JAMA Neurology | Original Investigation

Development of a New Classification System for Idiopathic Inflammatory Myopathies Based on Clinical Manifestations and Myositis-Specific Autoantibodies

Kubéraka Mariampillai, PhD; Benjamin Granger, MD; Damien Amelin, MSc; Marguerite Guiguet, PhD; Eric Hachulla, MD; François Maurier, MD; Alain Meyer, MD; Aline Tohmé, MD; Jean-Luc Charuel, PharmD; Lucile Musset, PharmD; Yves Allenbach, MD; Olivier Benveniste, MD

IMPORTANCE Idiopathic inflammatory myopathies are heterogeneous in their pathophysiologic features and prognosis. The emergence of myositis-specific autoantibodies suggests that subgroups of patients exist.

OBJECTIVE To develop a new classification scheme for idiopathic inflammatory myopathies based on phenotypic, biological, and immunologic criteria.

DESIGN, SETTING, AND PARTICIPANTS An observational, retrospective cohort study was performed using a database of the French myositis network. Patients identified from referral centers for neuromuscular diseases were included from January 1, 2003, to February 1, 2016. Of 445 initial patients, 185 patients were excluded and 260 adult patients with myositis who had complete data and defined historical classifications for polymyositis, dermatomyositis, and inclusion body myositis were enrolled. All patients were tested for anti–histidyl-ARN-t-synthetase (Jo1), anti–threonine-ARN-t-synthetase (PL7), anti–alanine-ARN-t-synthetase (PL12), anti–complex nucleosome remodeling histone deacetylase (Mi2), anti-Ku, anti–polymyositis/systemic scleroderma (PMScl), anti–topoisomerase 1 (Scl70), and anti–signal recognition particle (SRP) antibodies. A total of 708 variables were collected per patient (eg, cancer, lung involvement, and myositis-specific antibodies).

MAIN OUTCOMES AND MEASURES Unsupervised multiple correspondence analysis and hierarchical clustering analysis to aggregate patients in subgroups.

RESULTS Among 260 participants (163 [62.7%] women; mean age, 59.7 years; median age [range], 61.5 years [48-71 years]), 4 clusters of patients emerged. Cluster 1 (n = 77) included patients who were male, white, and older than 60 years and had finger flexor and quadriceps weakness and findings of vacuolated fibers and mitochondrial abnormalities. Cluster 1 regrouped patients who had inclusion body myositis (72 of 77 patients [93.5%]; 95% CI, 85.5%-97.8%; $P < .001$). Cluster 2 (n = 91) regrouped patients who were women and had high creatine phosphokinase levels, necrosis without inflammation, and anti–SRP or anti–3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies corresponding to immune-mediated necrotizing myopathy (53 of 91 [58.2%]; 95% CI, 47.4%-68.5%; $P < .001$). Cluster 3 (n = 52) regrouped patients who had dermatomyositis rash and anti-Mi2, anti–melanoma differentiation-associated protein 5 (MDA5), or anti–transcription intermediary factor-1γ (TIF1γ) antibodies, mainly corresponding with patients who had dermatomyositis (43 of 52 [82.7%]; 95% CI, 69.7%-91.8%; $P < .001$). Cluster 4 (n = 40) was defined by the presence of anti-Jo1 or anti-PL7 antibodies corresponding to antisynthetase syndrome (36 of 40 [90.0%]; 95% CI, 76.3%-97.2%; $P < .001$). The classification of an independent cohort (n = 50) confirmed the 4 clusters (Cohen κ light, 0.8; 95% CI, 0.6-0.9).

CONCLUSIONS AND RELEVANCE These findings suggest a classification of idiopathic inflammatory myopathies with 4 subgroups: dermatomyositis, inclusion body myositis, immune-mediated necrotizing myopathy, and antisynthetase syndrome. This classification system suggests that a targeted clinical-serologic approach for identifying idiopathic inflammatory myopathies may be warranted.

JAMA Neurol. doi:10.1001/jamaneurol.2018.2598
Published online September 10, 2018.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Kubéraka Mariampillai, PhD, Département de Médecine Interne et Immunologie Clinique, Centre de Référence Maladies Neuro-Musculaires, Assistance Publique–Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, 47-83, Boulevard de l'Hôpital, 75651 Paris Cedex 13, France (kuberaka.mariampillai@aphp.fr).

The idiopathic inflammatory myopathies (IIM) are a group of acquired myopathies characterized by muscle inflammation that are associated with motor weakness of varying severity. They are rare autoimmune diseases[1] and heterogeneous in their muscle phenotype and extramuscular manifestations.

The historical classification systems of myositis initially included 2 main entities: dermatomyositis (DM) and polymyositis (PM).[2,3] Later, it was shown that PM was overvalued.[4,5] Pathologic criteria were refined to isolate 2 new subgroups: inclusion body myositis (IBM)[6,7] and immune-mediated necrotizing myopathy (IMNM).[7] Each approach defines overlapping entities; for instance, antisynthetase syndrome is classified as both DM or PM.[8-10] A new classification system is beneficial to reduce confusion. Ideally, subgroups should share common characteristics in terms of phenotype, prognosis, and pathogenesis. Future clinical trials should be adapted on the basis of those subgroups.

There is increasing evidence that myositis-specific antibodies (MSA) or myositis-associated autoantibodies can help define subgroups of patients in terms of clinical or pathologic phenotypes, prognosis, and response to treatment.[11-15] We sought to propose a new classification system for IIM by performing unsupervised hierarchical clustering analysis, which permitted the aggregation of patients with IIM into 4 subgroups.

Key Points

Questions Does the identification of myositis-specific autoantibodies suggest the potential for identifying subgroups of idiopathic inflammatory myopathies, and is a new classification system for idiopathic inflammatory myopathies based on phenotypic, biological, and immunologic criteria warranted?

Findings In this cohort study of 260 patients with idiopathic inflammatory myositis, 4 clusters (dermatomyositis, inclusion body myositis, immune-mediated necrotizing myopathy, and anti-synthetase syndrome) were identified using unsupervised multivariate analyses. The developed decisional tree revealed that myositis-specific antibodies played a role in predicting the likelihood of belonging to a cluster.

Meaning This classification scheme for identifying subgroups of idiopathic inflammatory myopathies suggests that use of a targeted clinical-serologic approach for identifying idiopathic inflammatory myopathies may be warranted.

Methods

Study Design and Participants

This was an observational, retrospective, and multicentric study. Patients were identified from the myositis registry at the Neuromuscular Diseases Reference Centre of Paris (Groupe Hospitalier Pitié Salpêtrière, Paris, France), part of the myositis French network database from January 1, 2003, to February 1, 2016. An independent cohort from different centers of this network was then studied for external validation from October 25, 2013, to February 1, 2016. Patients were included if they met the following criteria: adult myositis defined according to historical classifications of Bohan and Peter[2,3] and Griggs et al[6] as PM, DM, and IBM; a follow-up period between January 1, 2003 (availability of antibody detection kits), and February 1, 2016 (final database lock); and an MSA screening using different generations of line blot assays (at least PMS8D [Blue Dot Polymyositis/Scleroderma[8] IgG], DTEK). Exclusion criteria were missing data (eFigure 1 in the Supplement). This project was approved by the local ethics committee (Comité de protection des personnes, Ile-de-France VI, Groupe Hospitalier Pitié Salpêtrière) and by the Ministry of Research (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé [reference number 14.323]). We also received research authorization for the database from the National Commission on Informatics and Liberties (authorization number 915139) according to French regulatory requirements. Written informed consent was provided by all patients for use of the database and the collection of biological samples (not evaluated in this project, reference MERS AC-2013-1868). A written waiver of informed consent was granted for 8 patients lost to follow-up via a letter sent to the patients defining nonobjection to study their retrospective anonymous data as part of research on myositis.

