Published Classification Criteria and A Proposal for Defining New Criteria for Idiopathic Inflammatory Myopathies (IIM)

International Myositis Classification Criteria Project Workshop

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The Problem

"The Master said,… If names are not correct, language is not in accordance with the truth of things. If language is not in accordance with the truth of things, affairs cannot be carried out to success…. Therefore a superior man considers it necessary that the names he uses be spoken appropriately…. What the superior man requires, is just that in his words there may be nothing incorrect."

Confucius, Chinese sage and philosopher, 551-479 BC, from Book XIII

Chronology of Published Diagnostic/Classification Criteria for IIM

- Medsger et al. 1970, Am. J. Med 48:715 (IIM)
- DeVere & Bradley 1975, Brain 98:637 (IIM)
- Bohan & Peter 1975, NEJM 292:344 and 403 (PM/DM)
- Dalakas 1991, NEJM 325:1487 (PM/DM/IBM)
- Griggs et al. 1995, Ann Neurol 38:705 (IBM)
- Tanimoto et al. 1995, J Rheum 22:668 (PM/DM)
- Targoff et al. 1997, Curr Opin Rheum 9:527 (IIM)
- Mastaglia & Phillips 2002, RDCNA 28:723 (PM/DM/IBM)
- Van der Meulen et al. 2003, Neurol 61:316 (PM/DM/other)
- Dalakas & Hohlfeld 2003, Lancet 362:971 (PM/DM)
- Hoogendijk, Amato et al. 2003, Neuro Dis 14:337 (ENMC for PM/DM)

Bohan and Peter 1975 PM/DM Criteria

First rule out all other forms of myopathy!

- Symmetrical weakness, usually progressive, of the limb-girdle muscles
- Muscle biopsy evidence of myositis
  - Necrosis of type I and type II muscle fibers, Phagocytosis, Degeneration and regeneration of myofibers with variation in myofiber size, Endomysial, perimysial, perivascular or interstitial mononuclear cells
- Elevation of serum levels of muscle-associated enzymes
  - CK, Aldolase, LD, Transaminases (ALT/SGPT and AST/SGOT)
- Electromyographic triad of myopathy
  - Short, small, low-amplitude polyphasic motor unit potentials
  - Fibrillation potentials, even at rest
  - Bizarre high-frequency repetitive discharges
- Characteristic rashes of dermatomyositis

Definite PM=all first 4, probable PM=3 of first 4, possible PM=2 of 4;
Definite DM= rash + 3 other; probable DM=rash + 2 other; possible DM=rash + 1 other

Bohan and Peter PM/DM Criteria Limitations

- Case series and data developed from a single institution and based on clinical observations
- No clear instructions as to how to rule out all other forms of myopathy – IBM had not yet been identified
- Degree or number of abnormalities of each criterion not specified and are observer-dependent
- Most criteria are non-specific
- Characteristic rashes of dermatomyositis not specified
- Sensitivity and specificity not studied for many confounding dermatologic or neuromuscular conditions
- However, in a cohort of PM/DM, SSc and SLE subjects, sensitivity = 93% and specificity = 93% (Oddis & Medsger 1995, Clin Rheum 9:497)

Tanimoto et al. 1995 Classification Criteria for PM and DM

Mutlicenter retrospective study by questionnaire in Japanese Dermatology, Neurology, Rheumatology academic centers assessing many features

- Rashes – Heliotrope rash or Gottron's sign or linear extensor erythema
- Proximal weakness, UE or LE and trunk
- Elevation of CK or Aldolase
- Muscle pain on grasping or spontaneous muscle pain
- Electromyographic triad of myopathy
- Anti-Jo-1 autoantibody
- Non-destructive arthritis or arthralgias
- Systemic inflammatory signs (fever >37 at axilla, elevated CRP or ESR)
- Muscle biopsy evidence of myositis
  - Inflammatory infiltrate with degeneration or necrosis of muscle, active phagocytosis, central nuclei or active regeneration

Definite PM = any 4 of 9 without rash (sensitivity = 99% [180/182]; specificity of PM and DM against all other diseases = 95% [373/392]

Definite DM = rash + 4 others (sensitivity = 94% [127/135]; specificity against SLE and SSc skin lesions = 90% [214/237]

Tanimoto et al. Classification Criteria Limitations

- Although rheumatologists, neurologists and dermatologists were included, their experience and training in myositis and consistency of evaluation and completion of questionnaires are unclear
- There were limited numbers and types of alternative disorders and IBM, CAM and juvenile myositis were excluded
- Based on questionnaires and retrospective chart reviews
- PM diagnosed only by rheumatologists and neurologists; DM diagnosed only by dermatologists and rheum
- Assessment of anti-Jo-1 not clear – likely ELISA which has sensitivity and specificity problems
- Gottron's papules not assessed?

