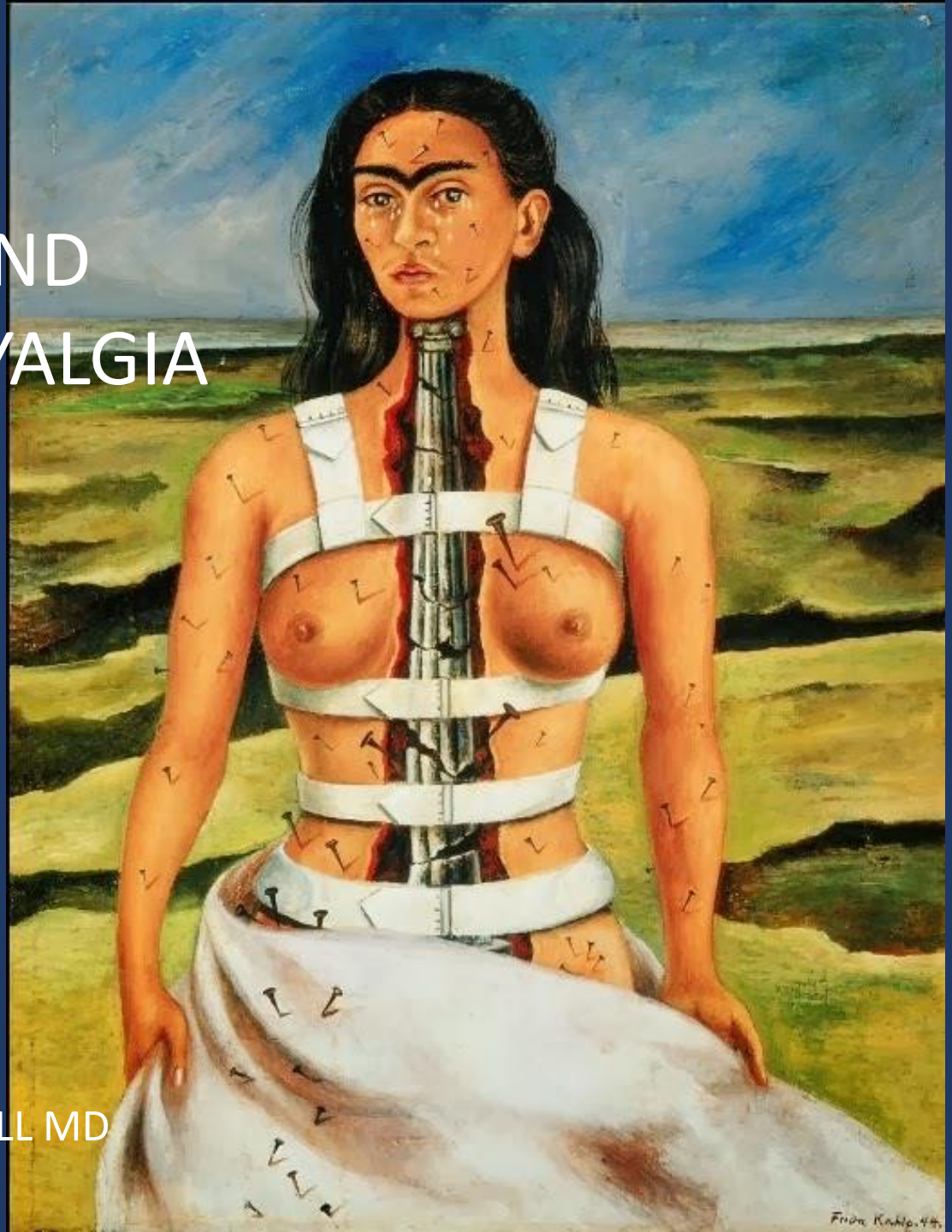
LUPUS AND FIBROMYALGIA



"I never painted dreams. I painted my own reality."

- Frida Kahlo

ALEXANDRA SMALL MD

INTRODUCTION

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown cause that can affect virtually any organ of the body.
- Immunologic abnormalities, especially the production of several antinuclear antibodies (ANA), are a prominent feature of the disease.
- Patients present with variable clinical features ranging from mild joint and skin involvement to life-threatening kidney, hematologic, or central nervous system involvement.
- The diagnosis of SLE is generally based on clinical and laboratory findings after excluding alternative diagnoses.
- Serologic findings are important in suggesting the possibility of SLE, with some antibodies (eg, anti-dsDNA and anti-Smith) highly associated with this condition.

https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-systemic-lupus-erythe

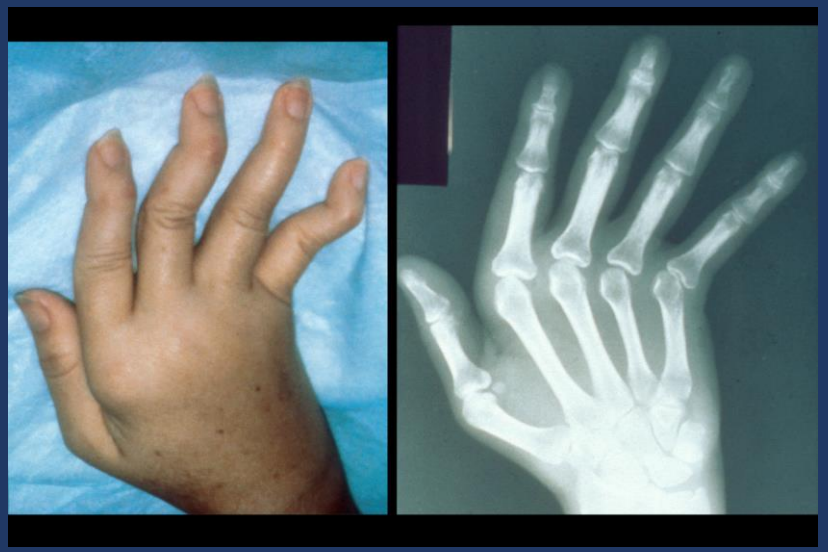
CLINICAL MANIFESTATIONS

- **Constitutional symptoms** — such as **fatigue, fever, and weight loss** are present in most patients with SLE at some point during the course of the disease.
  - **Fatigue** is the most common complaint, occurring in 80 to 100 percent of patients, and is frequently associated with **depression**, sleep disturbances, and concomitant fibromyalgia [2].
  - **Fever** – can be a manifestation of active disease and is seen in over 50 percent of patients with SLE [3].
  - **Myalgia** – Muscle pain is also common among patients with SLE.

2. Tench CM, McCurdie I, White PD, D'Cruz DP. The prevalence and associations of fatigue in systemic lupus erythematosus. Rheumatology (Oxford) 2000; 39:1249.
3. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003; 82:299.

ARTHRITIS AND ATHRALGIAS

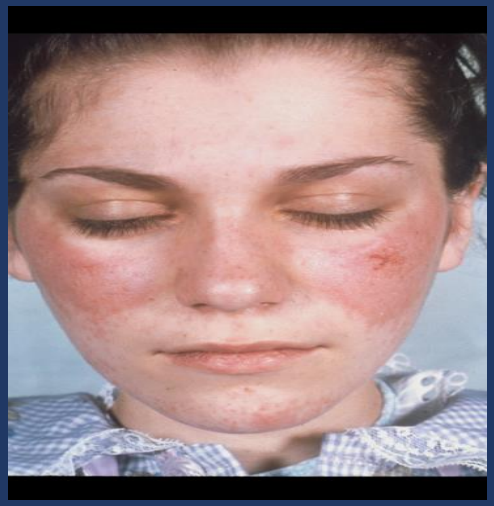
- Arthritis and arthralgias occur in **over 90 percent of patients with SLE** and are often one of the earliest manifestations [4].
- Arthritis, with demonstrable inflammation, occurs in 65 to 70 percent of patients and tends to be migratory, polyarticular, and symmetrical.
- The arthritis is moderately painful, usually does not cause erosion, and is rarely deforming.
- However, occasionally patients with SLE also develop a deforming erosive arthritis, which is similar to that of rheumatoid arthritis (RA).

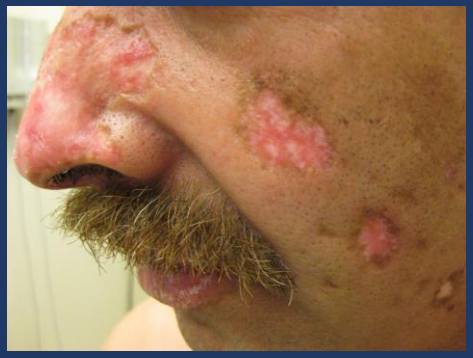


4. Greco CM, Rudy TE, Manzi S. Adaptation to chronic pain in systemic lupus erythematosus: applicability of the multidimensional pain inventory. Pain Med 2003; 4:39.

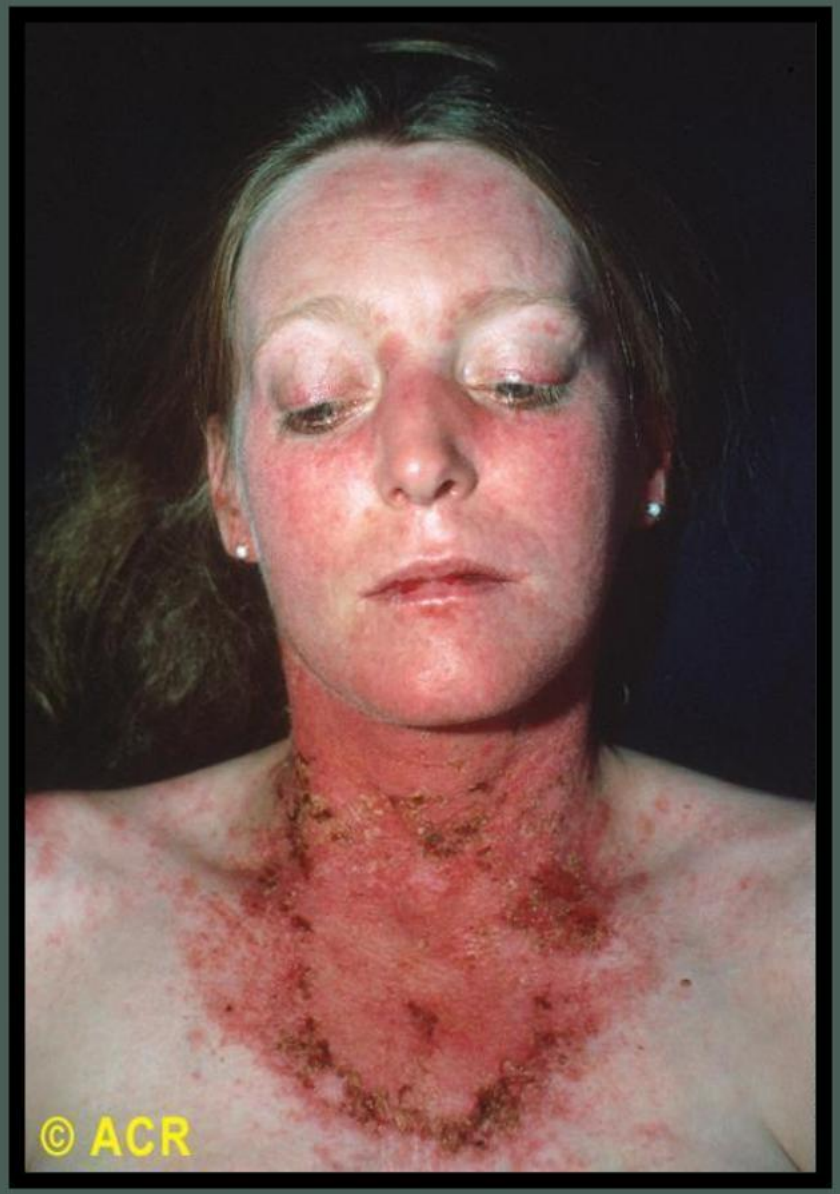
MUCOCUTAENOUS INVOLVEMENT

- The most common lesion is a facial rash known as a ”**malar rash”** or **“butterfly rash**" that presents as a flat or raised red rash over the **cheeks and nose** (but sparing the nasolabial folds) that appears after sun exposure.
- Some patients may develop **discoid lesions**, which are more inflammatory and tend to **scar**.
- **Photosensitivity** is also a common theme for skin lesions associated with SLE.
- Many patients develop **oral and/or nasal ulcers.**
- Nonscarring **alopecia** is also observed in many SLE patients at some point during the course of their disease.
- Scarring alopecia can occur in patients with discoid lupus erythematosus.