Data Collection

We developed an observational computerized database with electronic case report forms built with Voozanoo (EpiConcept) that included characteristics of the muscular and extramuscular manifestations (eTable 1 in the Supplement). As declared by the French legislation, race/ethnicity (relevant for myositis phenotype) was collected by the physicians (E.H., F.M., A.M., A.T., Y.A., and O.B.).

Detection of Antinuclear Antibodies and MSA- and Myositis-Associated Antibodies

Antinuclear antibodies were detected by indirect immunofluorescence on HEp-2000 cells (Immunoconcepts).[16] The screening for MSA was performed with different generations of line blot commercial assays (eTable 2 in the Supplement), as previously reported.[17]

Statistical Analyses

The statistical analyses were performed in 4 steps using R, version 3.4.0 (R Core Team). Step 1 was a preanalytical step to describe the data set. All collected data were crudely described, then grouped according to historical myositis classifications (PM, DM, and IBM) to study the association between different characteristics and historical myositis classifications. Quantitative data were described as medians (first quartile and third quartile). Qualitative data were categorized into frequency and percentages and binomial CIs. Nonparametric tests were used. The Kruskal-Wallis rank sum test was used to assess the association between quantitative data and historical classification. The Fisher exact test was used for qualitative data. Multiple comparisons problem was controlled by Bonferroni-adjusted P value method, and $P < .05$ was considered to be statistically significant. The agreement between the dosages of MSA determined for all patients with kits from DTEK and PMS8D (eTable 2 in the Supplement) was evaluated with the Cohen κ light coefficient.

Step 2 was an analytical phase seeking to define subgroups and to build a new classification. A multiple correspondence analysis was used as a multivariate statistical method for description to reduce the dimensions of the data set (eFigure 1 in the Supplement). A hierarchical cluster analysis from the multiple correspondence analysis was used to determine subgroups of patients according to various characteristics. The clustering of patients was performed using Euclidean distance and the Ward agglomerative method. Crude associations were performed between the different variables that participated in the construction and those that were positioned with clusters identified by the hierarchical cluster analysis.

Step 3 sought to construct a decisional algorithm tree to easily position the participants in the new classification scheme. We used classification and regression trees. We performed cross-validation to select the optimal tree and performed multiple runs to avoid overfitting. The selection of the best tree was defined by jointly visualizing the smallest cross-validated prediction error on the training set associated with the highest proportion of correct classification on the test set. The classification quality of the tree was judged on the basis of the sensitivity and specificity estimation of classification criteria.

Step 4 involved the external validation of the model of classification from an independent data set (including patients from other centers). A naive classification of these patients obtained from the hierarchical cluster analysis was compared with the objective classification from the tree resulting from the initial set. The agreement between the 2 classifications was evaluated by Cohen κ light analysis, and the 95% CI was calculated from the empirical distribution by bootstrap analysis.

Results

New Classification System

Data from 361 patients (230 [63.7%] women and 131 [36.3%] men; mean [SD] age, 59.6 [16.8] years; median age [range], 61 years [46-72]) with 708 variables were described (eTable 3 in the Supplement). Forty-seven discriminant variables were selected according to their relevance for distinguishing historical entities (PM, DM, and IBM) and/or their agreement with clinical practice from the point of view of expert physicians (Y.A. and O.B.). Ultimately, 260 patients (163 [62.7%] women; mean age, 59.7 years; median age [range], 61.5 years [48-71 years]) with no missing data for the 47 selected variables were included for the construction of the new classification system, starting with the multiple correspondence analysis (eFigures 1-3 and eTable 4 in the Supplement). We chose to perform multiple correspondence analysis on the first 39 dimensions, cumulatively explaining 90.4% of the variance. Then, we performed hierarchical clustering to identify clusters (**Figure 1**). The hierarchical tree suggested a partition into 4 clusters. Forty-one variables were discriminant for the hierarchical cluster analysis (eTable 5 in the Supplement). In addition to the description of the 41 selected variables, we also positioned relevant clinical-biological variables that were not used for hierarchical cluster analysis. These variables were excluded from the construction of the new classification scheme because of missing data (eg, newly available MSA dosages) or their potential weight in the classification in terms of historical diagnosis (PM, DM, and IBM) and/or recent diagnosis (PM, DM, IBM, IMNM, and antisynthetase syndrome) (eTable 6 in the Supplement). Finally, we identified the following characteristics (skin lesions, biological, muscular and extramuscular, histological, sociodemographic, and final status as well as the diagnosis) among the 4 identified clusters (**Table** and eTables 7-10 in the Supplement).