Targoff et al. 1997 Proposed Criteria for IIM

- First exclude all other myopathies by state-of-the art methods (this will change over time)
- 6 primary classification criteria for IIM
  - 5 per Bohan and Peter – but with DM specifically defined by Heliotrope rash or Gottron's papules or Gottron's sign - plus
  - Any of the myositis-specific autoantibodies now commercially available performed by a validated assay: anti-synthetase, anti-Mi-2 or anti-SRP
- Definitions of IIM
  - Definite IIM = any 4 of the 6 criteria
  - Probable IIM = any 3 of the 6 criteria
  - Possible IIM = any 2 of the 6 criteria
- Subclassification criteria - DM defined by any one of the rashes above; IBM defined by also meeting Griggs et al. 1995 criteria; JIIM defined by age of onset <18, amyopathic DM by AAD criteria, etc.)
- Further study is needed to develop new criteria for the future including: other specific signs, symptoms, biopsy findings, MRI, genetics (HLA DR3 already shown to be useful in IBM)

Van der Meulen et al. 2003 Criteria

- Of 269 retrospective subjects, 103 excluded due to IBM or other myopathies, insufficient data, no biopsy - leaving 165 for study
- Definite PM (seen in 9/5%)
  - CK > 2X ULN
  - Mononuclear cells (MNC) surrounding (ideally invading) endomysial myofibers
- Definite DM (seen in 54/33%)
  - “Typical skin rash” or perifascicular atrophy
- Unspecified myositis (seen in 38/23%)
  - Perimysial or perivascular MNC without endomysial MNC or perifascicular atrophy or rash
- Possible myositis (seen in 29/18%)
  - CK > 2X ULN and necrotizing myopathy with few or no MNC
- Each category further subdivided into isolated myositis or CTM (with defined CTD) or CAM (cancer within 2 yrs of myositis Dx)
- Conclusion - PM is an over diagnosed entity and other categories of myositis should be established

ENMC IIM Criteria - Overview

- Neuromuscular Disorders 2004;14:337-345
  - Takes into account advances in understanding of the immunopathogenesis (PM and DM), IBM as a clinical and histological Dx, and another under-appreciated form of myositis: immune-mediated necrotizing myopathies
  - Spells out in more detail the clinical features, laboratory, and histopathological feature required for inclusion and exclusion
  - May be less sensitive but should be more specific
  - Reliability and validity need to be assessed via prospective study

ENMC IIM Criteria – Inclusion and Exclusion Criteria

1. Clinical Features

Inclusion Criteria

a. Onset usually over 18 years (*post-puberty*), onset may be in childhood in DM and non-specific myositis

b. Subacute or insidious onset **[NOTE: IBM is an IIM but never begins subacutely]**

c. Pattern of weakness: symmetric proximal > distal, neck flexor > neck extensor

d. Rash typical of DM: heliotrope, periorbital edema, Gottron's papules/sign, V-sign, shawl sign, holster sign

Exclusion Criteria

a. Clinical features of IBM (see Griggs et al: asymmetric weakness, wrist/finger flexors same or worse that deltoids; knee extensors and/or ankle dorsiflexors same or worse than hip flexors

b. Ocular weakness, isolated dysarthria, neck extensor > neck flexor weakness

c. Toxic myopathy (e.g, recent exposure to myotoxic drugs), active endocrinopathy (hyper- or hypothyroid, hyperparathyroid), amyloidosis, family history of muscular dystrophy or proximal motor neuropathies (e.g., SMA)

ENMC IIM Criteria – Inclusion and Exclusion Criteria

2. Elevated serum creatine kinase level

3. Other Laboratory Criteria:
   1) Electromyography:
      Inclusion Criteria
      - Increased insertional and spontaneous activity in the form of fibrillation potentials, positive sharp waves, or complex repetitive discharges
      - Morphometric analysis reveals the presence of short duration, small amplitude, polyphasic MUAPs

      Exclusion Criteria
      - Myotonic discharges that would suggest proximal myotonic dystrophy or other channelopathy
      - Morphometic analysis reveals predominantly long duration, large amplitude MUAPs

   2) MRI: diffuse or patchy increased signal (edema) within muscle tissue on STIR images
   3) Myositis-specific antibodies detected in serum