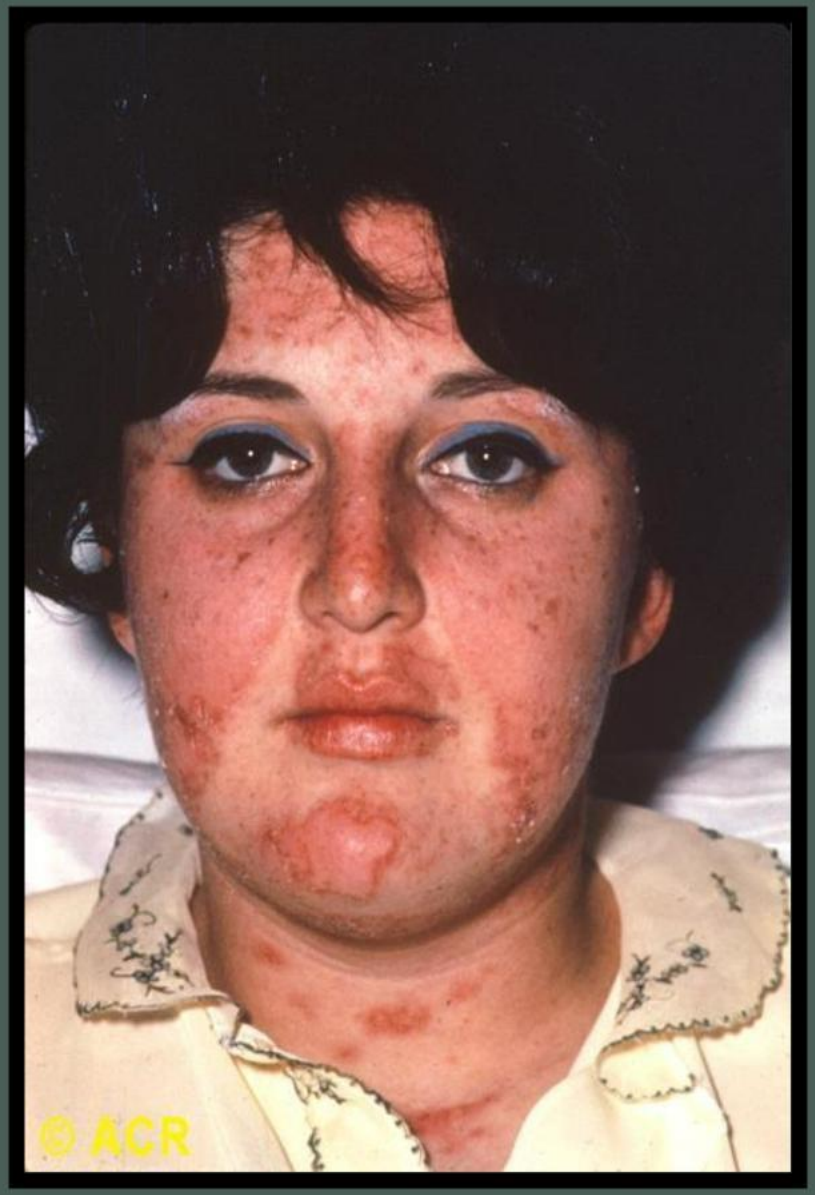




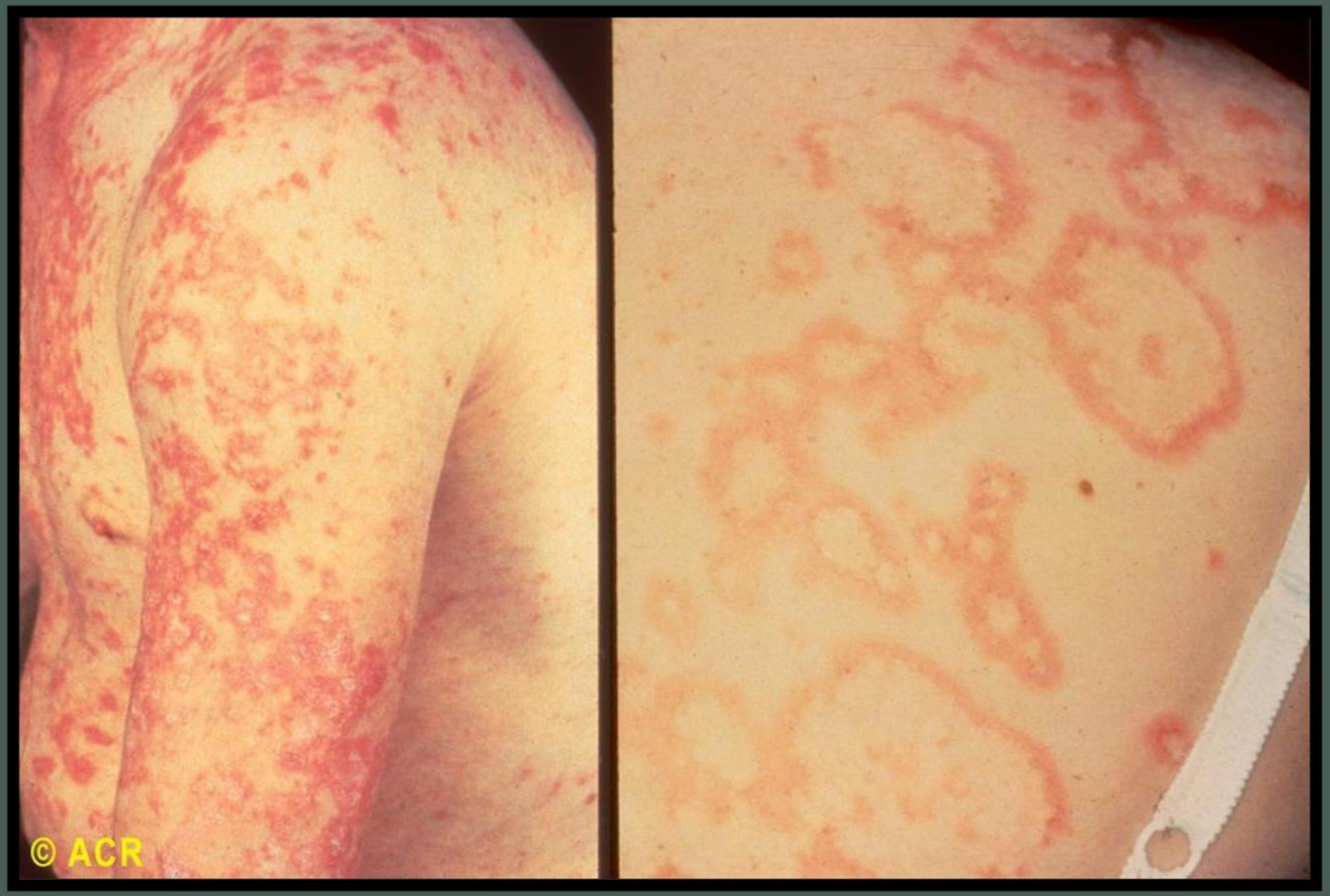
Systemic lupus erythematosus: photosensitivity, face and neck



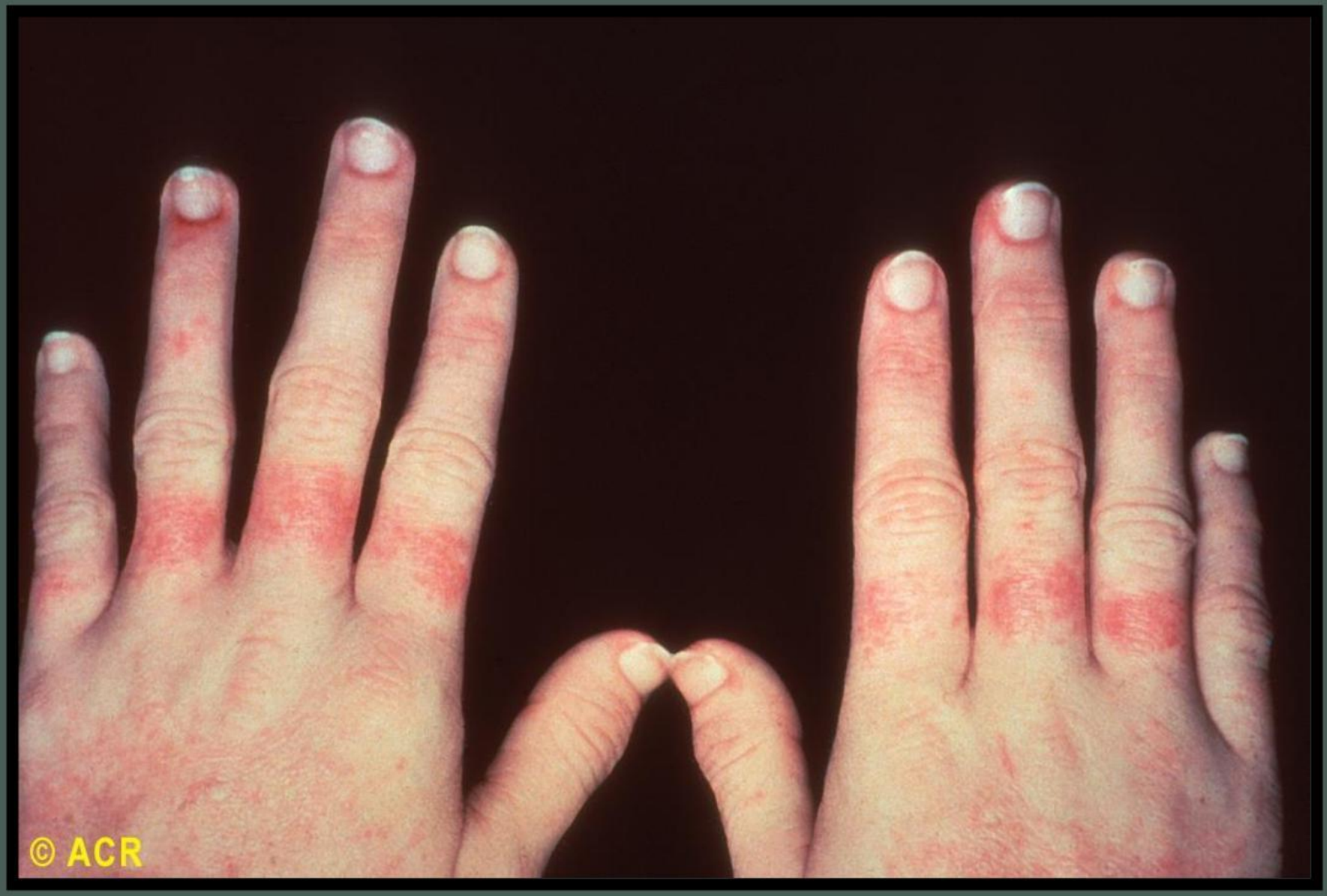
Systemic lupus erythematosus: rash, face and neck



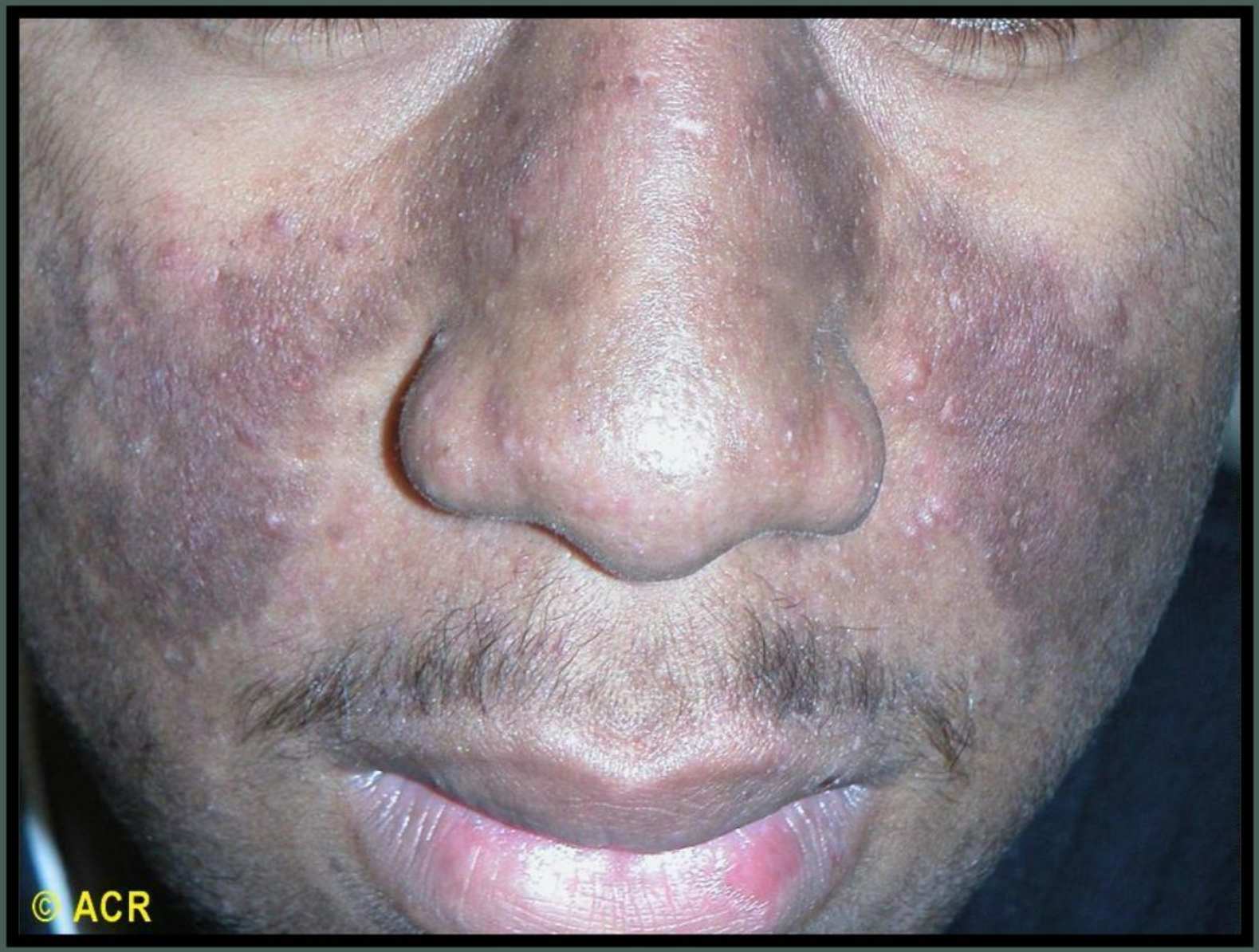
Subacute cutaneous lupus erythematosus



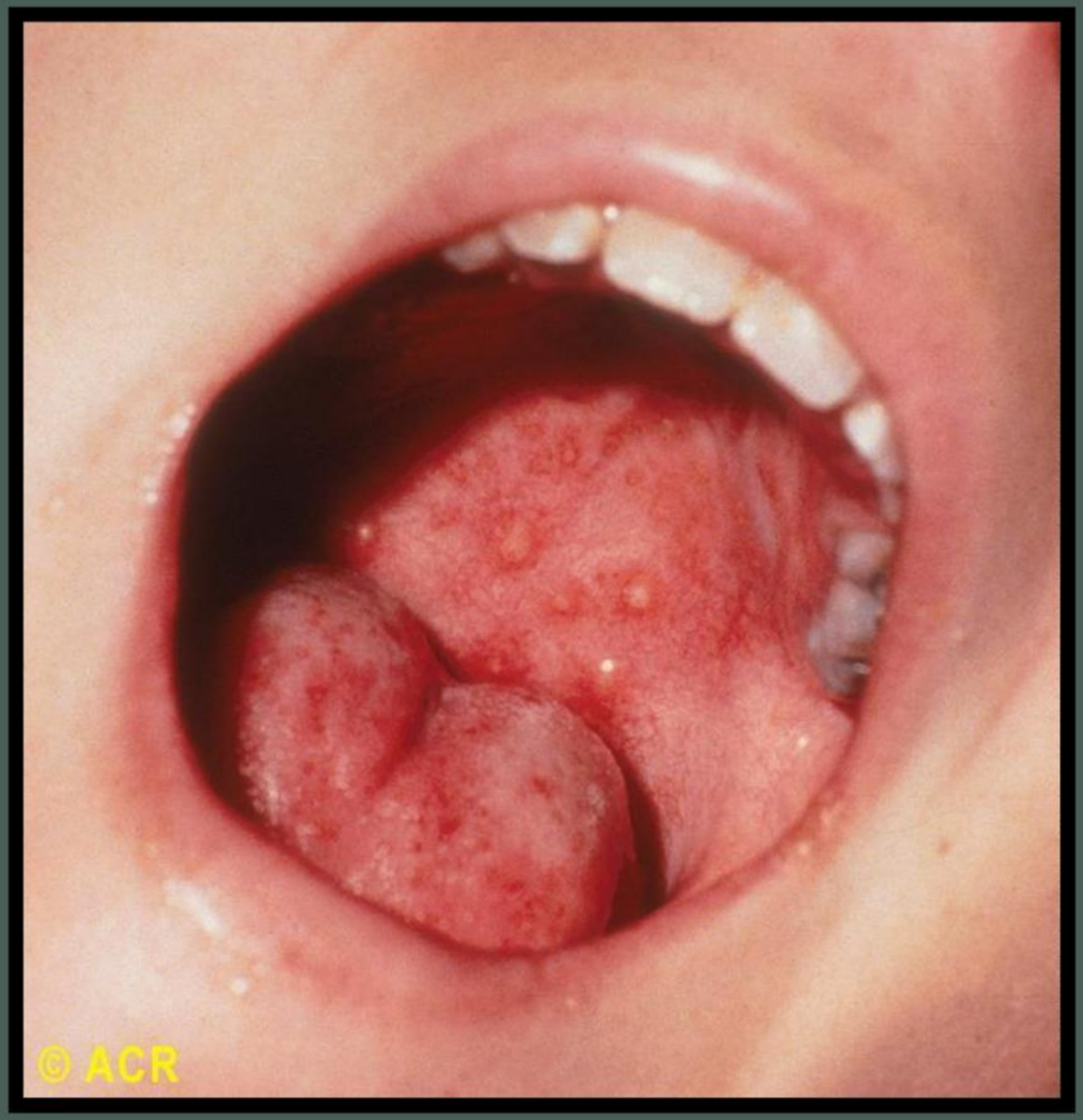
Systemic lupus erythematosus: interarticular dermatitis, hands