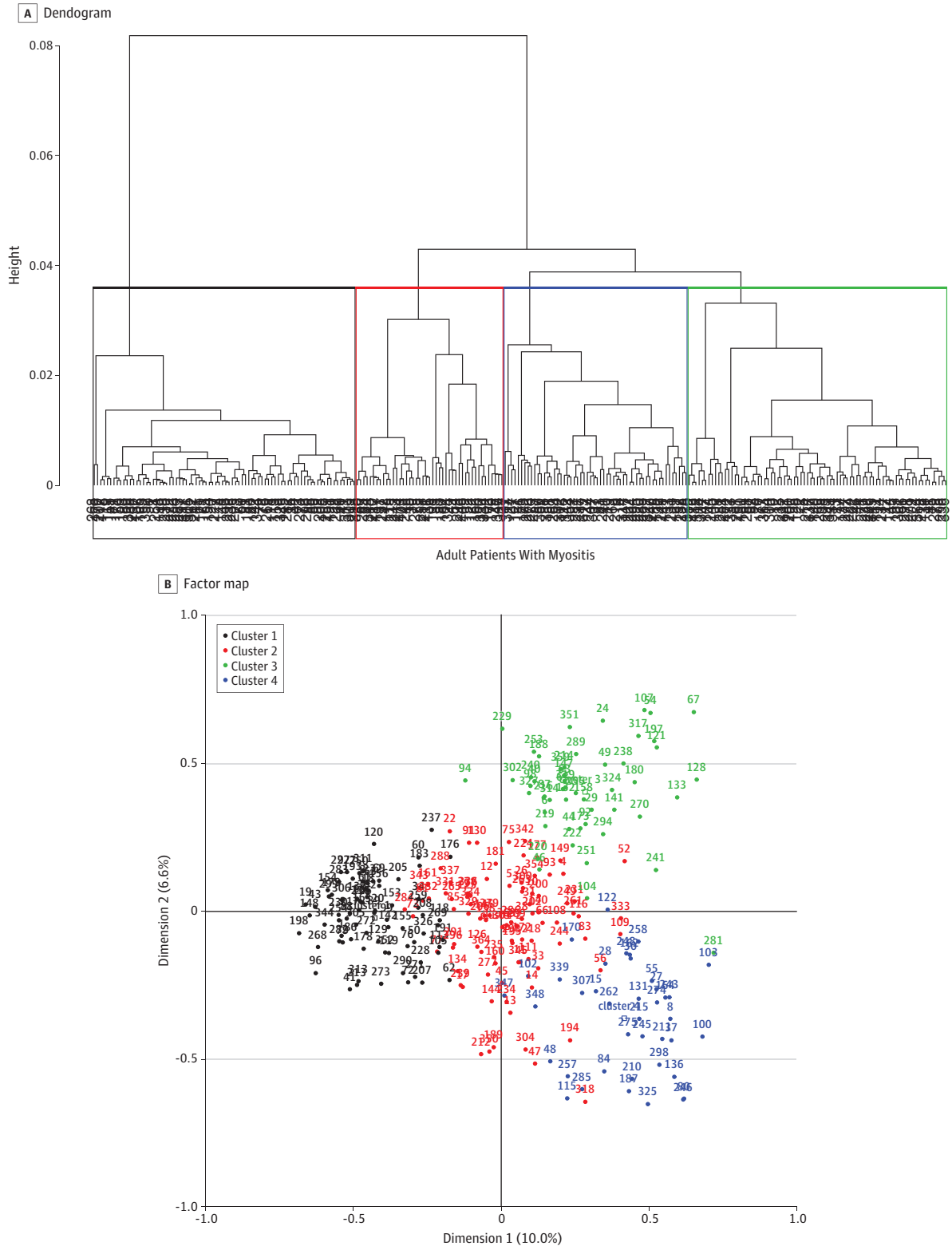
Cluster Subgroups

Of 260 study patients, 77 patients (29.6%) were included in the first cluster, of whom 46 patients (59.7%; 95% CI, 47.9%-70.8%; $P < .001$) were male, 74 (96.1%; 95% CI, 89.0%-99.2%; $P = <.001$) were white, and 58 (75.3%; 95% CI, 64.2%-84.4%; $P < .001$) were at least 60 years of age at the time of diagnosis. There were few patients with skin lesions (8 [10.4%]; 95% CI, 4.6%-19.4%; $P < .001$). Muscular evaluation was done using the Medical Research Council 5-point (MRC5) scale, which is a scale of 0 to 5 with lower numbers indicating more weakness: 5, muscle contracts against full resistance; 4, strength reduced, but contraction can still move joint against resistance; 3, strength further reduced such that joint can be moved only against gravity with examiner's resistance completely removed; 2: muscle can only move if resistance of gravity is removed; 1, only a trace or flicker of movement is seen or felt, or fasciculations are observed; and 0, no movement. Evaluated patients harbored a characteristic phenotype with distal weakness of finger flexors (MRC5 ≤ 3: 48 patients [62.3%]; 95% CI, 50.6%-73.1%; $P < .001$) and proximal weakness mainly affecting the quadriceps (MRC5 ≤ 3: 47 [61.0%]; 95% CI, 49.2%-71.9%; $P < .001$); weakness was less frequently found in the deltoids (MRC5 of 5: 28 [36.4%]; 95% CI, 25.7%-48.1%; $P = .04$). Swallowing difficulties also characterized the first cluster (59 patients [76.6%]; 95% CI, 65.6%-85.5%; $P < .001$). Creatine kinase (CK) levels ranged from 160 U/L to 793 U/L (33 patients [42.8%]; 95% CI, 31.6%-54.6%; $P < .001$) (to convert CK to microkatals per liter, multiply by 0.0167).

Assessment of muscle pathologic features revealed vacuolated fibers (62 of 77 patients [80.5%]; 95% CI, 69.9%-88.6%; $P < .001$), mitochondrial abnormalities (61 [79.2%]; 95% CI, 68.5%-87.6%; $P < .001$), muscle inflammation (77 [100%]; 95% CI, 95.3%-100%; $P < .001$), and invaded fibers (52 [67.5%]; 95% CI, 55.9%-77.8%; $P < .001$). The vacuolated fibers (V test, 11.308639; P value = 1.189197e−29), finger flexor weakness (V test, 8.976751; P value = 2.788792e−19), and mitochondrial abnormalities (V test, 8.761396; P value = 1.928476e−18) were the variables that most characterized cluster 1 (greater V test value and smaller P value) (eTable 7 in the Supplement). By positioning the variables, cluster 1 regrouped mainly IBM (93.5% 95% CI, 85.5%-97.8%; $P < .001$).

The second cluster included 91 of 260 patients (35.0%). Of these patients, 66 (72.5%; 95% CI, 62.2%-81.4%; $P = .02$) were women with no specific race/ethnicity and without skin lesions (36 of 91 patients [39.6%]; 95% CI, 29.5%-50.4%; $P = .02$). These patients had the most severe proximal muscle weakness of the lower limbs affecting the psoas (MRC5 ≤ 3: 57 patients [62.6%]; 95% CI, 51.9%-72.6%; $P = .04$), whereas the quadriceps (MRC5 of 5: 40 [43.9%]; 95% CI, 33.6%-54.7%;

Figure 1. Dendrogram and Hierarchical Cluster Analysis on Multiple Correspondence Analysis Factor Map



A, Dendogram generated using euclidean distance and the Ward agglomerative method. The bold vertical line indicates the height of fusion into clusters proposed and the x-axis indicates the individuals (n = 260) at the bottom of the dendrogram (leaf nodes). B, Factor map showing the raw data (individuals) used to generate the dendogram. The first 2 dimensions cumulatively explained 16.7% of the total variance. We obtained a hierarchical tree positioned on the factorial map on which colors indicate individuals according to the cluster to which they belong.