ENMC IIM Criteria – Muscle Biopsy Criteria

4. Muscle Biopsy Criteria
   a. Endomysial inflammatory cell infiltrate (T-Cells) surrounding and invading non-necrotic muscle fibers
   b. Endomysial CD8+ T-cells surrounding but no definite invasions of non-necrotic muscle fibers *or* ubiquitous MHC-1 expression
   c. Perifascicular atrophy
   d. MAC depositions on small blood vessels, *or* reduced capillary density, *or* tubuloreticular inclusions in endothelial cells on EM, *or* MHC-1 expression of perifascicular fibers
   e. Perivascular, perimysial inflammatory cell infiltrate
   f. Scattered endomysial CD8+ T-cells infiltrate that does not clearly surround or invade muscle fibers
   g. Many necrotic muscle fibers as the predominant abnormal histological feature. Inflammatory cells are or only sparse perivascular, perimysial infiltrate is not evident. MAC deposition on small blood vessels or pipestem capillaries on EM may be seen, but tubuloreticular inclusions in endothelial cells are uncommon or not evident.
   h. Rimmed vacuoles, ragged red fibers, cytochrome oxidase-negative fibers that would suggest IBM
   i. MAC deposition on the sarcolemma of non-necrotic fibers and other indications of muscular dystrophies with immunopathology

ENMC IIM Criteria - DM

Dermatomyositis

Definite dermatomyositis

1. All clinical criteria
2. Muscle biopsy criteria includes *c*

Probable dermatomyositis

1. All clinical criteria
2. Muscle biopsy criteria includes *d or e*, *or* elevated serum CK, *or* other laboratory criteria (1 of 3)

Amyopathic dermatomyositis

1. Rash typical of DM: heliotrope, periorbital oedema, Gottron's papules/sign, V-sign, shaw sign, holster sign
2. Skin biopsy demonstrates a reduced capillary density, deposition of MAC on small bloodvessels along the dermal-epidermal junction, and variable kerotinocyte decoration MAC
3. No objective weakness
4. Normal serum CK
5. Normal EMG
6. Muscle biopsy, if done, does not reveal features compatible with definite or probable DM

Possible dermatomyositis sine dermatitis

1. All clinical criteria with the exception of rash
2. Elevated serum CK
3. Other laboratory criteria (1 of 3)
4. Muscle biopsy criteria includes *c or d*

ENMC IIM Criteria – IBM and PM

Inclusion body myositis as per Griggs et al. (Ann Neurol 1995;38:705-713)

Polymyositis

Definite polymyositis

1. All clinical criteria with the exception of rash
2. Elevated serum CK
3. Muscle biopsy criteria includes *a*, and excludes *c,d,h,i*

Probable polymyositis

1. All clinical criteria with the exception of rash
2. Elevated serum CK
3. Other laboratory criteria (1 of 3)
4. Muscle biopsy criteria includes *b*, and excludes *c,d,g,h,i*

ENMC IIM Criteria – Other forms

Non-specific myositis

1. All clinical criteria with the exception of rash
2. Elevated serum CK
3. Other laboratory criteria (1 of 3)
4. Muscle biopsy criteria includes *e or f*, and excludes all others

Immune-mediated necrotizing myopathy

1. All clinical criteria with the exception of rash
2. Elevated serum CK
3. Other laboratory criteria (1 of 3)
4. Muscle biopsy criteria includes *g*, and excludes all others

Inclusion Body Myositis Criteria

Griggs et al., Ann Neurol 1995;38:705-713

- A. Clinical Features
  - 1. Duration > 6 mos
  - 2. Age of onset > 30 yrs
  - 3. Pattern of Weakness
    a. Finger flexor weakness
    b. Wrist flexor > wrist extensor weakness
    c. Quadriceps weakness (= or < MRC grade 4)

IBM Criteria – cont.

Griggs et al., Ann Neurol 1995;38:705-713

- B. Laboratory Features
  - 1. Serum CK < 12 x normal
  - 2. Muscle biopsy
    - a. mononuclear inflammatory cells invasion of non-necrotic muscle fibers
    - b. vacuolated muscle fibers
    - c. either
      - i. Intracellular amyloid deposits
      - ii. 15-18 nm tubulofilaments by EM
  - 3. EMG
    - a.“Features of an inflammatory myopathy”
    - b. May have long-duration MUAPs

IBM Criteria – cont.