Systemic lupus erythematosus: malar rash, face



Systemic lupus erythematosus: bullous lesions, palate



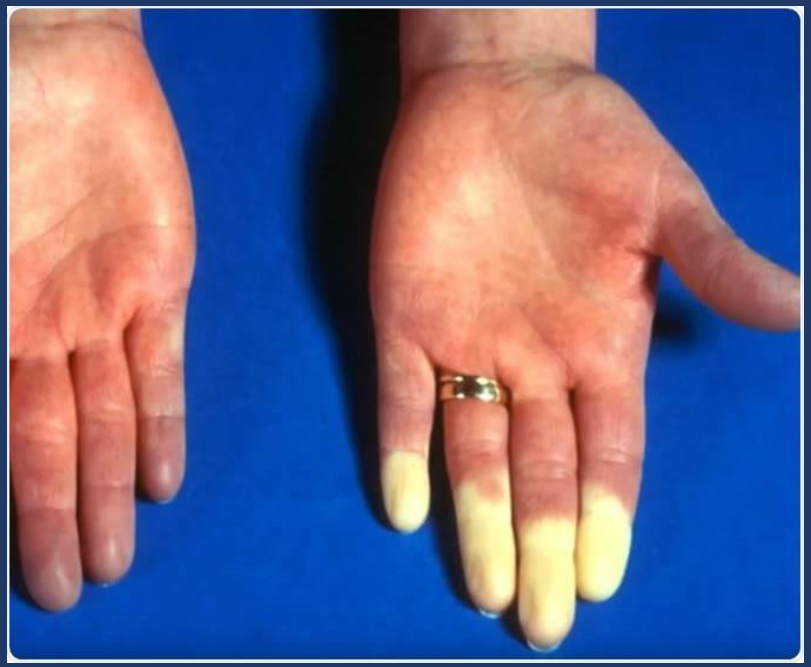
CARDIAC INVOLVEMENT

- Cardiac disease is common in SLE and can involve the pericardium, myocardium, valves, conduction system, and coronary arteries.
- **Pericarditis**, with or without an effusion, is the most common cardiac manifestation of SLE, occurring in approximately 25 percent of patients at some point during their disease course [5].
- Verrucous (Libman-Sacks) endocarditis is usually clinically silent, but it can produce valvular insufficiency and can serve as a source of emboli.
- Myocarditis is uncommon but may be severe.
- Patients with SLE also have an increased risk of coronary artery disease.
- Neonatal lupus, which can occur in babies of women with SLE expressing anti-Ro/SSA and anti-La/SSB, can cause **congenital heart block** of varying degrees.

5. Miner JJ, Kim AH. Cardiac manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 2014; 40:51.

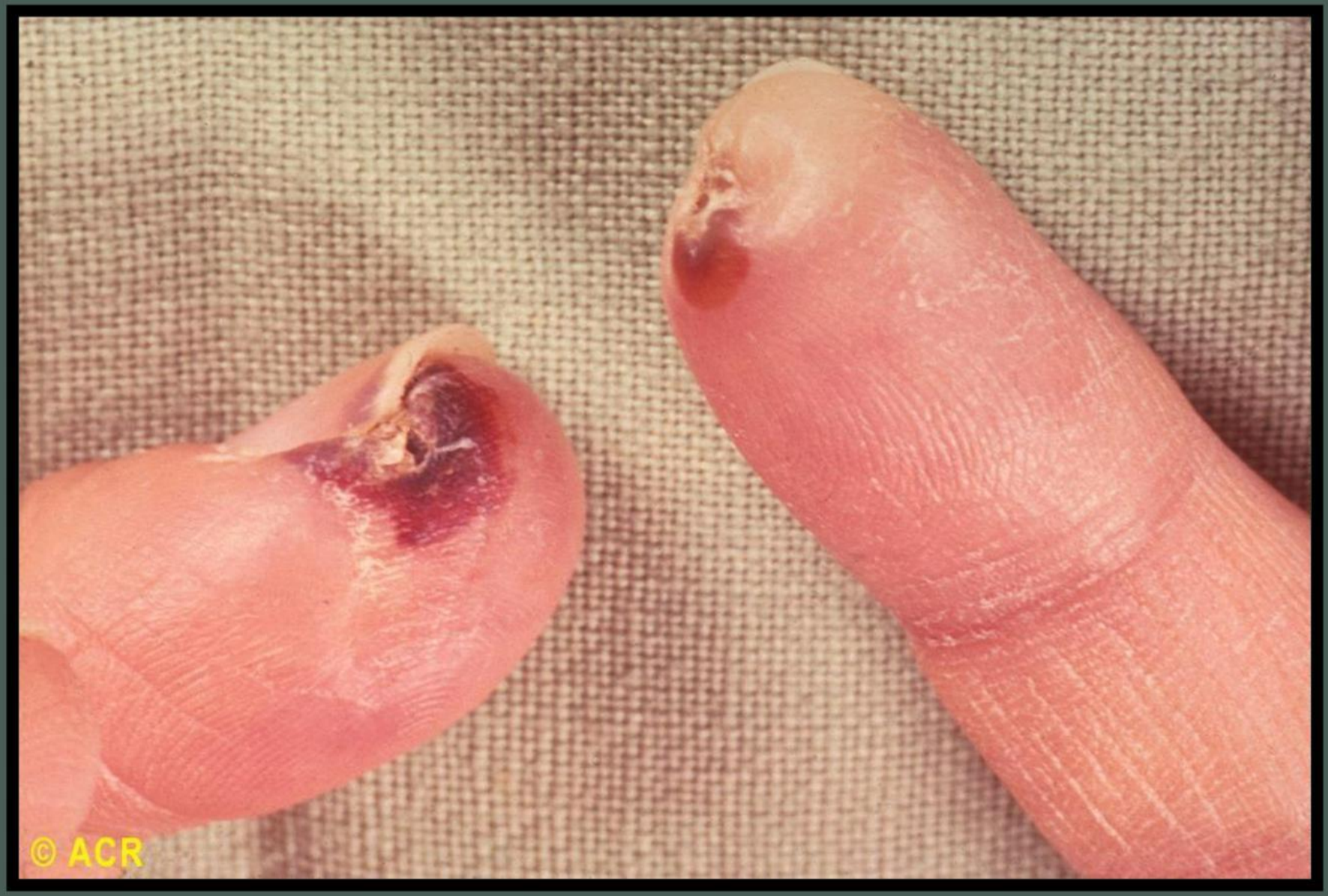
VASCULAR MANIFESTATIONS

- **Raynaud phenomenon** – common in SLE, induced by cold that occurs in up to 50 percent of patients [6]. Characterized by intermittent acral pallor (white) followed by cyanosis (blue) and erythroderma (red).
- **Vasculitis** – Inflammation of blood vessels. Estimates of the prevalence of vasculitis in SLE patients range from 11 to 36 percent [7]. Can involve vessels of all sizes. Small vessel involvement is the most common, often as cutaneous lesions.
- **Thromboembolic disease** – Blood clots can complicate SLE, particularly in the context of antiphospholipid antibodies. Can affect both the venous and arterial circulations.

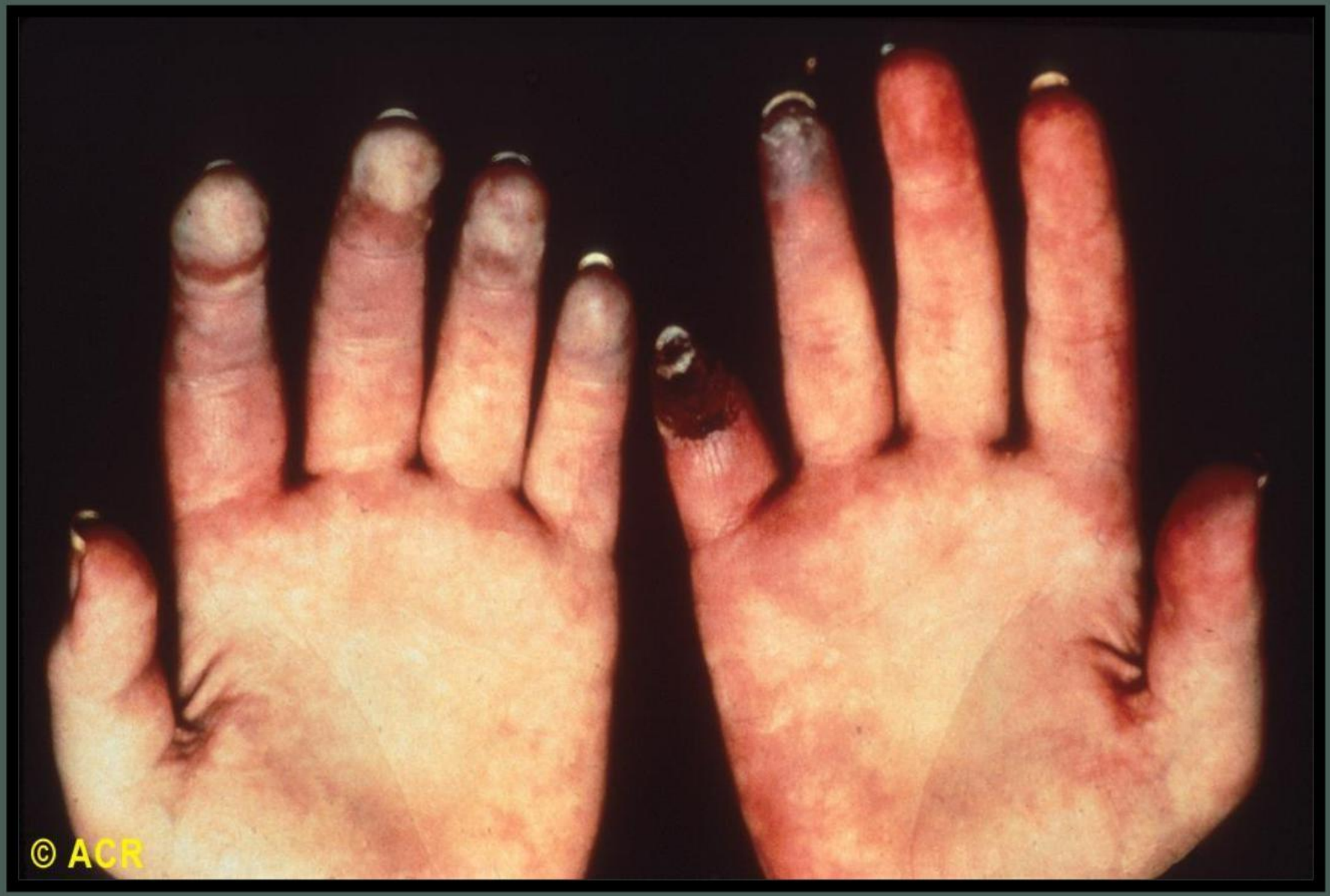


6. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003; 82:299.
7.Barile-Fabris L, Hernández-Cabrera MF, Barragan-Garfias JA. Vasculitis in systemic lupus erythematosus. Curr Rheumatol Rep 2014; 16:440.

Vasculitis: fingers



Systemic lupus erythematosus: digital gangrene, hands



KIDNEY INVOLVEMENT

- Kidney involvement is clinically apparent in approximately 50 percent of SLE patients and is a significant cause of morbidity and mortality [8].
- Thus, periodic screening for the presence of **lupus nephritis** with urinalyses, quantitation of proteinuria, and estimation of the glomerular filtration rate is an important component of the ongoing management of SLE patients.
- Several forms of glomerulonephritis can occur, and **kidney biopsy** is useful to define the type and extent of kidney involvement.

8. Danila MI, Pons-Estel GJ, Zhang J, et al. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology (Oxford) 2009; 48:542.

Systemic lupus erythematosus: classification of nephritis

Normal glomeruli

a) Nil by all techniques

b) Normal by light but deposits on EM or IF

Mesangial glomerulonephritis

Focal glomerulonephritis

Diffuse glomerulonephritis

Diffuse membranous glomerulonephritis

Advanced sclerosing glomerulonephritis

GASTROINTESTINAL INVOLVEMENT

- SLE-related gastrointestinal abnormalities can involve almost any organ along the gastrointestinal tract and include esophagitis, intestinal pseudo-obstruction, protein-losing enteropathy, lupus hepatitis, acute pancreatitis, mesenteric vasculitis or ischemia, and peritonitis.