Table. Clusters by Hierarchical Cluster Analysis

Variable	Cluster, No. (%)				*P* Value[a]
	1 (n = 77)	2 (n = 91)	3 (n = 52)	4 (n = 40)	
Female	31 (40.3)	66 (72.5)	38 (73.1)	28 (70.0)	<.001
Age at diagnosis, y					
≤40	1 (1.3)	26 (28.6)	19 (36.5)	15 (37.5)	<.001
>40 to 60	18 (23.4)	40 (43.9)	22 (42.3)	19 (47.5)	
>60	58 (75.3)	25 (27.5)	11 (21.1)	6 (15.0)	
Race/ethnicity					
White	74 (96.1)	62 (68.1)	45 (86.5)	26 (65.0)	<.001
African origin	1 (1.3)	12 (13.2)	2 (3.8)	9 (22.5)	
Other[b]	2 (2.6)	17 (18.7)	5 (9.6)	6 (15.0)	
Historical diagnosis					
Dermatomyositis	2 (2.6)	7 (7.7)	43 (82.7)	2 (5.0)	<.001
Inclusion body myositis	72 (93.5)	7 (7.7)	0	0	
Polymyositis	3 (3.9)	77 (84.6)	9 (17.3)	38 (95.0)	
Recent diagnosis					
Dermatomyositis	2 (2.6)	7 (7.7)	43 (82.7)	2 (5.0)	<.001
Inclusion body myositis	72 (93.5)	7 (7.7)	0	0	
Immune-mediated necrotizing myopathy	2 (2.6)	53 (58.2)	2 (3.8)	0	
Polymyositis	1 (1.3)	21 (23.1)	7 (13.5)	2 (5.0)	
Antisynthetase syndrome	0	3 (3.3)	0	36 (90.0)	
Dermatologic changes					
Typical rash criteria	8 (10.4)	36 (39.6)	52 (100)[c]	32 (80.0)	<.001
Shawl sign	2 (2.6)	7 (7.7)	42 (80.8)[c]	7 (17.5)	<.001
Dermatomyositis rash	0	6 (6.6)	46 (88.4)[c]	6 (15.0)	<.001
Heliotrope rash	0	5 (5.5)	39 (75.0)[c]	3 (7.5)	<.001
Alopecia	1 (1.3)	4 (4.4)	10 (19.2)	2 (5.0)	.001
Calcinosis	0	0	5 (9.6)	1 (2.5)	<.001
Limb edema	5 (6.5)	7 (7.7)	18 (34.6)	10 (25.0)	<.001
Panniculitis	0	0	4 (7.7)	0	.002
Skin ulcers	0	2 (2.2)	9 (17.3)	4 (10.0)	<.001
Mechanic hands	0	3 (3.3)	5 (9.6)	22 (55.0)[c]	<.001
High CK levels, μkatal/L					
≤160	8 (10.4)	7 (7.7)	5 (9.6)	2 (5.0)	<.001
>160 to 793	33 (42.8)	10 (10.9)	6 (11.5)	6 (15.0)	
>793 to 2300	28 (36.4)	16 (17.6)	15 (28.8)	6 (15.0)	
>2300 to 7000	5 (6.5)	30 (33.0)	13 (25)	11 (27.5)	
>7000	3 (3.9)	28 (30.8)	13 (25)	15 (37.5)	
Type of antibody					
Myositis-specific autoantibodies	30 (38.9)	50 (54.9)	20 (38.5)	38 (95.0)	<.001
MSA of antisynthetase syndrome	0	3 (3.3)	0	35 (87.5)[c]	<.001
Anti-Jo1	0	0	0	31 (77.5)[c]	<.001
Anti-PL12	0	2 (2.2)	0	1 (2.5)	.44
Anti-PL7	0	1 (1.1)	0	3 (7.5)	.02
Anti-EJ (n = 193)	0	0	0	1 (2.5)	.39
Anti-SRP	0	23 (25.3)[c]	1 (1.9)	0	<.001
Anti-HMGCR (n = 182)	1 (1.3)	20 (21.9)	0	0	<.001
Anti-SAE1 (n = 165)	0	0	2 (3.8)	0	.08
Anti-SAE2 (n = 165)	0	0	1 (1.9)	0	.39
Anti-Mi2	0	2 (2.2)	10 (19.2)[c]	0	<.001
Anti-MDA5 (n = 191)	0	0	3 (5.8)	2 (5)	.02
Anti-TIF1γ, (n = 180)	0	0	2 (3.8)	0	.04
Anti-NXP2 (n = 165)	0	1 (1.1)	1 (1.9)	0	.82
Myositis-associated autoantibodies	36 (46.7)	61 (67.1)	41 (78.8)	38 (95.0)	<.001
Anti-ANA	27 (35.1)	55 (60.4)	39 (75.0)	25 (62.5)	<.001
Anti-Ku	0	5 (5.5)	0	0	.03
Anti-DNA (n = 222)	2 (2.6)	4 (4.4)	9 (17.3)	3 (7.5)	.007

(continued)

Table. Clusters by Hierarchical Cluster Analysis (continued)

Variable	Cluster, No. (%)				*P* Value[a]
	1 (n = 77)	2 (n = 91)	3 (n = 52)	4 (n = 40)	
Anti-RNP	0	6 (6.6)	5 (9.6)	2 (5.0)	.03
Anti-SSA/Ro52	11 (14.3)	27 (29.7)	7 (13.5)	31 (77.5)[c]	<.001
Anti-SSA/Ro60	5 (6.5)	7 (7.7)	1 (1.9)	14 (35.0)	<.001
Anti-SSB	4 (5.2)	1 (1.1)	3 (5.8)	4 (10.0)	.09
Pathologic characteristics					
Necrotic fibers	65 (84.4)	75 (82.4)	30 (57.7)	29 (72.5)	.002
Muscle inflammation	77 (100)	57 (62.6)	46 (88.5)	33 (82.5)	<.001
Mitochondrial abnormalities	61 (79.2)[b]	20 (21.9)	12 (23.1)	7 (17.5)	<.001
Perifascicular atrophy	13 (16.9)	8 (8.8)	29 (55.8)[c]	9 (22.5)	<.001
Presence of vacuoles	62 (80.5)[c]	9 (9.9)	7 (13.5)	1 (2.5)	<.001
Invaded fibers	52 (67.5)	17 (18.7)	9 (17.3)	8 (20.0)	<.001
Perivascular infiltrates	26 (33.8)	25 (27.5)	35 (67.3)	21 (52.5)	<.001
Proximal deficit	77 (100)	85 (93.4)	50 (96.1)	36 (90)	.03
Distal deficit	74 (96.1)	45 (49.4)	25 (48.1)	15 (37.5)	<.001
Axial deficit	54 (70.1)	60 (65.9)	38 (73.1)	17 (42.5)	.01
Swallowing disorders	59 (76.6)	47 (51.6)	31 (59.6)	14 (35.0)	<.001
MRC5 score					
Deltoids					
≤3	23 (29.9)	40 (43.9)	29 (55.8)	8 (20.0)	<.001
4	26 (33.8)	35 (38.4)	18 (34.6)	10 (25.0)	
5	28 (36.4)	16 (17.6)	5 (9.6)	22 (55.0)	
Fingers flexors					
≤3	48 (62.3)[c]	8 (8.8)	5 (9.6)	2 (5.0)	<.001
4	21 (27.3)	24 (26.4)	8 (15.4)	7 (17.5)	
5	8 (10.4)	59 (64.8)	39 (75.0)	31 (77.5)	
Psoas					
≤3	38 (49.3)	57 (62.6)	31 (59.6)	14 (35.0)	.02
4	28 (36.4)	19 (20.9)	18 (34.6)	19 (47.5)	
5	11 (14.3)	15 (16.5)	3 (5.8)	7 (17.5)	
Quadriceps					
≤3	47 (61.0)	25 (27.5)	12 (23.1)	6 (15.0)	<.001
4	20 (25.9)	26 (28.6)	27 (51.9)	10 (25.0)	
5	10 (12.9)	40 (43.9)	13 (25.0)	24 (60.0)	
History of connective tissue disease (n = 249)	5 (6.5)	39 (42.8)	14 (26.9)	15 (55.0)	<.001
History of Raynaud phenomenon	4 (5.2)	32 (35.1)	16 (30.8)	17 (42.5)	<.001
Rheumatologic disorders	14 (18.2)	33 (36.2)	19 (36.5)	36 (90.0)	<.001
Mobility (n = 164)					
Without help	11 (14.3)	41 (45.0)	21 (40.4)	17 (42.5)	.001
Cane	12 (15.6)	9 (9.9)	2 (3.8)	1 (2.5)	
Rollator	3 (3.9)	0	1 (1.9)	0	
Wheelchair	10 (12.9)	10 (10.9)	3 (5.8)	1 (2.5)	
Bedridden	3 (3.9)	8 (8.8)	6 (11.5)	5 (12.5)	
Cancer, ≥3 y of myositis	15 (19.5)	10 (10.9)	11 (21.2)	1 (2.5)	.02
Heart involvement (n = 232)	13 (16.9)	17 (27.5)	10 (19.2)	6 (15.0)	.97
High blood pressure	35 (45.4)	22 (24.2)	8 (15.4)	7 (17.5)	<.001
Lung involvement	46 (59.7)	69 (75.8)	37 (71.1)	40 (100)[c]	<.001
Diffuse interstitial lung disease (n = 238)	7 (9.1)	27 (29.7)	9 (17.4)	34 (85.0)	<.001
Expiratory volume in 1 s <70% (n = 240)	59 (76.6)	59 (64.8)	40 (76.9)	20 (50.0)	.001
Forced vital capacity <70% (n = 230)	62 (80.5)	65 (71.4)	41 (78.8)	19 (47.5)	<.001
Diffusing capacity of lung for carbon monoxide corrected <70% (n = 146)	14 (18.2)	22 (24.2)	14 (26.9)	5 (12.5)	.02
Relapse (n = 243)	7 (9.1)	49 (53.8)	30 (57.7)	28 (70.0)	<.001
Remission (n = 241)	2 (2.6)	12 (13.2)	20 (38.5)	6 (15.0)	<.001

Abbreviations: ANA, antinuclear antibody; CK, creatine kinase; EJ, glycine-ARN-t-synthetase; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; Jo1, histidyl-ARN-t- synthetase; MDA5, melanoma differentiation-associated protein 5; Mi2, complex nucleosome remodeling histone deacetylase; MRC5, Medical Research Council 5-point scale (scale of 0 to 5 with lower numbers indicating more weakness); MSA, myositis-specific antibodies; NXP2, nuclear matrix protein-2; PL7, threonine-ARN-t-synthetase; PL12, alanine-ARN-t-synthetase; RNP, ribonucleoprotein; SAE1, SUMO-activating enzyme subunit SAE1; SAE2, SUMO-activating enzyme subunit SAE2; SRP, signal recognition particle; SSA/Ro52, anti-cytoplasmic ribonucleoprotein of 52 kDa; SSA/Ro60, anti-cytoplasmic ribonucleoprotein of 60 kDa; SSB, Sjögren syndrome type B; SUMO, small ubiquitin-like modifier; TIF1γ, transcription intermediary factor-1γ (p155/140).

SI conversion factor: To convert CK to microkatals per liter, multiply by 0.0167.

[a] Global *P* value.

[b] Other is defined as Asian, South American, other islands, or mixed individuals (ie, mother is white and father is African).

[c] Most-characterizing variables.

P = .009) and distal muscles with finger flexors (MRC5 of 5: 59 [64.8%]; 95% CI, 54.1%-74.5%; *P* = .004) did not show weakness. A high CK level was noted (>2300 U/L and ≤7000 U/L: 30 patients [33.0%]; 95% CI, 23.5%-43.6%; *P* = .004; ≥7000 U/L: 28 [30.8%]; 95% CI, 21.5%-41.3%; *P* = .03). Assessment of muscle pathologic features revealed a high frequency of necrotic

fibers (75 patients [82.4%]; 95% CI, 73.0%-89.6%; $P = .002$), and muscle inflammation was the lowest compared with the other clusters (57 [62.6%]; 95% CI, 51.9%-72.6%; $P < .001$). Anti-signal recognition particle (SRP) antibodies (23 patients [25.3%]; 95% CI, 16.7%-35.5%; $P < .001$, which represents 95.8% of anti-SRP–positive patients) and anti-Ku antibodies (5 [5.5%]; 95% CI, 1.8%-12.4%; $P = .005$) were characteristic. By positioning these variables, cluster 2 mainly involved IMNM (53 patients [58.2%]; 95% CI, 47.4%-68.5%; $P < .001$) and, less frequently, PM in recent diagnostic criteria (21 [23.1%]; 95% CI, 14.9%-33.1%; $P < .001$). In cluster 2, we also found almost all anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies (20 patients [21.9%]; 95% CI, 18.4%-40.6%; $P < .001$, which represents 95.2% of anti-HMGCR–positive patients).

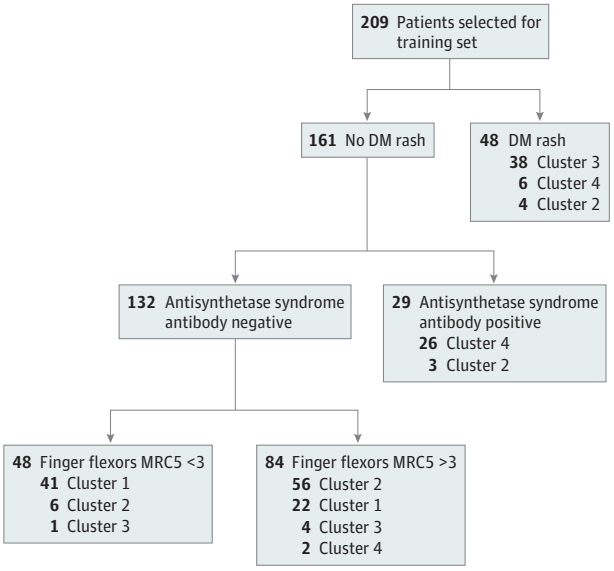
The third cluster included 52 of 260 patients (20.0%) and was composed of patients 40 years or younger at diagnosis (19 of 52 patients [36.5%]; 95% CI, 23.6%-51.0%; $P = .02$). They harbored skin lesion criteria (52 patients [100%]; 95% CI, 93.1%-100%; $P < .001$), predominantly DM rash (46 [88.4%]; 95% CI, 76.6%-95.6%; $P < .001$), heliotrope rash (39 [75%]; 95% CI, 61.0%-85.9%; $P < .001$), shawl sign (42 [80.8%]; 95% CI, 67.5%-90.4%; $P < .001$), limb edema (18 [34.6%]; 95% CI, 21.9%-49.1%; $P < .001$), skin ulcers (9 [17.3%]; 95% CI, 8.2%-30.3%; $P < .001$), alopecia (10 [19.2%]; 95% CI, 9.6%-32.5%; $P < .001$), calcinosis (5 [9.6%]; 95% CI, 3.2%-21.0%; $P = .001$), and panniculitis (4 [7.7%]; 95% CI, 2.1%-18.5%; $P = .001$). Patients in cluster 3 had severe proximal muscle weakness, mostly affecting the deltoids (MRC5 ≤ 3: 29 patients [55.8%]; 95% CI, 41.3%-69.5%; $P = .005$). In addition, quadricep weakness was infrequent (MRC5 of 4: 27 patients [51.9%]; 95% CI, 37.6%-65.9%; $P < .001$). There was less distal muscle weakness, mainly with the finger flexors (MRC5 of 5: 39 patients [75.0%]; 95% CI, 61.0%-85.9%; $P < .001$). The muscle pathologic analysis demonstrated perifascicular atrophy (29 patients [55.8%]; 95% CI, 41.3%-69.5%; $P < .001$) and inflammation with perivascular infiltrates (35 [67.3%]; 95% CI, 52.9%-79.7%; $P < .001$) but rarely the presence of necrotic fibers (30 [57.7%]; 95% CI, 43.2%-71.3%; $P < .001$) or invaded fibers (9 [17.3%]; 95% CI, 8.2%-30.3%; $P = .005$). Anti-complex nucleosome remodeling histone deacetylase (Mi2) antibodies were mainly observed in cluster 3 (10 patients [19.2%]; 95% CI, 9.6%-32.5%; $P < .001$, which represents 83.3% of anti-Mi2–positive cases) as were antinuclear antibodies (39 [75.0%]; 95% CI, 61.0%-85.9%; $P = .002$). In addition, the majority of cancers were observed in this cluster (11 patients [21.2%]; 95% CI, 11.0%-34.7%; $P = .02$). By positioning these variables, cluster 3 regrouped mainly patients who had DM (43 patients [82.7%]; 95% CI, 69.7%-91.8%; $P < .001$). Anti-melanoma differentiation-associated protein 5 (MDA5) (3 patients [5.8%]; 95% CI, 1.7%-21.9%; $P = .02$) and anti-transcription intermediary factor-1γ (TiF1γ) antibody levels were also specific (2 [3.8%]; 95% CI, 0.7%-18.7%; $P = .04$). More long-term clinical remissions were observed in this cluster (20 patients [38.5%]; 95% CI, 28.2%-57.8%; $P < .001$). Skin lesion criteria, such as DM rash (including Gottron papules), heliotrope rash, and shawl signs, as well as perifascicular atrophy and the presence of anti-Mi2 antibodies, were the most characterizing variables in cluster 3.

The fourth cluster included 40 of 260 patients [15.4%] characterized by patients who were of African origin (9 of 40 [22.5%]; 95% CI, 10.8%-38.4%; $P = .005$) and 40 years or younger at diagnosis (15 [37.5%]; 95% CI, 22.7%-54.2%; $P = .03$). Cluster 4 patients presented with skin lesion criteria (32 [80.0]%; 95% CI, 64.3%-90.9%; $P < .001$), and most had mechanic hands (22 [55.0%]; 95% CI, 38.5%-70.7%; $P < .001$). Normal or subnormal muscle strength was frequently observed in proximal muscles: deltoids (MRC5 of 5: 22 patients [55.0%]; 95% CI, 38.5%-70.7%; $P < .001$), psoas (MRC5 of 4: 19 [47.5%]; 95% CI, 31.5%-63.9%; $P = .03$), and quadriceps (MRC5 of 5: 24 [60.0%]; 95% CI, 43.3%-75.1%; $P < .001$). Axial deficit (ie, neck flexors) (MRC5 of 5; 17 patients [42.5%]; 95% CI, 27.0%-59.1%; $P = .001$) and distal deficit (ie, finger flexors) (31 [77.5%]; 95% CI, 61.5%-89.1%; $P < .001$) were frequently normal. The CK levels were highly elevated (≥7000 U/L: 15 patients [37.5%]; 95% CI, 22.7%-54.2%; $P = .02$). Perivascular infiltrates were frequently observed (21 patients [52.5%]; 95% CI, 36.1%-68.5%; $P < .001$). Cluster 4 patients had a high frequency of MSA with a group of antisynthetase antibodies (35 patients [87.5%]; 95% CI, 73.2%-95.8%; $P < .001$), with the presence of anti-histidyl-ARN-t-synthetase (Jo1) (31 [77.5%]; 95% CI, 61.5%-89.2%; $P < .001$; 100% of anti-Jo1–positive cases were present in this cluster). Anti-cytoplasmic ribonucleoprotein of 52 kDa (SSA/Ro52) (31 patients [77.5%]; 95% CI, 61.5%-89.1%; $P < .001$) and anti-cytoplasmic ribonucleoprotein of 60 kDa (SSA/Ro60) (14 [35.0%]; 95% CI, 20.6%-51.7%; $P < .001$) antibodies were also frequently observed. All patients presented with lung-specific involvement (40 [100%]; 95% CI, 91.2%-100%; $P < .001$). Rheumatologic disorders, such as arthralgia and arthritis, were frequently observed (36 patients [90.0%]; 95% CI, 76.3%-97.2%; $P < .001$), as was Raynaud phenomenon (17 [42.5%]; 95% CI, 27.0%-59.1%; $P = .02$). Cancers were very rare (1 patient [2.5%]; 95% CI, 0.1%-13.1%; $P = .01$). By positioning the variables using the historical classification, cluster 4 was composed mainly of patients with PM (38 [95%]; 95% CI, 83.1%-99.4%; $P < .001$) and rarely of patients with DM (2 [5.0%]; 95% CI, 0.6%-16.9%; $P < .001$). All patients with DM in cluster 4 were anti-MDA5 antibody positive. With use of MSA, cluster 4 was mainly composed of patients with antisynthetase syndrome (36 [90%]; 95% CI, 76.3-97.2; $P < .001$). Anti-threonine-ARN-t-synthetase (PL7) antibodies were distinguished in cluster 4 (3 patients [7.5%]; 95% CI, 1.5%-20.4%; $P = .02$). Diffuse interstitial lung disease was frequently observed (34 patients [85.0%]; 95% CI, 70.1%-94.3%; $P < .001$). Many relapses were observed (28 patients [70.0%]; 95% CI, 55.1%-84.9%; $P < .001$). The presence of antisynthetase antibodies (35 patients 87.5%) with the presence of anti-Jo1 and mechanic hands, characterized cluster 4.

Prediction of Clusters With Classification and Regression Tree

The best tree was obtained by removing variables related to muscle biopsy (eTable 5 and eFigures 4 and 5 in the Supplement), with 78.4% correct estimation using only the following 3 variables: DM rash (including Gottron papules), antisynthetase syndrome antibodies, and finger flexor scores of 3 or less (**Figure 2**). The classification quality of the tree was appreciated on the basis of all classification criteria, with an overall sensitivity of 77.0% (95% CI, 0.7%-0.8%) and a specificity of 92.0% (95% CI, 0.9%-0.9%).

Figure 2. Pruned Model of Prediction Without Histology Criteria



A pruned model was built (ie, by cutting terminal branches, a number of smaller and less complex trees was derived from the maximal previous tree) (information on the tree is given in the Statistical Analysis subsection of the Methods section). Dermatomyositis (DM) rash includes Gottron papules, periungual erythema, purplish rash, holster sign, and eruption on the dorsal hands. MRC5 indicates Medical Research Council 5-point scale (scale of 0 to 5 with lower numbers indicating more weakness).

External Validation

An independent set of patients (n = 50) in the myositis database, taken from different centers of the French myositis network, were used for external validation of our model. These patients fell into the 4 previously described clusters; the agreement between the 2 classification runs was excellent (Cohen κ light, 0.83; 95% CI, 0.65-0.96).

Discussion

This study identified 4 clusters emerging from unsupervised analysis. Each group corresponded to well-known entities, such as DM, IBM, IMNM, and antisynthetase syndrome. No unknown entity was revealed. The classification aggregated patients into subgroups based on epidemiologic, clinical, biological, serologic, and morphologic data. The decisional algorithm showed that MSA played a key role in estimating the connection to a cluster, whereas the pathologic data were dispensable.

To our knowledge, no study of a large group of patients with IIM seeking to establish subgroups without a priori knowledge has been performed. Of note, patients with IBM were also included, even if they could have been considered as a separate entity (based on degenerative characteristics).[7,18,19] They belonged to IIM and may have shared common features with patients with PM.[20] On the basis of the historical definition, patients with PM were present in the 4 clusters but mainly in clusters 2 (IMNM) and 4 (antisynthetase syndrome). This finding indicates that patients with PM do not represent a subgroup of patients and use of this term should probably be discontinued. Although the 4 clusters identified were associated with well-known entities, we identified new characteristics. The phenotypes of patients in cluster 1 matched with IBM[21-23] with regard to sociodemographic features (male, white, and older age at diagnosis), severe limb involvement (finger flexors and quadriceps), and typical histologic features (vacuolated fibers and mitochondrial abnormalities). For cluster 2, the pathologic characteristics of muscle (the absence of inflammation, with mainly necrosis) and the serologic markers (anti-SRP and anti-HMGCR antibodies) are associated with the definition of IMNM.[7] As previously reported,[24,25] those patients had lower limb involvement (psoas [MRC5 ≤ 3] whereas there was no involvement in the quadriceps) that was more severe than for patients in the other 3 clusters. Patients in cluster 3, corresponding to DM (based on the skin change[7]), had more severe involvement of the upper limbs (deltoids [MRC5 ≤ 3]). Finally, patients in cluster 4, corresponding to antisynthetase syndrome, appeared to be a group distinct from those with DM, although antisynthetase syndrome was still frequently considered to be an entity overlapping with DM or PM[10-12] based on clinical criteria (Gottron papules and mechanic hands) or pathologic criteria (perifascicular atrophy). Antisynthetase syndrome was the least severe disease for muscle deficits, whereas CK levels were the most elevated with IMNM.

Our study was complementary to the work of Lundberg et al[26] that aimed to respond to the question, "Does this patient suffer from a myositis?" whereas we aimed to stress the question, "What kind of myositis does the patient have?" American College of Rheumatology/European League Against Rheumatism diagnosis criteria defined a novel probability-score model to diagnose patients with IIM from among a group of patients with myositis and without myositis. If they also aimed to classify the major subgroups of patients with IIM using a classification tree approach, they acknowledged a limited number of IMNM cases in their study,[27] which explains why they only predicted 3 subgroups of IIMs: DM (including juvenile and amyopathic subgroups), PM, and IBM. Our study completed the American College of Rheumatology/European League Against Rheumatism classification criteria by showing the presence of 4 entities comprising the IIM group. We did not define diagnosis criteria. The decisional algorithm was used to highlight the most relevant variables estimating the appurtenance to a subgroup but was not designed for clinical practice. We recommend the use of the established diagnosis criteria for these 4 IIM subgroups.[9,23,27,28] The algorithm showed that MSA were crucial for IIM classification and were probably more relevant than morphologic data in a large number of cases (eFigure 5 in the Supplement).

We noted that MSA known to be associated with IIM subgroups[13,15,29] fell into the corresponding clusters. This emphasizes that muscle biopsy may no longer be necessary for diagnosis of IIM in patients with MSA and corresponding phenotypes. Dermatologists and pneumologists already do not consistently perform a muscle biopsy when the clinical phenotype and MSA are clinical characteristics. In addition, the latest definition of IMNM showed that muscle biopsy is no longer required to diagnose IMNM in the presence of either anti-

SRP or anti-HMGCR antibodies.[23] For all situations with nonevocative phenotypes or the absence of MSA, muscle biopsy analysis remains warranted. Together, those data also suggest that IIM subgroup diagnosis criteria could be refined using MSA as a key element (eg, for DM diagnosis criteria).

Limitations

Although the external validation confirmed the classification in 4 subgroups among IIM, the number of patients included remains small (n = 50). Moreover, the classification was built with only 5 MSA (those tested in all patients) and needed to be amended and made accurate with a large collection of the new MSA, notably for the seronegative patients. The algorithm created with the classification tree cannot be applied to patients without myositis. It remains an epidemiologic tool in intrasyndromic patients to identify the best predictors of the subgroups. The prediction rates of the subgroups did not reach 100% but an optimal and parsimonious model with minimal elements was presented, taking in account the best prediction rates and reduction of overlapping between subgroups.

Conclusions

This study highlighted the characteristics of IIM subgroups, and the classification and regression trees method showed the variables to predict the adjoining group but did not define diagnostic criteria. Finally, these findings suggest the association of this new classification with prognosis and new therapeutic approaches in IIM warrants further study.

ARTICLE INFORMATION

Accepted for Publication: July 8, 2018.

Published Online: September 10, 2018. doi:10.1001/jamaneurol.2018.2598

Author Affiliations: Centre de Recherche en Myologie, Unité Mixte de Recherche Scientifique 974, Université Pierre et Marie Curie, Institut National de la Santé et de la Recherche Médicale, Paris, France (Mariampillai, Amelin, Allenbach, Benveniste); Département de Médecine Interne et Immunologie Clinique, Centre de Référence Maladies Neuro-Musculaires, Assistance Publique–Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, DHUi2B, Paris, France (Mariampillai, Allenbach, Benveniste); Département de Biostatistiques, Santé Publique et Information Médicale, Assistance Publique–Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, Paris, France (Granger); Institut Pierre Louis d'Epidémiologie et de Santé Publique, Université Pierre et Marie Curie–Paris 6, Sorbonne Universités, Groupe de Recherche Clinique–08, Epidémiologie et Evaluation des Maladies Ostéoarticulaires Inflammatoires et Systémiques, Paris, France (Granger); Sorbonne Universités, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Université Pierre et Marie Curie–Paris 6, Unité Mixte de Recherche Scientifique 1136, Paris, France (Guiguet); Service de Médecine Interne, Centre Hospitalier Universitaire, Lille, France (Hachulla); Service de Médecine Interne, Hôpital Belle-Isle, Metz, France (Maurier); Département de Physiologie, Centre Hospitalier Universitaire de Strasbourg, Strasbourg, France (Meyer); Service de Médecine Interne, Centre Hospitalier Universitaire Hôtel Dieu De France, Beirut, Lebanon (Tohmé); Laboratoire Immunochimie, Assistance Publique–Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, Paris, France (Charuel, Musset).

Author Contributions: Drs Mariampillai and Benveniste had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Mariampillai, Granger, Guiguet, Allenbach, Benveniste.
Acquisition, analysis, or interpretation of data: Mariampillai, Granger, Amelin, Guiguet, Hachulla, Maurier, Meyer, Tohmé, Charuel, Musset, Allenbach, Benveniste.
Drafting of the manuscript: Mariampillai, Granger, Allenbach, Benveniste.
Critical revision of the manuscript for important intellectual content: Mariampillai, Granger, Amelin, Guiguet, Hachulla, Maurier, Meyer, Tohmé, Charuel, Musset, Allenbach, Benveniste.
Statistical analysis: Mariampillai, Granger.
Obtained funding: Benveniste.
Administrative, technical, or material support: Mariampillai, Amelin, Hachulla, Maurier, Meyer, Tohmé, Charuel, Musset, Benveniste.
Supervision: Granger, Guiguet, Allenbach, Benveniste.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by Association française contre les myopathies (Dr Mariampillai) and CSL Behring (partly funded the electronic case report forms development).

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The clinicians of the Neuromuscular Diseases Reference Centre of Paris, including Serge Herson, MD, PUPH, PhD; Bruno Eymard; MD, PUPH, PhD; Tanya Stojkovic, MD; Anthony Behin, MD; Aude Rigolet, MD; Anne Simon, MD; Baptiste Hervier, MD, PhD; Gaelle Leroux, MD; and Nicolas Champtiaux, MD, performed record keeping of patient medical files and answered Dr Mariampillai's questions. Patrice Cacoub, MD, PUPH, PhD, of the Sorbonne Universités, Université Pierre et Marie Curie–Paris 6, and Andrew Mammen, MD, PUPH, PhD, from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health; and Johns Hopkins University School of Medicine, reviewed the article and provided advice. No financial compensation was provided to these individuals.

REFERENCES

1. Meyer A, Meyer N, Schaeffer M, Gottenberg JE, Geny B, Sibilia J. Incidence and prevalence of inflammatory myopathies: a systematic review. *Rheumatology (Oxford)*. 2015;54(1):50-63. doi:10.1093/rheumatology/keu289

2. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med*. 1975;292(7):344-347. doi:10.1056/NEJM197502132920706

3. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med*. 1975;292(8):403-407. doi:10.1056/NEJM197502202920807

4. van der Meulen MF, Bronner IM, Hoogendijk JE, et al. Polymyositis: an overdiagnosed entity. *Neurology*. 2003;61(3):316-321. doi:10.1212/WNL.61.3.316

5. Amato AA, Griggs RC. Unicorns, dragons, polymyositis, and other mythological beasts. *Neurology*. 2003;61(3):288-289. doi:10.1212/WNL.61.3.288

6. Griggs RC, Askanas V, DiMauro S, et al. Inclusion body myositis and myopathies. *Ann Neurol*. 1995;38(5):705-713. doi:10.1002/ana.410380504

7. Hoogendijk JE, Amato AA, Lecky BR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10-12 October 2003, Naarden, the Netherlands. *Neuromuscul Disord*. 2004;14(5):337-345. doi:10.1016/j.nmd.2004.02.006

8. Matsushita T, Hasegawa M, Fujimoto M, et al. Clinical evaluation of anti-aminoacyl tRNA synthetase antibodies in Japanese patients with dermatomyositis. *J Rheumatol*. 2007;34(5):1012-1018.

9. Hamaguchi Y, Fujimoto M, Matsushita T, et al. Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome. *PLoS One*. 2013;8(4):e60442. doi:10.1371/journal.pone.0060442

10. Marguerie C, Bunn CC, Beynon HL, et al. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. *Q J Med*. 1990;77(282):1019-1038. doi:10.1093/qjmed/77.1.1019

11. Troyanov Y, Targoff IN, Tremblay JL, Goulet JR, Raymond Y, Senécal JL. Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies: analysis of 100 French Canadian patients. *Medicine (Baltimore)*. 2005;84(4):231-249. doi:10.1097/01.md.0000173991.74008.b0

12. Love LA, Leff RL, Fraser DD, et al. A new approach to the classification of idiopathic

inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. *Medicine (Baltimore)*. 1991;70(6):360-374. doi:10.1097/00005792-199111000-00002

13. Mammen AL. Autoimmune myopathies: autoantibodies, phenotypes and pathogenesis. *Nat Rev Neurol*. 2011;7(6):343-354. doi:10.1038/nrneurol.2011.63

14. Allenbach Y, Benveniste O. Usefulness of autoantibodies for the diagnosis of autoimmune myopathies. [in French]. *Rev Neurol (Paris)*. 2013;169(8-9):656-662. doi:10.1016/j.neurol.2013.01.622

15. Benveniste O, Stenzel W, Allenbach Y. Advances in serological diagnostics of inflammatory myopathies. *Curr Opin Neurol*. 2016;29(5):662-673. doi:10.1097/WCO.0000000000000376

16. Benveniste O, Drouot L, Jouen F, et al. Correlation of anti-signal recognition particle autoantibody levels with creatine kinase activity in patients with necrotizing myopathy. *Arthritis Rheum*. 2011;63(7):1961-1971. doi:10.1002/art.30344

17. Drouot L, Allenbach Y, Jouen F, et al; French Myositis Network [CN]. Exploring necrotizing autoimmune myopathies with a novel immunoassay for anti-3-hydroxy-3-methyl-glutaryl-CoA reductase autoantibodies. *Arthritis Res Ther*. 2014;16(1):R39. doi:10.1186/ar4468

18. Askanas V, Engel WK. Inclusion-body myositis, a multifactorial muscle disease associated with aging: current concepts of pathogenesis. *Curr Opin Rheumatol*. 2007;19(6):550-559. doi:10.1097/BOR.0b013e3282efdc7c

19. Askanas V, Engel WK, Nogalska A. Sporadic inclusion-body myositis: a degenerative muscle disease associated with aging, impaired muscle protein homeostasis and abnormal mitophagy. *Biochim Biophys Acta*. 2015;1852(4):633-643. doi:10.1016/j.bbadis.2014.09.005

20. Bronner IM, Linssen WH, van der Meulen MF, Hoogendijk JE, de Visser M. Polymyositis: an ongoing discussion about a disease entity. *Arch Neurol*. 2004;61(1):132-135. doi:10.1001/archneur.61.1.132

21. Benveniste O, Guiguet M, Freebody J, et al. Long-term observational study of sporadic inclusion body myositis. *Brain*. 2011;134(pt 11):3176-3184. doi:10.1093/brain/awr213

22. Allenbach Y, Benveniste O, Decostre V, et al. Quadriceps strength is a sensitive marker of disease progression in sporadic inclusion body myositis. *Neuromuscul Disord*. 2012;22(11):980-986. doi:10.1016/j.nmd.2012.05.004

23. Lloyd TE, Mammen AL, Amato AA, Weiss MD, Needham M, Greenberg SA. Evaluation and construction of diagnostic criteria for inclusion body myositis. *Neurology*. 2014;83(5):426-433. doi:10.1212/WNL.0000000000000642

24. Pinal-Fernandez I, Parks C, Werner JL, et al. Longitudinal course of disease in a large cohort of myositis patients With autoantibodies recognizing the signal recognition particle. *Arthritis Care Res (Hoboken)*. 2017;69(2):263-270. doi:10.1002/acr.22920

25. Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. *Arthritis Rheum*. 2011;63(3):713-721. doi:10.1002/art.30156

26. Lundberg IE, Tjärnlund A, Bottai M, et al; International Myositis Classification Criteria Project Consortium, the Euromyositis Register, and the Juvenile Dermatomyositis Cohort Biomarker Study and Repository (UK and Ireland). 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Arthritis Rheumatol*. 2017;69(12):2271-2282. doi:10.1002/art.40320

27. Allenbach Y, Mammen AL, Benveniste O, Stenzel W; Immune-Mediated Necrotizing Myopathies Working Group. 224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. *Neuromuscul Disord*. 2018;28(1):87-99. doi:10.1016/j.nmd.2017.09.016

28. Bottai M, