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Classification Criteria of Connective Tissue Disorders in Dermatology

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ABSTRACT

Connective tissue diseases are a group of multisystem disorders that have an underlying autoimmune pathogenesis. The cutaneous signs are often presenting clinical features and represent early stages of disease. Classification criteria traditionally have high specificity which generally comes at the expense of somewhat lower sensitivity, thus missing high proportion of patients with disease. Classification criteria should only be employed if there is reason to believe a patient could have a disease. With revisions both sensitivity and specificity of classification criteria have increased over time.

Keywords: Classification criteria, connective tissue disease, cutaneous lupus erythematosus, dermatomyositis, scleroderma

INTRODUCTION

Connective tissue diseases are a group of multisystem disorders that have an underlying autoimmune pathogenesis. The cutaneous signs are often presenting clinical features and represent early stages of disease. Classification criteria are primarily intended to create homogenous cohorts for clinical studies and research. Though classification criteria may be different from diagnostic criteria, in reality they are two ends if a continuum.[1] Classification criteria traditionally have high specificity which generally comes at the expense of somewhat lower sensitivity, thus missing high proportion of patients with disease. In other words, though false positivity is less, but false negativity in more.[2] Hence, diagnosing disease depends on clinical experience of trained physician.[3,4] Classification criteria should only be employed if there is reason to believe a patient could have a disease. Latest classification criteria have high sensitivity and specificity, so they can be used as diagnostic criteria.

SYSTEMIC LUPUS ERYTHEMATOSUS:

Systemic lupus erythematosus (SLE) is a systemic disease that can virtually involve all organ systems with varied manifestation.[5,6] Diagnosing SLE therefore poses challenges as manifestation is varied. This makes classification key for diagnosis, inclusion in studies and research. EULAR/ACR 2019 criteria has high specificity of the ACR criteria (both 93%) while reaching a high sensitivity of 96%, not statistically different from the SLICC 2012 criteria (97%).[3,4] The only new item is (non-infectious) fever over ACR 1982, ACR 1997 and SLICC 2012, which should help in identifying patients with early SLE.[7,8,9]

EULAR/ACR 2019 criteria: -

Entry criterion: Antinuclear antibodies (ANA) at a titer of ≥ 1:80 on HEp-2 cells or an equivalent positive test (ever), at least once. If absent, do not classify as SLE. If present, apply additive criteria.

Additive criteria:

- Do not count a criterion if there is a more likely explanation than SLE
- Occurrence if a criterion on at least one occasion is sufficient

- SLE classification requires at least one clinical criterion and ≥ 10 points
- Criterion need not to occur simultaneously
- Within each domain, only the highest weighted criterion is counted

Table 1. EULAR/ACR 2019 criteria for SLE.

CLINICAL DOMAIN AND CRITERIA	WEIGHT	IMMUNOLOGY DOMAIN AND CRITERIA	WEIGHT
CONSTITUTIONAL:		*ANTIPHOSPHOLIPID ANTIBODIES*	
Fever	2	Anti-cardiolipin antibodies OR	
		Anti-β2GP1 antibodies OR	
		Lupus anticoagulant	2
HAEMATOLOGIC:		*COMPLEMENT PROTEINS*	
Leukopenia	3	Low C3 OR low C4	3
Thrombocytopenia	4	Low C3 and low C4	4
Autoimmune hemolysis	4	*SLE-SPECIFIC ANTIBODIES*	
		Anti-dsDNA antibody OR	
		Anti-Smith antibody	6
NEUROPSYCHIATRIC:			
Delirium	2		
Psychosis	3		
Seizure	5		
MUCOCUTANEOUS			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous/			
Discoid lupus	4		
Acute cutaneous lupus	6		
SEROSAL			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
MUSCULOSKELETAL			
Joint involvement	6		
RENAL			
Proteinuria >0.5g/24h	4		
Renal biopsy:-			
Class II OR V lupus nephritis	8		
Class III or IV lupus nephritis	10		

Classify as SLE when score is 10 or more if entry criterion is fulfilled.

SYSTEMIC SCLEROSIS

Systemic sclerosis is a multisystem disorder with autoimmunity, vasculopathy and fibrosis involved in pathogenesis. As there is no single diagnostic criteria, it was recognized that for diagnosis classification criteria were needed.[10] The new ACR EULAR criteria has excellent sensitivity and specificity over 1980 criteria and LeRoy and Medsger criteria. The improvement in sensitivity has been attributed to inclusion of Raynaud's phenomenon and puffy fingers.[11,12,13] The new American College of Rheumatology (ACR)–European League Against Rheumatism (EULAR) classification criteria for systemic sclerosis:-

ENTRY CRITERION: Any patient considered for inclusion in a SSC study

EXCLUSION CRITERION: Symptoms better explained by systemic sclerosis like disorders such as-

- Nephrogenic sclerosing fibrosis
- Scleredema diabeticorum
- Scleromyxedema
- Erythromelalgia
- Porphyria
- Lichen sclerosis
- Graft versus host disease
- Diabetic cheiroarthropathy.
- Patients with skin thickening sparing the fingers.

Table 2. ACR EULAR criteria for systemic sclerosis.