9. Tian XP, Zhang X. Gastrointestinal involvement in systemic lupus erythematosus: insight into pathogenesis, diagnosis and treatment. World J Gastroenterol 2010; 16:2971.

PULMONARY INVOLVEMENT

- During the course of their disease, many patients develop symptoms secondary to pulmonary involvement of SLE.
- Pulmonary manifestations of SLE include **pleuritis** (with or without effusion), pneumonitis, interstitial lung disease, pulmonary hypertension, shrinking lung syndrome, and alveolar hemorrhage.
- Respiratory symptoms must also be distinguished from infection, particularly in patients on immunosuppressive therapy.
- The risk of thromboembolic involvement is increased in those with antiphospholipid antibodies or with lupus anticoagulant.

9. Tian XP, Zhang X. Gastrointestinal involvement in systemic lupus erythematosus: insight into pathogenesis, diagnosis and treatment. World J Gastroenterol 2010; 16:2971.

HEMATOLOGIC ABNORMALITIES

- Hematologic abnormalities are common in SLE, and all three blood cell lines (WBC, RBC, PLT) can be affected.
- **Anemia** (low RBCs or hemoglobin) is common.
  - Anemia of chronic disease (or anemia of inflammation) is the most common type of anemia among patients with SLE.
  - Autoimmune hemolytic anemia is relatively rare but can be severe, requiring immediate therapy.
- **Leukopenia** (low WBCs) is common in SLE patients, occurring in approximately 50 percent of patients [10].
  - **Leukopenia** can be due to lymphopenia and/or secondary neutropenia and generally correlates with clinically active disease.
  - Neutropenia may also result from toxicity due to immunosuppressive medications.
- **Thrombocytopenia** is also a common hematologic abnormality.
  - Rarely, severe thrombocytopenia can occur and requires treatment.

10. Newman K, Owlia MB, El-Hemaidi I, Akhtari M. Management of immune cytopenias in patients with systemic lupus erythematosus - Old and new. Autoimmun Rev 2013; 12:784.

OPTHALMOLGIC INVOLVEMENT

- Any structure of the eye can be involved in SLE, with keratoconjunctivitis sicca (**dry eyes**) being the most common manifestation as a result of secondary **Sjögren's syndrome** [11]
- The next most common pathologic condition involving the eye in lupus patients is retinal vasculopathy in the form of cotton wool spots.
- Other less common ophthalmologic manifestations of SLE include optic neuropathy, choroidopathy, episcleritis, scleritis, and anterior uveitis (iritis, iridocyclitis).

11. Silpa-archa S, Lee JJ, Foster CS. Ocular manifestations in systemic lupus erythematosus. Br J Ophthalmol 2016; 100:135.

NEUROLOGIC AND NEUROPSYCHIATRIC INVOLVEMENT

- Neuropsychiatric involvement of SLE consists of a broad range of neurologic and psychiatric manifestations, including stroke, seizures, cognitive dysfunction, delirium, psychosis, depression, and/or peripheral neuropathies.
- Other less common problems are movement disorders, cranial neuropathies, myelitis, and meningitis.
- Thromboembolic events, often in association with antiphospholipid antibodies or with lupus anticoagulant, may occur in a substantial minority (20 percent) of patients with SLE [12].
- Arterial thromboemboli may cause focal neurologic problems, such as stroke or seizures and/or more diffuse cognitive defects.

12. Romero-Díaz J, García-Sosa I, Sánchez-Guerrero J. Thrombosis in systemic lupus erythematosus and other autoimmune diseases of recent onset. J Rheumatol 2009; 36:68.

LABORATORY TESTING

- Complete blood count (CBC) and differential may reveal leukopenia, mild anemia, and/or thrombocytopenia.
- Elevated serum creatinine may be suggestive of kidney dysfunction.
- Urinalysis with urine sediment may reveal hematuria, pyuria, proteinuria, and/or cellular casts.
- Serum protein electrophoresis may demonstrate a hypergammaglobulinemia that is suggestive of a systemic inflammatory process.

LABORATORY TESTING

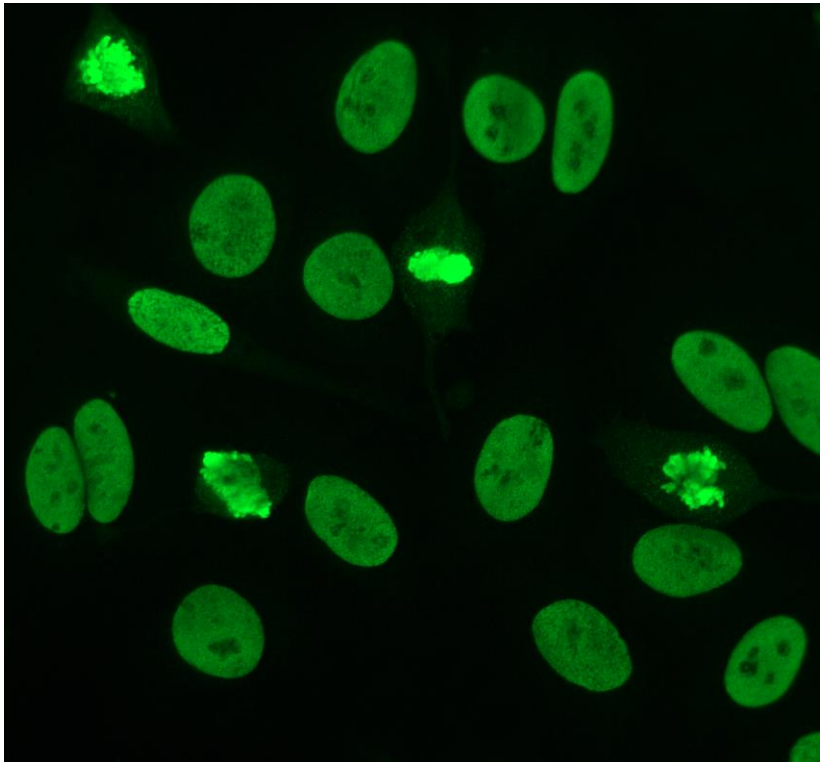
- Antiphospholipid antibodies
  - lupus anticoagulant [LA], immunoglobulin [Ig] G and IgM anticardiolipin [aCL] antibodies, and IgG and IgM anti-beta2-glycoprotein [GP]
- **C3** and **C4** or CH50 complement levels
- Erythrocyte sedimentation rate (**ESR**) and/or C-reactive protein (**CRP**) levels
- Urine protein-to-creatinine ratio
- **Anti-dsDNA** and **anti-Sm antibodies** are highly specific for SLE, but anti-Sm antibodies lack sensitivity.
  - Anti-dsDNA and anti-Sm antibodies are seen in approximately 70 and 30 percent of patients with SLE, respectively [13].
- **Anti-Ro/SSA and anti-La/SSB antibodies** are present in approximately 30 and 20 percent of patients with SLE, respectively; however, both antibodies are more commonly associated with **Sjögren's syndrome** [13].
- Anti-U1 RNP antibodies are observed in approximately 25 percent of patients with SLE, but they also occur in patients with other conditions, and high levels are almost always present in patients with mixed connective tissue disease (MCTD) [13].
- Antiribosomal P protein antibodies have a high specificity for SLE but low sensitivity for SLE. They also lack specificity for involvement of a particular organ system or disease manifestation.

DIAGNOSIS

- The diagnosis of SLE is based upon the judgment of an experienced clinician who recognizes characteristic constellations of symptoms and signs in the setting of supportive serologic studies after excluding alternative diagnoses.
- The **ACR criteria** require that a patient satisfy at least **4 of 11 criteria**.
- The **SLICC criteria** require either that a patient satisfy at least **4 of 17 criteria**, including at least 1 of the 11 clinical criteria and one of the six immunologic criteria, **or** that the patient has **biopsy-proven nephritis** compatible with SLE in the presence of antinuclear antibodies (**ANA) or anti-double-stranded DNA** (anti-dsDNA) antibodies.
- According to the **EULAR/ACR criteria**, a patient can be classified as having SLE if they have a **positive ANA ≥1:80 and score 10 or more points**.

Antinuclear Antibodies (ANA)

- Blood test
- ANA are a group of autoantibodies produced by a person's immune system
  - Anti-dsDNA is a specialty test within the ANA group
- Technique
  - Indirect fluorescent antibody (IFA)
- Results
  - Amount of antibody present (titer)
  - Patterns of cellular fluorescence



Autoantibody-disease associations: SLE and drug-induced lupus

Antigen	SLE	Drug-Induced LE
dsDNA	40%	No
ssDNA	70%	75%-80%
Histone	70%	>95%
Sm antigen	30%	No
Nuclear RNP	30%	No
Ribosomal RNP	10%	
SS-A/Ro	35%	No
SS-B/La	15%	No

Diagnostic criteria in SLE

S	• Serositis [pleuritis, pericarditis]
O	• Oral ulcers
A	• Arthritis
P	• Photosensitivity
M	Malar rash

B	• Blood [all are low - anemia, leukopenia, thrombocytopenia]
R	• Renal [protein]
A	• ANA
I	• Immunologic [DS DNA, etc.]
N	• Neurologic [psych, seizures]
D	Discoid rash

knowmedge
MEDICAL MNEMONICS

Mnemonic: "SOAP BRAIN MD"

2012 SLICC Classification Criteria for

SYSTEMIC LUPUS ERYTHEMATOSUS

Biopsy proven LUPUS NEPHRITIS and ANA or anti-DNA

CLINICAL

- Acute cutaneous LE
- Chronic cutaneous LE
- Oral ulcer
- Alopecia
- Synovitis
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leucopenia/ lymphopenia
- Thrombocytopenia

IMMUNOLOGIC

- ANA
- Anti-dsDNA
- Anti-Sm
- aPL antibodies
- Low complement
- Direct Coomb's test

AT LEAST 4 CRITERIA
(1 Needs to be IMMUNOLOGIC)

Petri M, Orbai AM, Alarcon GS, et al. Arth & Rheum 2012; 64 (8): 2677-86.

New EULAR/ACR criteria for the classification of SLE

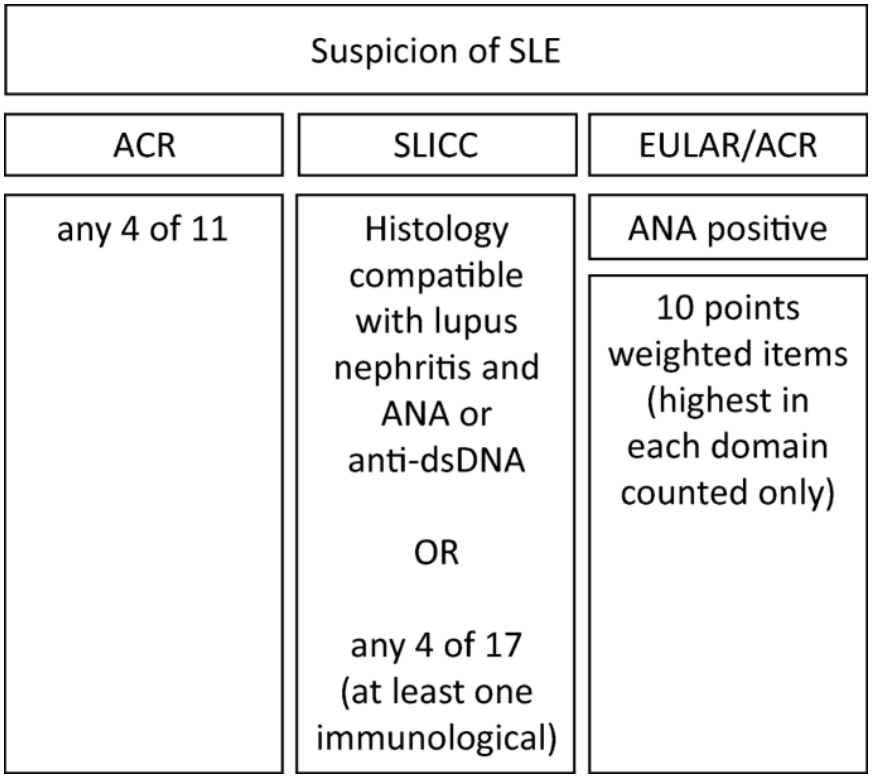
Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria > 0.5 g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG > 40 GPL *or* anti-β2GP1 IgG > 40 units *or* lupus anticoagulant	2
Complement proteins domain	
Low C3 *or* low C4	3
Low C3 *and* low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Sm antibody	6

REFERENCE: Aringer et al. Abstract #2928. 2018 ACR/ARHP Annual Meeting

- ✓ **Classification criteria are not diagnosis criteria**
- ✓ All patients classified as having SLE must have ANA ≥ 1:80 (entry criterion)
- ✓ Patients must have ≥ 10 points to be classified as SLE
- ✓ Items can only be counted for classification if there is no more likely cause
- ✓ Only the highest criterion in a given domain counts
- ✓ SLE classification requires points from at least one clinical domain

@Lupusreference


Suspicion of SLE
ACR
SLICC
EULAR/ACR
any 4 of 11
Histology compatible with lupus nephritis and ANA or anti-dsDNA
OR
any 4 of 17 (at least one immunological)
ANA positive
10 points weighted items (highest in each domain counted only)

LUPUS MEDICATIONS

- NSAIDs
- Antimalarial drugs
  - hydroxychloroquine
- Corticosteroids
  - prednisone
- Immunosuppressants
  - azathioprine, mycophenolate, methotrexate, cyclosporine, voclosporin, etc.
- Biologics
  - Belimumab
  - Rituximab
  - anifrolumab

FIBROMYALGIA

Circle the one number that describes how you feel.

Considering all the ways in which illness and health conditions may affect you at this time, how you are doing?

1 2 3 4 5 6 7 8 9 10

Very well — Very poorly

How severe is your pain over the past week?

1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as it could be

What is your usual level of daytime energy?

1 2 3 4 5 6 7 8 9 10

Very low — Excellent

How is your concentration?

1 2 3 4 5 6 7 8 9 10

Very poor — Excellent

How would you rate your quality of sleep?

1 2 3 4 5 6 7 8 9 10

Very poor — Excellent

How would you rate your enjoyment of life?

1 2 3 4 5 6 7 8 9 10

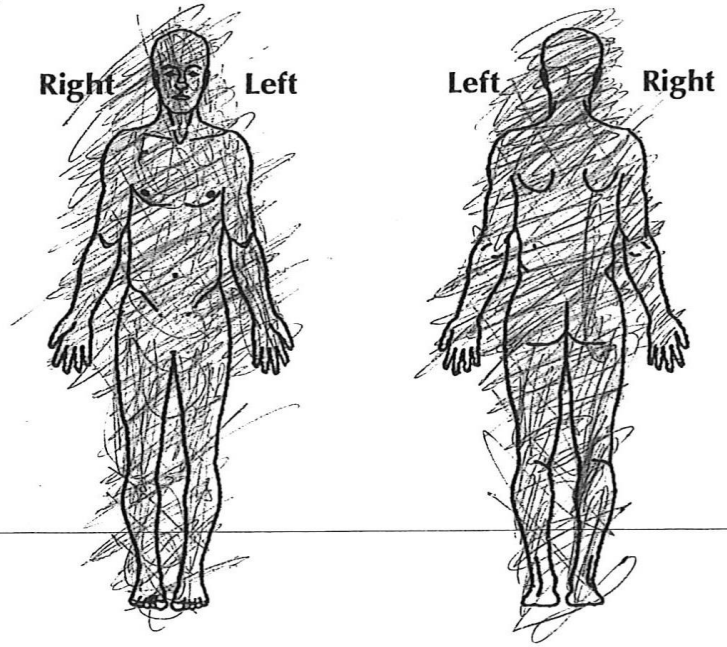
Very poor — Excellent

How is your mood currently?

1 2 3 4 5 6 7 8 9 10

Very depresse[illegible]

On the diagram, shade in the areas where you feel pain.



Where do you hurt? Please circle

neck	hands	hips
shoulders	mid back	~~knees~~
elbows	~~low back~~	feet

OVER

Circle the one number that describes how you feel.

How severe is your pain over the past week?

1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as it could be

What is your usual level of daytime energy?

1	2	3	4	5	6	7	8	9	10

Very low — Excellent

How is your concentration?

1	2	3	4	5	6	7	8	9	10

Very poor — Excellent

How would you rate your quality of sleep?

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Very poor — Excellent

How is your mood currently?

1	2	3	4	5	6	7	8	9	10

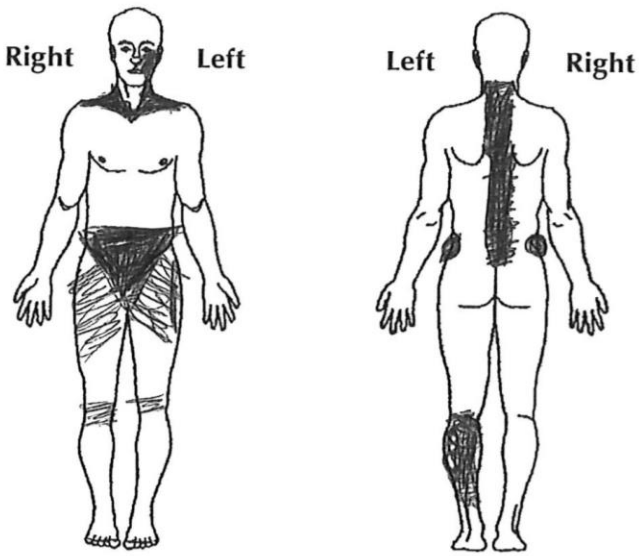
Very depressed — Excellent

Considering all the ways in which illness and health conditions may affect you at this time, how you are doing?

1	2	3	4	5	6	7	8	9	10

Very well — Very poorly

On the diagram, shade in the areas where you feel pain.



Where do you hurt? Please circle

neck	hands	hips
shoulders	mid-back	knees
elbows	low back	feet

Please check which symptoms you have experienced since your last visit?

Rash:	Dry Eyes/ Dry Mouth:	Trouble Swallowing:	Heart Palpitations/ Chest Pain:	Indigestion/ Reflux/ Upset Stomach:	Numbness/Tingling:
Headache:	Sore Throat/ Oral Ulcers:	Swollen Glands:	Shortness of Breath/ Cough:	Difficulty Urinating:	Weight Change:

Circle the one number that describes how you feel.

How severe is your pain over the past week?

1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as it could be

What is your usual level of daytime energy?

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1 2 3 4 5 6 7 8 9 10

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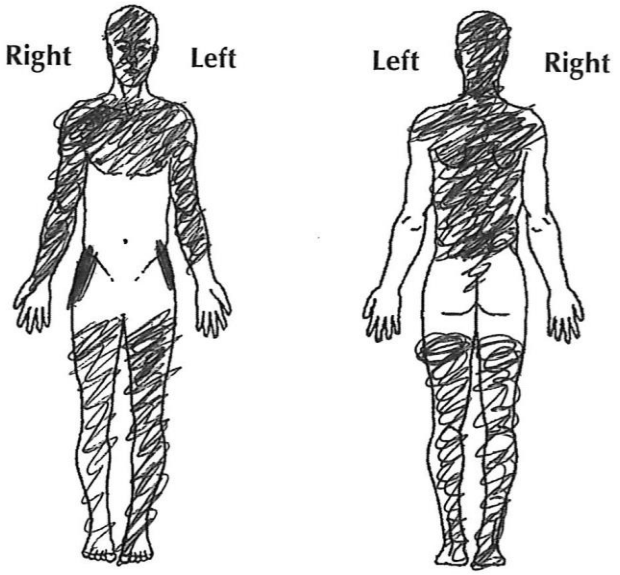
Considering all the ways in which illness and health conditions may affect you at this time, how you are doing?

1 2 3 4 5 6 7 8 9 10

Very well — Very poorly

On the diagram, shade in the areas where you feel pain.



Where do you hurt? Please circle

neck, shoulders, elbows, hands, mid back, low back, hips, knees, feet

Please check which symptoms you have experienced since your last visit?

Rash:	Dry Eyes/ Dry Mouth: ✓	Trouble Swallowing:	Heart Palpitations/ Chest Pain:	Indigestion/ Reflux/ Upset Stomach: ✓	Numbness/Tingling: ✓
Headache:	Sore Throat/ Oral Ulcers: ✓	Swollen Glands: ✓	Shortness of Breath/ Cough: ✓	Difficulty Urinating:	Weight Change:

HISTORY OF FIBROMYALGIA

- Sir William Gowers coined the term “fibrositis” in 1904. Fibromyalgia is a more recent term.
- Smyth and Moldofsky in the mid 1970s described tender points in fibromyalgia and the sleep disturbance.
- In 1990, the American College of Rheumatology published criteria for the classification of fibromyalgia.
- In 2010, the American College of Rheumatology revised the criteria for diagnosis. No tender points.

OVERVIEW: WHAT IS FIBROMYALGIA

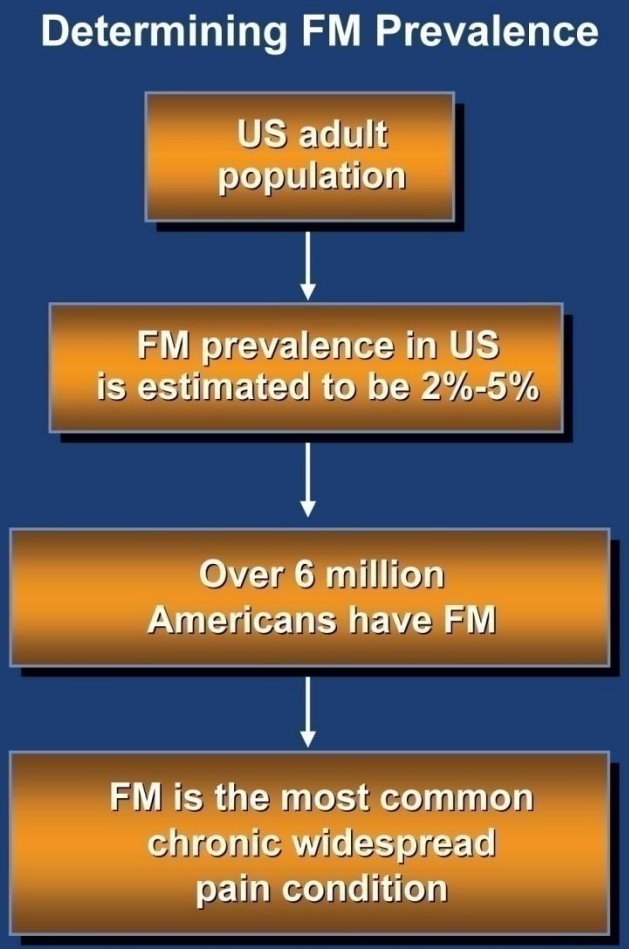
- FIBROMYALGIA is a chronic **widespread pain** condition

  - FM patients often have heightened sensitivity to pain (hyperalgesia); in addition, noxious stimuli may result in pain (allodynia).

  - Patients may present with a wide range of additional symptoms including tenderness, sleep disturbance, fatigue, morning stiffness, and cognitive complaints.

Epidemiology of Fibromyalgia

- Prevalence
  - FM is common worldwide and affects 2%-5% of US adult population
  - Majority of patients between the ages of 35 and 60 years
- Gender differences
  - Women are more likely to be diagnosed with FM than men



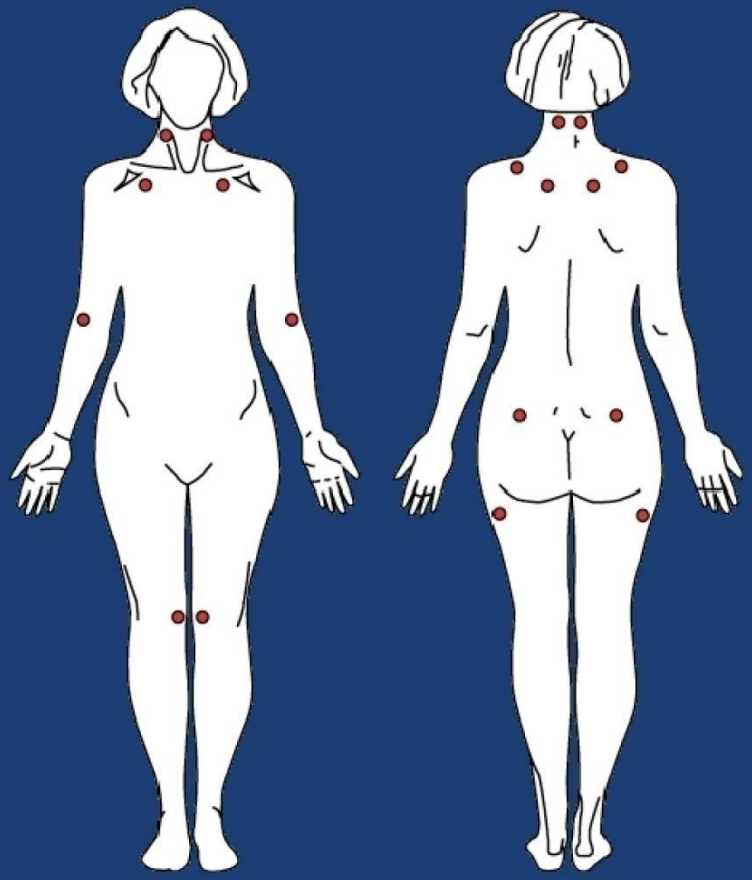
Wolfe et al. *Arthritis Rheum*. 1995;38:19-28; Lawrence et al. *Arthritis Rheum*. 1998;41:778-799; Wolfe. *Am J Med*. 1986(suppl 3A);81:7-14; Weir et al. *J Clin Rheumatol*. 2006;12:124-128.

SYMPTOMS

- Widespread chronic pain (10%-12% of the U.S. population has chronic widespread pain).
- Pain intensity - usually exceeds 5 on a scale of zero to ten
- Patients may emphasize localized symptoms, but actually have widespread musculoskeletal pain. Need to go through checklist of musculoskeletal regions.
- Sleep disturbance. Usually multiple awakenings with difficulty getting back to the sleep. Sleep is nonrestorative.
- Significant fatigue
- Tender points
- Cognitive difficulties “fibrofog”

American College of Rheumatology (ACR) Criteria for FM

- ACR criteria
  - History of chronic widespread pain ≥3 months
  - Patients must exhibit ≥11 of 18 tender points
- Widespread pain was found in 97% of patients with FM, compared with 70% in controls
- FM can be identified from among other rheumatologic conditions with use of ACR criteria
  - Criteria need further refinement as knowledge about FM evolves



ACR criteria are both sensitive (88.4%) and specific (81.1%)

Wolfe et al. *Arthritis Rheum*. 1990:33:160-172.

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ORIGINAL ARTICLE

The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors as Provisional. This signifies that the criteria set has been quantitatively validated using patient data, but it has not undergone validation based on an external data set. All ACR-approved criteria sets are expected to undergo intermittent updates.

As disclosed in the manuscript, these criteria were developed with support from the study sponsor, Lilly Research Laboratories. The study sponsor placed no restrictions, offered no input or guidance on the conduct of the study, did not participate in the design of the study, see the results of the study, or review the manuscript or submitted abstracts prior to the submission of the paper. The recipient of the grant was Arthritis Research Center Foundation, Inc. The authors received no compensation. The ACR found the criteria to be methodologically rigorous and clinically meaningful.

ACR is an independent professional, medical and scientific society which does not guarantee, warrant or endorse any commercial product or service. The ACR received no compensation for its approval of these criteria.

Objective. **To develop simple, practical criteria for clinical diagnosis of fibromyalgia that are suitable for use in primary and specialty care and that do not require a tender point examination, and to provide a severity scale for characteristic fibromyalgia symptoms.**

Methods. **We performed a multicenter study of 829 previously diagnosed fibromyalgia patients and controls using physician physical and interview examinations, including a widespread pain index (WPI), a measure of the number of painful body regions. Random forest and recursive partitioning analyses were used to guide the development of a case definition of fibromyalgia, to develop criteria, and to construct a symptom severity (SS) scale.**

Results. **Approximately 25% of fibromyalgia patients did not satisfy the American College of Rheumatology (ACR) 1990 classification criteria at the time of the study. The most important diagnostic variables were WPI and categorical scales for cognitive symptoms, unrefreshed sleep, fatigue, and number of somatic symptoms. The categorical scales were summed to create an SS scale. We combined the SS scale and the WPI to recommend a new case definition of fibromyalgia: (WPI ≥7 AND SS ≥5) OR (WPI 3–6 AND SS ≥9).**

Conclusion. **This simple clinical case definition of fibromyalgia correctly classifies 88.1% of cases classified by the ACR classification criteria, and does not require a physical or tender point examination. The SS scale enables assessment of fibromyalgia symptom severity in persons with current or previous fibromyalgia, and in those to whom the criteria have not been applied. It will be especially useful in the longitudinal evaluation of patients with marked symptom variability.**

INTRODUCTION

The introduction of the American College of Rheumatology (ACR) fibromyalgia classification criteria 20 years ago began an era of increased recognition of the syndrome (1). The criteria required tenderness on pressure (tender points) in at least 11 of 18 specified sites and the presence of widespread pain for diagnosis. Widespread pain was defined as axial pain, left- and right-sided pain, and upper and lower segment pain.