Griggs et al., Ann Neurol 1995;38:705-713

- Definite IBM
  - Patient must exhibit all muscle biopsy features
  - None of the clinical or other laboratory features are required if patient meets Bx criteria
- Possible IBM
  - Bx shows only inflammation and invasion of fibers without vacuoles, amyloid, or TF on EM
  - Meets all Clinical Criteria (1,2,3) and other lab criteria (1,3)

Survey of Pediatric Rheumatologists Suggests Biopsy and EMG Often Not Used in JDM Diagnosis

Finding	***Extremely or Very Important***	***Not important***
Skin rash	90%	
Proximal weakness	87%	
Muscle enzyme elevation	69%	
EMG	(used 26%)	54%
Muscle Biopsy	(used 25%)	41%
MRI	43% (used 39%)	

Moenkemoeller, A&R, 2001, S293

NETWORK FOR JUVENILE DERMATOMYOSITIS

REVISION OF DIAGNOSTIC CRITERIA FOR JUVENILE DERMATOMYOSITIS

Proposed Criteria	Use (%)	Access (%)
Proximal Muscle Weakness	100	100
Characteristic Skin Rash	100	100
Elevated Muscle Enzymes (Aldolase; Creatine Kinase; Transaminases; Lactic Dehydrogenase)	86.8	87.2
Myopathic Changes on Electromyogram	55.5	89.1
Changes on Muscle Biopsy Typical of Myositis	61.3	87.4
Abnormalities on MRI Suggestive of Inflammatory Myositis	58	70.6
Other (Nailfold Capillaroscopy; Factor VIII; Muscle Ultrasound; Calcinosis; Neopterin; Dysphagia; Dysphonia; Myalgia; Myositis specific/related antibodies; Skin Biopsy; Skin Ulcerations)	35.3	-

NETWORK FOR JUVENILE DERMATOMYOSITIS

Ranking of Other Proposed Criteria

- 90 (68.7%) responders from ~70 centres in 31 countries

Median Values of Other Proposed Diagnostic Criteria for JDM

MRI	2
Muscle Biopsy	2
Electromyogram	2.5
Nailfold Capillaroscopy	3
Calcinosis	3
Dysphonia	3.5
Dysphagia	4
Factor VIII	4
Myalgia	4
Myositis Specific/ Myositis Related Antibodies	4
Muscle Ultrasound	4
Skin Biopsy	4
Skin Ulcerations	4
Neopterin	5

IIM Published Criteria Summary

- Many diagnostic/classification criteria have been proposed for different forms of IIM over the last 3 decades
- Most have been based on clinical impressions rather than data analyses and none have been fully tested for sensitivity or specificity using appropriately powered studies against all the appropriate disease confounders
- Differences in criteria by different specialties threaten to create difficulties in comparing studies and clinical trials
- Large, multicentered and multispecialty studies are required to develop improved IIM criteria

A Proposal for Developing and Validating New Classification Criteria for IIM

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Proposed International Myositis Classification Criteria Project - Overview

- Goal is to develop and validate classification criteria for IIM and subgroups in adults and children for clinical research
- Experts from multiple disciplines will determine variables to assess in a retrospective evaluation of at least 300 IIM and 900 comparator non-IIM subjects
- Each expert will submit data on 10 IIM and 30 non-IIM cases they consider to be “classic examples” of the disorder in question
- Additional focused assessments may be needed for specific disorders or variables underrepresented in the first set of cases
- Multiple statistical approaches will evaluate the variables for possible new criteria for sensitivity and specificity
- Experts will then assess these data and consider clinical sensibility to recommend the final criteria

Proposed International Myositis Classification Criteria Project - Disorders

- IIM subgroups
  - Polymyositis, dermatomyositis, overlap myositis, inclusion body myositis, non-specific myositis, immune-mediated necrotizing myopathy, and cancer-associated myositis – in adults and children
- Non-IIM subgroups that might mimic IIM
  - Non-inflammatory inclusion body myopathies
  - Dystrophies - Limb-girdle, Fascioscapulohumeral (FSH) dystrophies, others
  - Motor neuron and other neurologic diseases
  - Drug/toxin associated myopathies (statins, penicillamine, ethanol, etc.)
  - Metabolic myopathies
  - Mitochondrial myopathies
  - Infectious myopathies
  - Endocrine myopathies
  - Rheumatic conditions including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, vasculitis, polymyalgia rheumatica
  - Dermatologic conditions including psoriasis, eczema, rosacea, infectious or allergic conditions, hydroxyurea-associated and other rashes

Proposed International Myositis Classification Criteria Project - Support

- American College of Rheumatology/European League Against Rheumatic Diseases grant has been funded to support meetings
- Application submitted to The Myositis Association for funds to support possible additional pathologic, immunologic and statistical analyses

Proposed International Myositis Classification Criteria Project - Timeline

- Oct. 2004 – Planning meeting held at NIH
- Sept. 2005 – Pilot project performed on 50 variables
- Nov. 2005 – Variables and project plans finalized
- Aug. 2006 – Complete data collection of initial 1200 pts
- Dec. 2006 – Complete analyses of initial data to determine needs for additional data collection
- June 2007 – Complete all data collection
- Sept. 2007 – Completion of all data analyses
- Nov. 2007 – Experts determine final proposed criteria and possible future plans