Criterion	Sub-criterion	Weight
Skin thickening of the fingers of both hands extending proximal to metacarpophalangeal joints *(Sufficient Criterion)*		9
Skin thickening of the fingers	Puffy fingers	2
(Count the highest score)	Whole finger, distal to MCP	4

Table 2 To Be Continued…		
Fingertip lesions *(count the highest score)*	Digital tip ulcers Pitting scars	2 3
Telangiectasia		2
Abnormal nail-fold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies	Anti-centromere/anti-topoisomerase/anti-RNA polymerase III	3

Patients having score ≥ 9 are classified as having definite systemic sclerosis.

DERMATOMYOSITIS

Bohan and Peter classification criteria are most widely used as both diagnostic and classification criteria for Idiopathic inflammatory myopathies.[14] Bohan and Peter criteria do not clearly specify how to exclude other forms of myopathy.[15,16] The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) developed and published new criteria for IIM and its major subgroups in 2017.[17,18] In most of the studies the sensitivity and specificity of the EULAR/ ACR criteria in patients with DM were higher than Bohn & Peter criteria.[19]

Table 4. Bohn and Peter classification of Dermatomyositis.

CRITERIA	DESCRIPTION
A	Proximal and symmetrical muscle weakness of the pelvic and scapular girdle, anterior flexors of the neck, progressing for weeks to months, with or without dysphagia or involvement of respiratory muscles
B	Elevation of skeletal muscle enzymes in serum: Creatine kinase Aspartate aminotransferase Lactate dehydrogenase aldolase
C	Electromyography characteristic of myopathy
D	Muscle biopsy showing necrosis, phagocytosis, regeneration, perifascicular atrophy, perivascular inflammatory exudate
E	Typical Cutaneous changes: Heliotrope rash with periorbital oedema and violaceous erythema Gottron's sign: vasculitis in the elbow, metacarpophalangeal and proximal interphalangeal joints
POLYMYOSITIS	DERMATOMYOSITIS
Definite: all of A-D Probable: any three of A-D Possible: any two of A-D	Definite: E + three of A-D Probable: E + two of A-D Possible: E + one of A-D

Table 5. ACR-EULAR classification criteria for adult and juvenile idiopathic inflammatory myopathies When no better explanation for the signs and symptoms exists: -

Variable	Score points		Definition
	Without Biopsy	With muscle biopsy	
Age of onset			
≥18 and < 40 years	1.3	1.5	Age of onset of first symptom assumed to be related to the disease
≥40 years	2.1	2.2	
Muscle weakness			
Objective symmetric weakness of the proximal upper extremities	0.7	0.7	Defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Objective symmetric weakness of the proximal lower extremities	0.8	0.5	
Neck flexors are relatively weaker than neck extensors	1.9	1.6	Defined by manual muscle testing or other objective strength testing
In the legs proximal muscles are relatively weaker than distal muscles	0.9	1.2	
Skin manifestations			
Heliotrope rash	3.1	3.2	Purple, lilac-colored or erythematous patches over the eyelids or in a periorbital distribution, often associated with periorbital edema
Gottron´s papules	2.1	2.7	Erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. May occur over the finger joints, elbows, knees, malleoli and toes
Gottron's sign	3.3	3.7	Erythematous to violaceous macules over the extensor surfaces of joints, which are not palpable

Table 5 To Be Continued…			
Other clinical manifestations			
Dysphagia or esophageal dysmotility	0.7	0.6	Difficulty in swallowing or objective evidence of abnormal motility of the esophagus
Laboratory measurements			
Anti-Jo-1 (anti-histidyl-tRNA synthetase) autoantibody present	3.9	3.8	Performed with standardized and validated test
Elevated serum levels of creatine kinase *or* lactate dehydrogenase *or* aspartate aminotransferase (SGOT)* *or* alanine aminotransferase (SGPT)*	1.3	1.4	Most abnormal test values during the disease course
Muscle biopsy			
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres		1.7	Endomysial mononuclear cells abutting the sarcolemma of otherwise healthy, non-necrotic muscle fibers
Perimysial and/or perivascular infiltration of mononuclear cells		1.2	Mononuclear cells are located in the perimysium and/or located around blood vessels
Perifascicular atrophy		1.9	Muscle fibers are smaller in the perifascicular region than that are centrally located
Rimmed vacuoles		3.1	Rimmed vacuoles are bluish by Hematoxylin and Eosin staining and reddish by modified Gomori-Trichrome stains

- Definite IIM (probability of ≥90%) corresponds to total aggregate score of ≥7.5 without muscle biopsy and ≥8.7 with muscle biopsy
- Probable IIM (probability ≥55% and <90%) corresponds to total aggregated score of ≥5.5, or ≥6.7 if biopsies are included
- Possible IIM a minimum score of 5.3 without biopsies and 6.5 with biopsies
- Non-IIM (probability <50%) corresponds to total aggregate score of maximum 5.3 without biopsies; 6.5 with biopsies.

For a dermatologist, when pathognomonic skin rashes of DM or JDM are present classification criteria which does not include muscle biopsy data can be used. However, where no skin rash is present, a muscle biopsy is required for diagnosis.

Declaration by Authors

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