Over time, a series of objections to the ACR classification criteria developed, some practical and some philosophi-

Supported by Lilly Research Laboratories.

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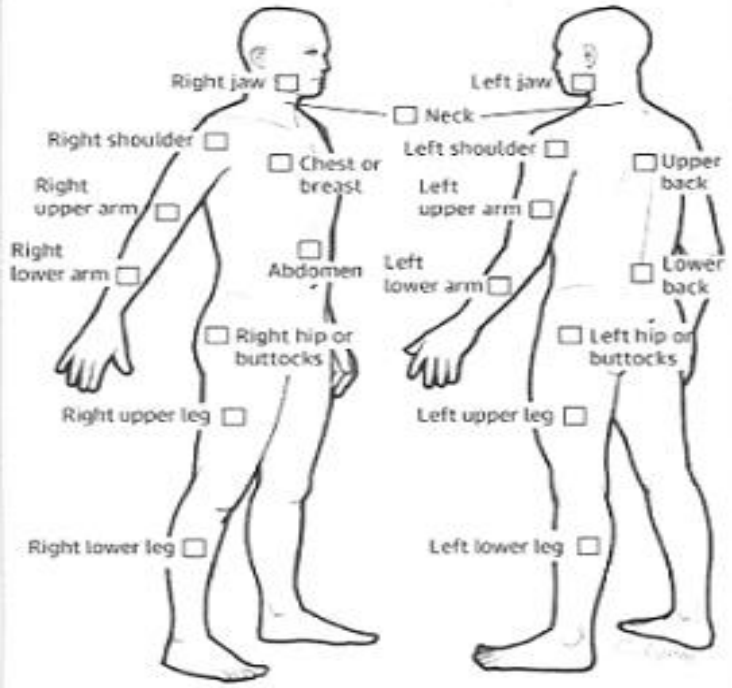
REVISED 2010 ACR CRITERIA FOR DIAGNOSIS OF FIBROMYALGIA

(1) Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
Check the boxes in the diagram for each area in which you have had pain or tenderness.



(2) For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.

- **No problem**
- **Slight or mild problem**: generally mild or intermittent
- **Moderate problem**: considerable problems; often present and/or at a moderate level
- **Severe problem**: continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	☐	☐	☐	☐
B. Trouble thinking or remembering	☐	☐	☐	☐
C. Waking up tired (unrefreshed)	☐	☐	☐	☐

(3) During the **past 6 months** have you had any of the following symptoms?

Points	0	1
A. Pain or cramps in lower abdomen	☐ No	☐ Yes
B. Depression	☐ No	☐ Yes
C. Headache	☐ No	☐ Yes

Additional criteria (no score)

(4) Have the symptoms in questions 2 and 3 and widespread pain been present at a similar level for at **least 3 months**?

☐ No ☐ Yes

(5) Do you have a disorder that would otherwise explain the pain?

☐ No ☐ Yes

SYNDROMES ASSOCIATED WITH FIBROMYALGIA

- Migraine
- Irritable bowel syndrome
- Paresthesias
- Pelvic floor pain
- Interstitial cystitis
- Chronic Fatigue Syndrome
- Chest Wall Pain
- TMJ (temporomandibular joint) syndrome

Laboratory findings are generally negative, but some patients will have a positive ANA, positive rheumatoid factor, mild elevation of the sedimentation rate, and/or elevated C-reactive protein. Other autoimmune antibodies may be present.

DIFFERENTIAL DIAGNOSIS

- Inflammatory polyarthritis
- Lupus
- Hypothyroidism

- FM may occur concurrently with arthritis (OA) and autoimmune disease (RA, SLE)

- Fibromyalgia is invisible, not picked up by doctors. Many people think it's a wastebasket diagnosis and not worth taking seriously.

- It is a **real** diagnosis. As much as migraine and IBS are real diagnoses.

- Dr. Fredrick Wolfe said internists should focus primarily on how they can make life better for these patients. "Try to encourage people to get better, to find resources in the community, to find friends and strength," he said "What patients want to know is that you're there for them and that you believe them and that you listen to their story and that you help them for flare-ups."

A CENTRAL CONCERN FOR PATIENTS WITH FIBROMYALGIA

- A central concern of patients with fibromyalgia is disbelief, that their physicians and the medical profession do not believe them. That physicians see their symptoms as ordinary (something that everyone has at one time or another, not serious, psychosomatic, “in your head”, a mental problem, or the result of depression).
- Sensing disbelief, the commentaries of fibromyalgia patients and their interactions with the medical system are filled with the sense of betrayal, and anger. A positive diagnosis of fibromyalgia is resulted with reduced health care utilization and reduction in investigations. No longer should fibromyalgia be a diagnosis of exclusion.

Diagnosis Delay in Fibromyalgia

- It takes 5-7 years from the time the patient first reports symptoms to the time when fibromyalgia is formally diagnosed[1]
- Causes:
  - Lack of a gold standard test for diagnosis[2]
  - Patients don't present with specific complaints
  - Fibromyalgia overlaps with many other diseases
  - Physicians don't want to label their patients with a chronic and debilitating disease

1. Goldenberg DL. *Arch Intern Med*. 1999;159:777-785; 2. Nampiaparampil DE, Shmerling RH. *Am J Manag Care*. 2004;10:794-800.

FIBROFOG

- Fibromyalgia cognitive problems, sometimes colloquially called “fibrofog.”
- These patients have a perception of poor memory, “am I developing Alzheimer's?”, sometimes poor job performance because of memory and concentration difficulties

Differences in the time course of information transmission from presentation of sensory information of a 3-second duration to short-term memory in the neural networks of the participant groups, and their impact on the strength of the memory trace sent into long-term memory

Group	Time consumed in lexical storehouse	Time available for processing information in short-term memory	Output from short-term memory
Fibromyalgia syndrome	620 msec*	2 minutes, 380 msec	Weak memory trace
Control	417 msec	2 minutes, 583 msec	Strong memory trace

* 203 msec represents the extra consumption of time in the lexical storehouse (620 msec − 417 msec = 203 msec) in fibromyalgia.

Newer Medications

- The first FDA-approved drug for fibromyalgia management is pregabalin (Lyrica). Pregabalin is approved for managing pain that results from diabetic neuropathy and postherpetic neuralgia, and as an adjunctive therapy for seizure disorder.

- The mixed serotonin/norepinephrine reuptake blockers Cymbalta (duloxetine), Savella (milnacipran).

Antidepressants in Fibromyalgia

	Compound	Relative activity: Norepinephrine (NE)	Relative activity: Serotonin (5-HT)	Efficacy
SSRI	Paroxetine	1	60	Variable
	Fluoxetine	1	55	Variable
SNRI	Venlafaxine	1	30	Modest
	Duloxetine	1	8	Significant
TCA	Amitriptyline	1.6	1	Significant
NSRI	Milnacipran	3.3	1	Significant

Analgesics*: Published Trials

Study	Agent	N	Study Duration (weeks)	Primary End Point	Significant Improvement with Tramadol
Bennett et al (2005)	Tramadol/ acetaminophen vs PBO	313	13	SF-36, FIQ	Yes
Bennett et al (2003)	Tramadol/ acetaminophen vs PBO	315	13	Time to discontinuation	Yes
Kemple et al (2003)	Opioid†	38	200	Improvement in pain	No
Russell et al (2000)	Tramadol vs PBO	100	9	Time to discontinuation	Yes
Biasi et al‡ (1998)	Tramadol vs PBO	12	1	VAS	Yes
Sorensen et al (1995)	Morphine (IV) vs PBO	9	1	Reduction in pain intensity	No

***No analgesic is currently FDA approved for FM.**

†Doses of morphine equivalent per 24 hour were determined; ‡Single-dose cross-over trial with 1 week washout period.
SF-36 = short-form 36; IV = intravenous; VAS = visual analog score.

Bennett et al. *Arthritis Rheum*. 2005;53:519-527; Bennett et al. *Am J Med*. 2003;114:537-545; Kemple et al. *Arthritis Rheum*. 2003;48:S88; Russell et al. *J Clin Rheumatol*. 2000;6:250-257; Biasi et al. *Int J Clin Pharmacol Res*. 1998;18:13-19; Sorensen et al. *Scand J Rheumatol*. 1995;24:360-365.

Self Reported Surgery

Women with FMS were significantly more likely than women without FMS to report having had surgery. For men, no statistically significant differences were found between those with FMS and those without FMS with respect to rates of self-reported surgery.

Type of Surgery	FMS n (%)	Non-FMS n (%)	P-value
Women:			
Cholecystectomy	119 (26%)	9 (12%)	0.01
Hysterectomy or other female surgery	224 (48%)	24 (32%)	0.008
Other	170 (37%)	14 (19%)	0.002
None	55 (12%)	18 (24%)	0.004

Goals of Treatment

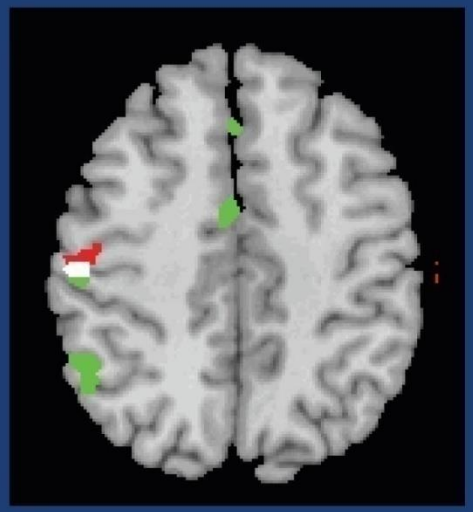
- Improving sleep, specifically getting patients to sleep all the way through the night may help general symptoms including pain and fatigue.
- Amitriptyline, doxepin and trazodone are particularly helpful.
- Sometimes low dose muscle relaxants like cyclobenzaprine are helpful, but try to avoid sedation.
- Exercise is important for stamina and sense of well being. Light aerobic exercise is recommended, refer for physical therapy
- Cognitive behavioral therapy
- Alternative therapies- no evidence they work but can be tried by the patient.

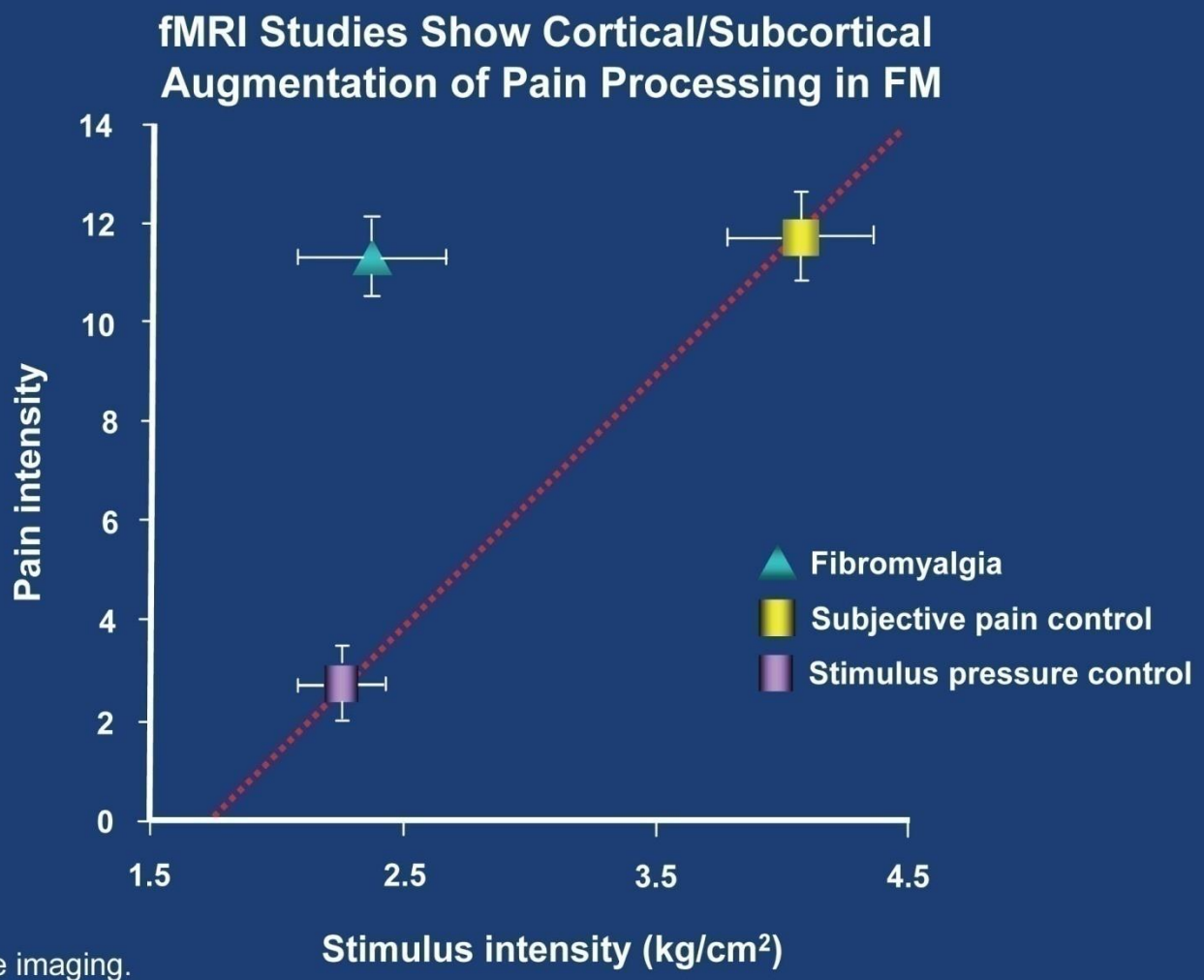
Pathophysiology of Fibromyalgia: Overview

- Central pain mechanisms in FM
  - Recent data suggest that alterations of the CNS may contribute to the chronic widespread pain of FM
  - CNS mechanisms (i.e, central sensitization) may explain generalized heightened pain sensitivity of FM patients
  - Increased levels of excitatory neurotransmitters (glutamate and substance P) may contribute to neuronal hyperactivity and central sensitization
- FM is believed to be a chronic, central pain state

-fmRI data provided supporting evidence that FM involves altered central pain processing

Fibromyalgia May Be a Central Pain Processing Disorder: fMRI Evidence





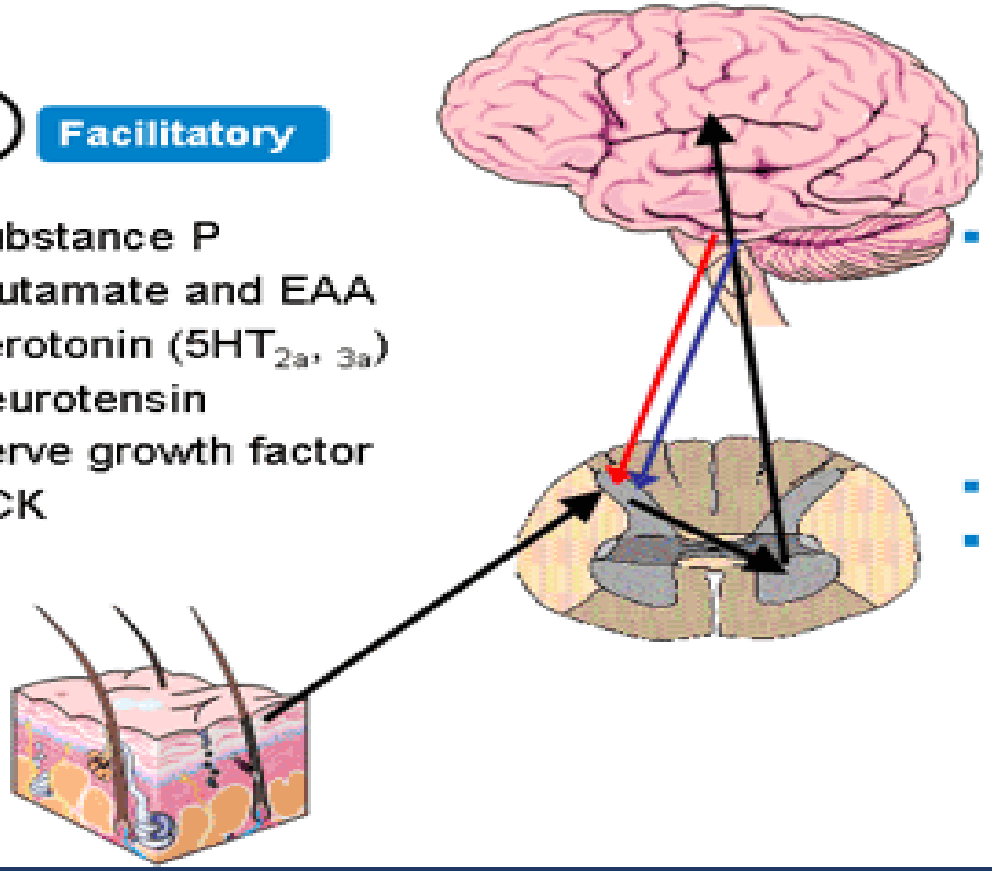
fMRI = functional magnetic resonance imaging.

Gracely et al. *Arthritis Rheum*. 2002;46:1333-1343.

Descending Influences on Nociceptive Processing

Facilitatory

- Substance P
- Glutamate and EAA
- Serotonin ($5HT_{2a,\ 3a}$)
- Neurotensin
- Nerve growth factor
- CCK

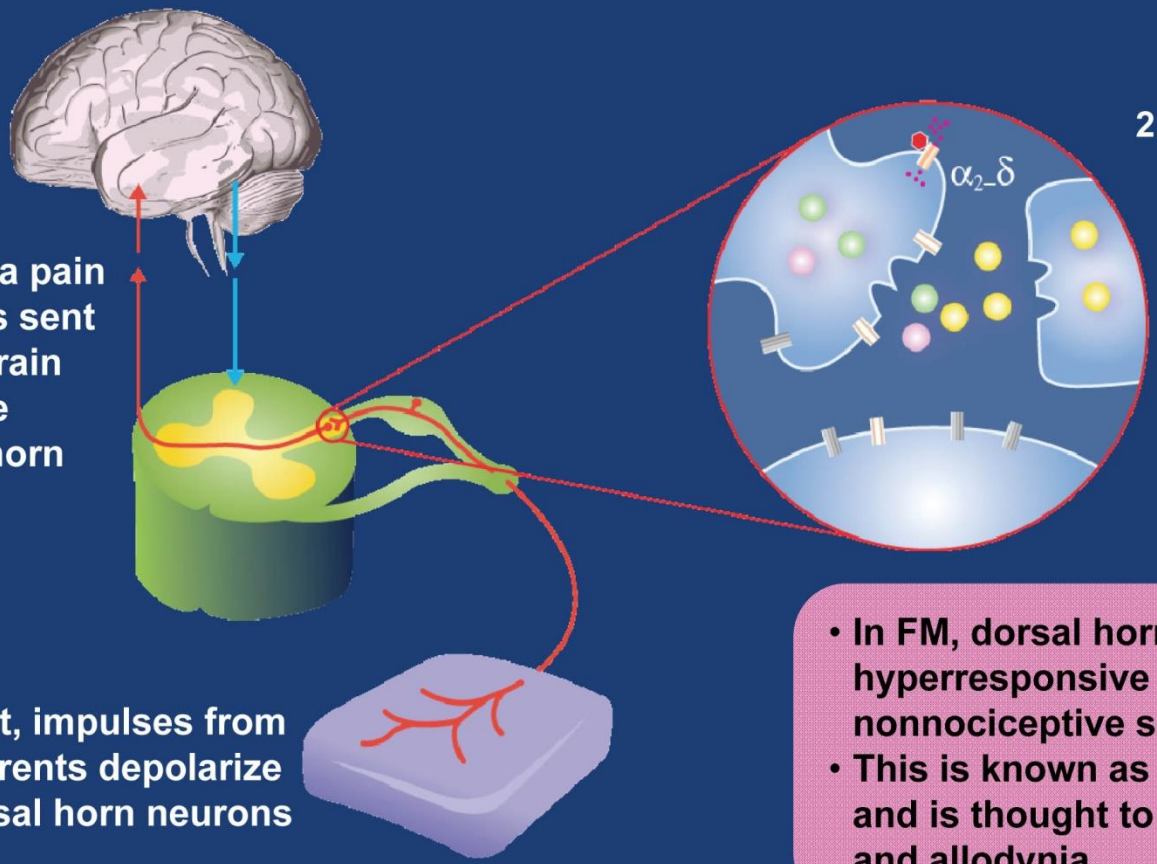


Inhibitory

- Descending antinociceptive pathways
  - Norepinephrine – serotonin ($5HT_{1a,b}$)
  - Opioids
- GABA
- Cannabinoids

Medscape

Pathophysiology of Fibromyalgia: The Role of Central Sensitization



3. Finally, a pain signal is sent to the brain from the dorsal horn

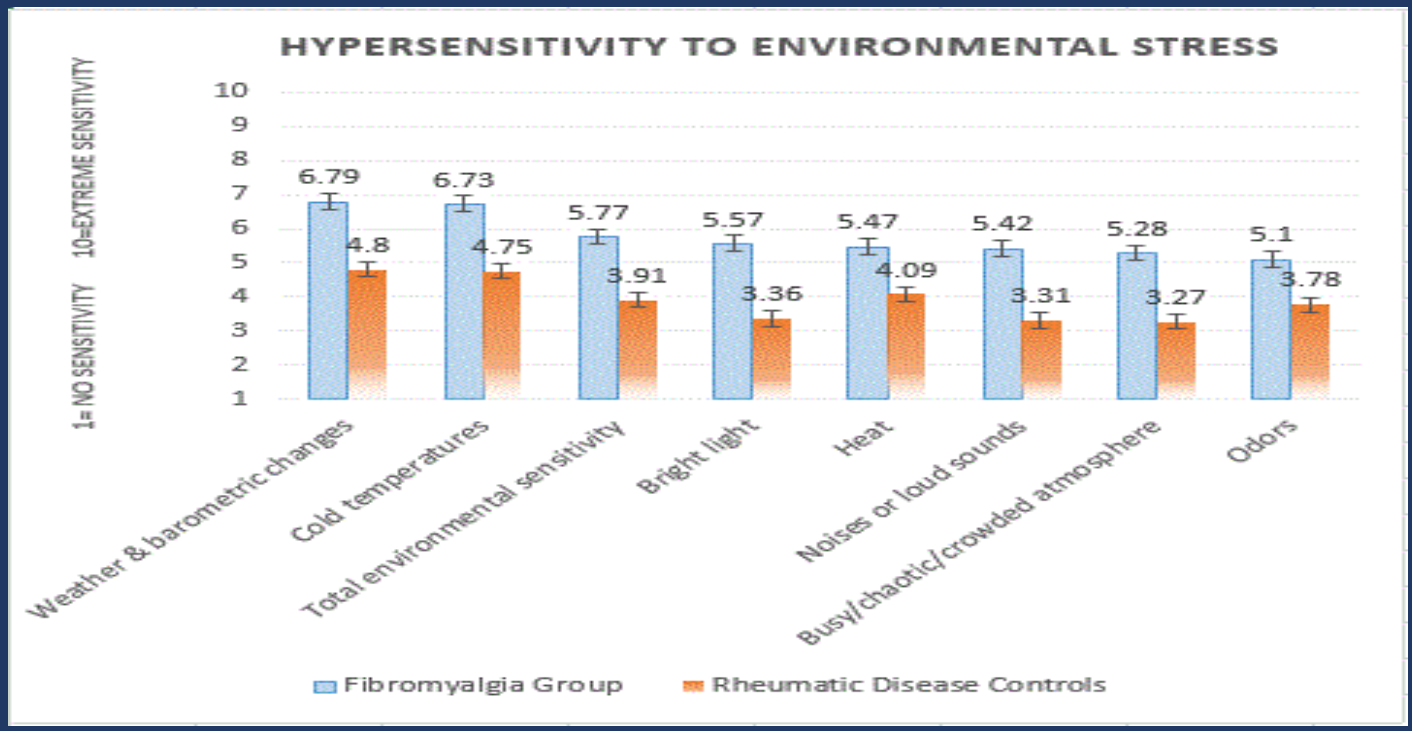
2. Then, extracellular Ca^{2+} and nitric oxide diffuse into neurons and cause exaggerated release of substance P and glutamate; this results in neuronal hyperexcitability

1. First, impulses from afferents depolarize dorsal horn neurons

- In FM, dorsal horn neurons become hyperresponsive to nociceptive and nonnociceptive somatic stimulation
- This is known as central sensitization and is thought to result in hyperalgesia and allodynia

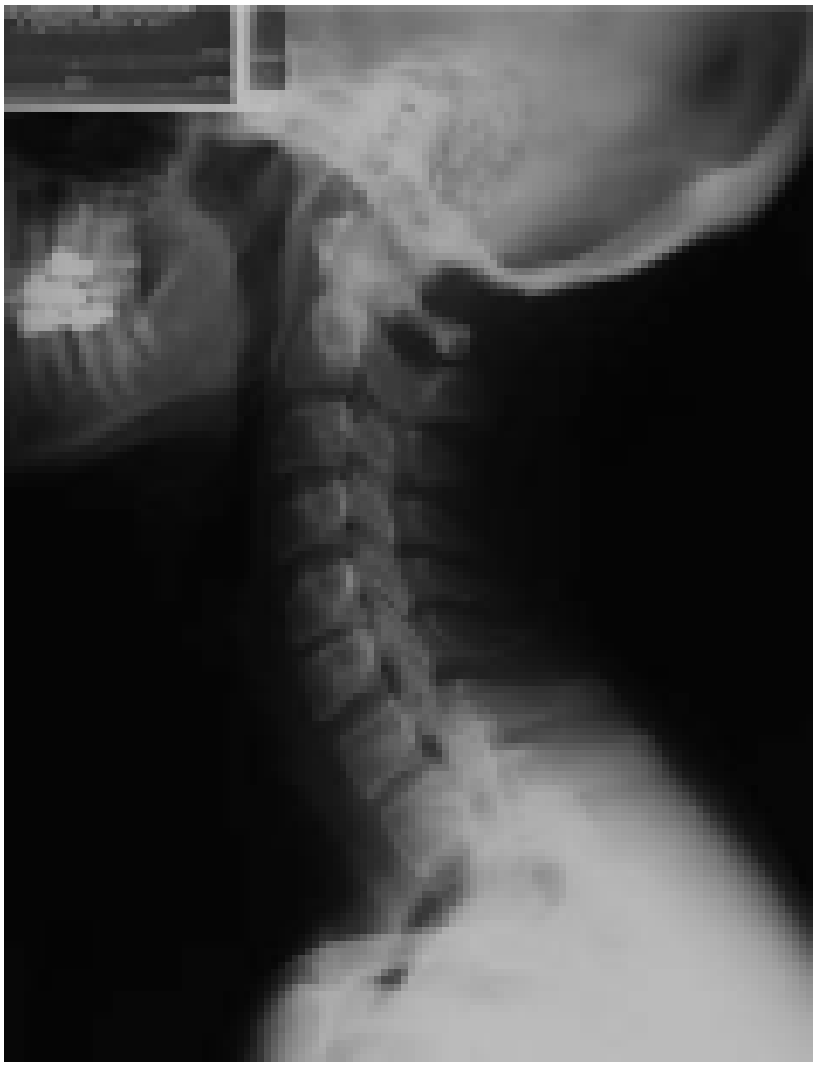
Despite extensive research, the pathogenesis of pain in FM is not clearly understood. However, central sensitization has emerged as a leading theory of disease mechanism.

Staud. *Arthritis Res Ther* [serial online]. 2006;8:208; Henriksson. *J Rehabil Med*. 2003;41(suppl 41):89-94.

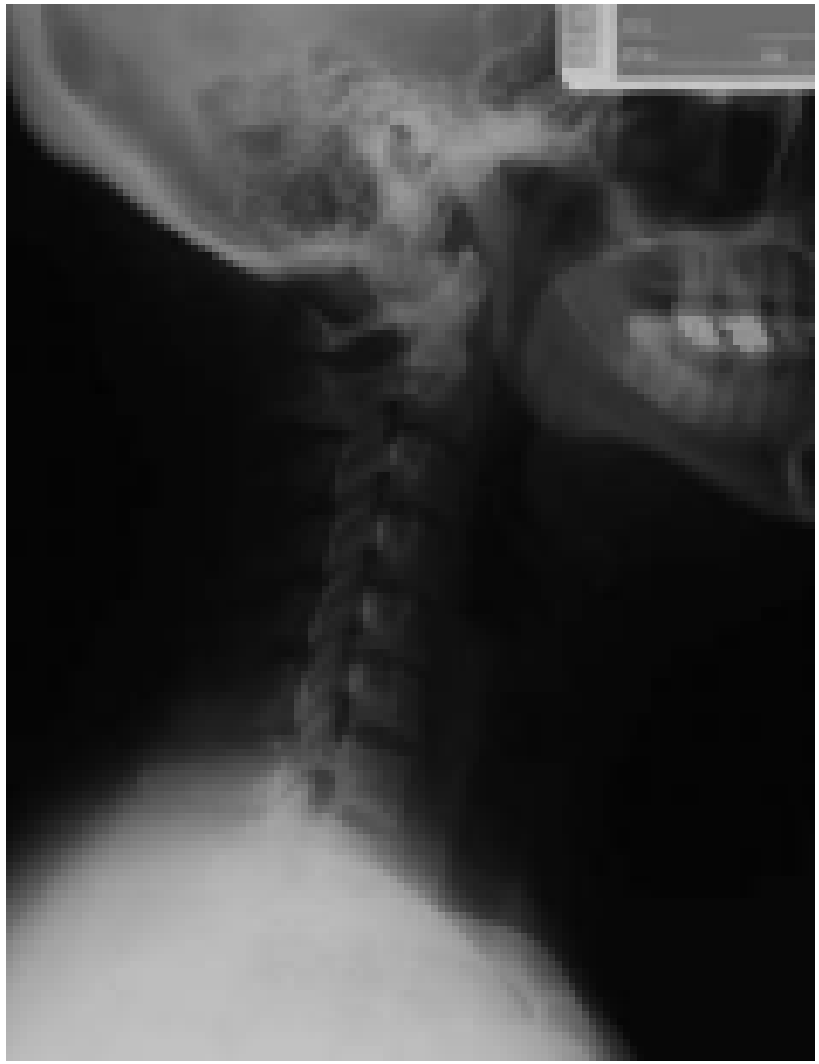

HYPERSENSITIVITY TO ENVIRONMENTAL STRESS
1= NO SENSITIVITY 10=EXTREME SENSITIVITY
10
9
8
7
6
5
4
3
2
1
6.79
4.8
6.73
4.75
5.77
3.91
5.57
3.36
5.47
4.09
5.42
3.31
5.28
3.27
5.1
3.78
Weather & barometric changes
Cold temperatures
Total environmental sensitivity
Bright light
Heat
Noises or loud sounds
Busy/chaotic/crowded atmosphere
Odors
Fibromyalgia Group
Rheumatic Disease Controls

Muscle Pressure

- Intra-muscular pressure/tension is significantly higher in patients with FMS compared to normal healthy controls. FMS patients may have chronically tense muscles, which could be a possible mechanism for the diffuse pain these patients experience. The precise explanation for increased muscle tension in FMS patients is uncertain and should be explored further to attempt to understand the pathophysiology of this enigmatic disorder.



Normal lordosis



Abnormal lordosis

LUPUS AND FIBROMYALGIA

- Patients with SLE may present with generalized arthralgias, myalgias and fatigue much like patients with FMS.
- However, other characteristic features of SLE such as photosensitive rash arthritis and multisystem organ involvement are absent.
- FMS occurs more commonly in patients with systemic rheumatic diseases than in the general population.
- Concomitant fibromyalgia has been reported in at least 22 percent of patients with SLE.
- Having fibromyalgia or concomitant fibromyalgia seems to be associated with higher pain scores and worse response to treatment.
- Concomitant fibromyalgia is an under recognized problem and can interfere with the assessment and treatment of patients with other rheumatic diseases. It can also interfere with an activity assessment indices including lupus assessment tools such as the SLEIDA and the BILAG.

The prevalence and clinical impact of fibromyalgia in systemic lupus erythematosus

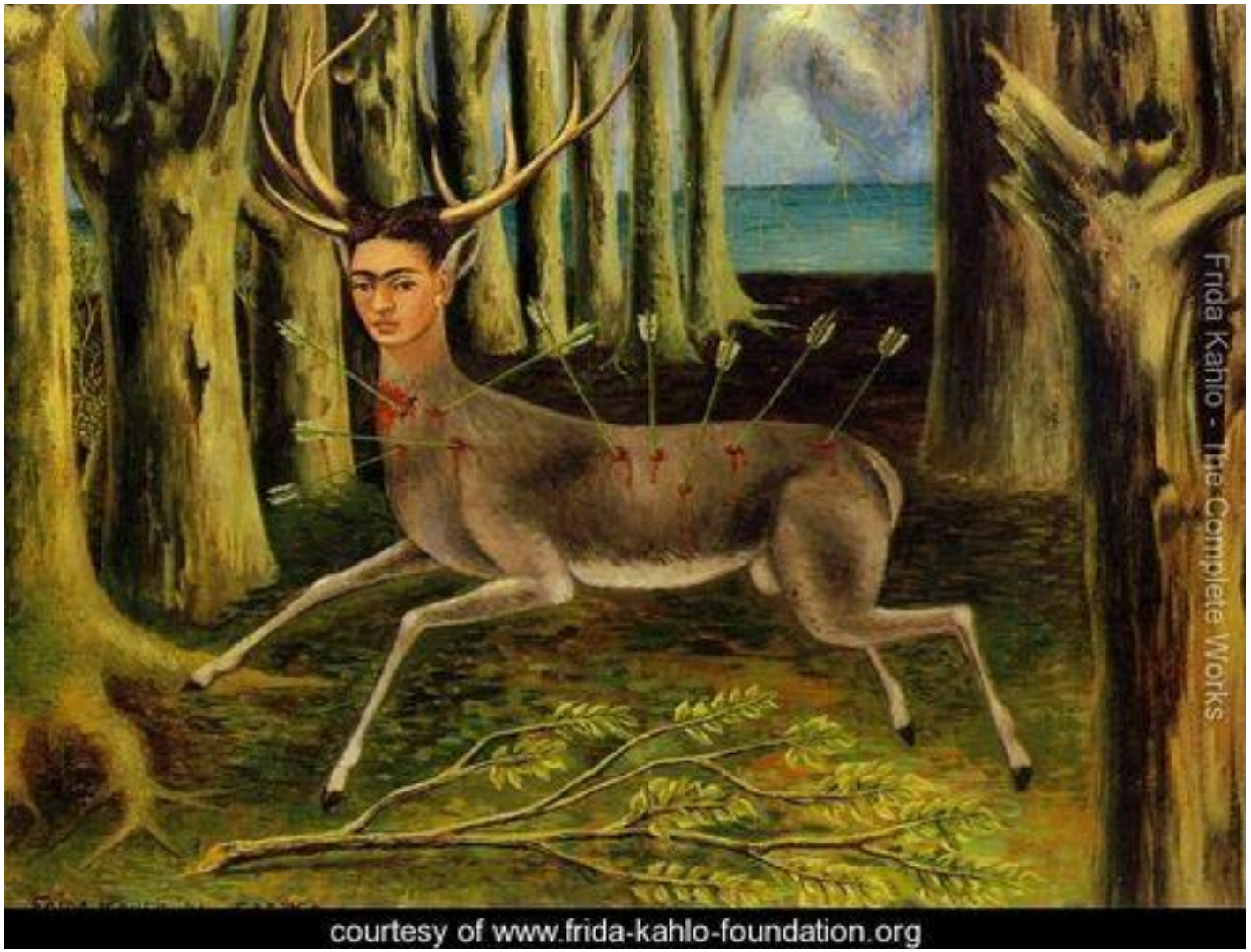
Gregg Middleton MD, Jackie Mcfarlin RN, MPH, MSN, Peter E. Lipsy MD

- Abstract
- *Objective*. To ascertain the prevalence of fibromyalgia syndrome (FMS) in systemic lupus erythematosus (SLE) and to evaluate its clinical impact and relationship to SLE disease activity.
- *Methods*. A cross-sectional analysis of 102 patients from a public hospital SLE clinic. Information was obtained on symptoms of FMS, disability, tender points, pain thresholds, and SLE disease activity.
- *Results*. Twenty-two SLE patients (22%) met the American College of Rheumatology criteria for FMS, and another 24 (23%) had clinical FMS but did not meet the classification criteria. The patients who met the criteria for FMS had a significantly increased frequency and severity of symptoms commonly associated with FMS, and were much more likely to be unable to perform daily activities. The FMS patients also were less likely to be employed, and more likely to be divorced and to be receiving welfare or medical disability benefits. However, patients with and those without FMS did not differ in measures of SLE activity.
- *Conclusion*. FMS is very common in SLE patients, and accounts for many of the symptoms and much of the disability in these patients.

Fibromyalgia in systemic lupus erythematosus

Dan Buskila, Joseph Press & Mahmoud Abu-Shakra

- Fibromyalgia (FM) is common in SLE patients, and is the source of many of the symptoms and much of the disability in these patients. The association of FM and SLE may pose diagnostic dilemmas.
- Fibromyalgia does not correlate with SLE disease activity, but the clinical features of FM in these patients may contribute to a misinterpretation of lupus activity. The recognition of the association between SLE and FM is relevant to every physician who treats lupus patients.


Frida Kahlo - The Complete Works
courtesy of www.frida-kahlo-foundation.org

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Costs of Fibromyalgia

TABLE 1. EMPLOYMENT STATUS OF RESPONDENTS

	Fibromyaliga n=672	Controls n=175
Working full time	20.0%	45.1%***
Working part time	12.4%	18.4%*
Unemployed and seeking employment	2.4%	2.3%
Unemployed and not seeking employment	4.4%	4.0%
Retired by choice	4.4%	11.5%***
Retired not by choice	4.7%	2.3%
Disabled and receiving disability benefits	32.0%	2.4%***
Disabled and disability benefits pending, in litigation	7.6%	0.0 %***
Disabled and disability denied	7.4%	0.0%***

*$p<0.05$

**$p<0.01$

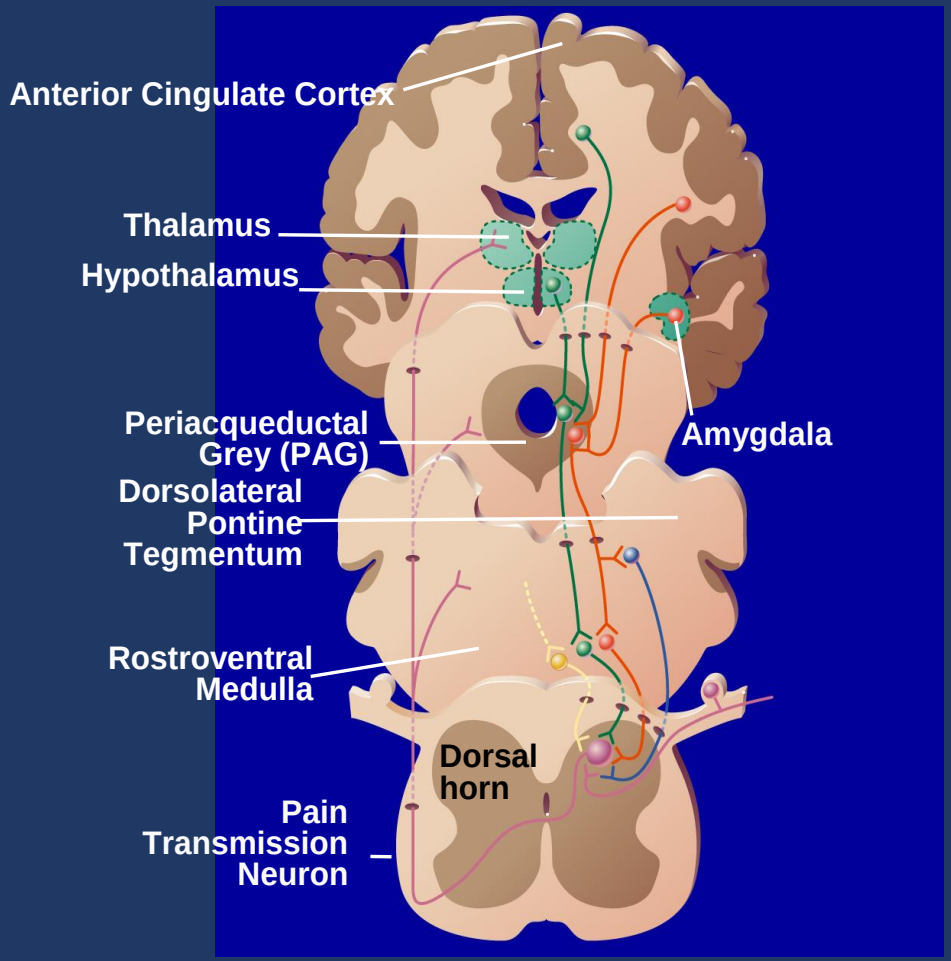
***$p<0.001$

Fibromyalgia imposes incalculable
personal, emotional, and economic costs on
the individual in the form of lost productivity,
mental impairment, role limitations, and disruptions
in life style.

The study showed that 47% of individuals
who were productively employed left their job due to
ill health. Fibromyalgia is a debilitating illness that
can affect almost every aspect of one's life.

Pain Modulation: Serotonin and Norepinephrine

- Pain is associated with increased excitation and decreased inhibition of ascending pain pathways[1,2]
- Descending pathways modulate ascending signals[1,2]
- Norepinephrine (NE) and serotonin (5-HT) are key neurotransmitters in descending inhibitory pain pathways[1,2]
- Increasing the availability of NE and 5-HT may promote pain inhibition centrally[1]



Descending Modulation → PAG indirectly controls pain transmission in the dorsal horn[2]

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2. Fields H. *Nat. Rev. Neuro*. 2004; 5:565-575
3. Fields HL and Basbaum AI. In: Wall PD, Melzack R, eds. *Textbook of Pain*. 1999:310.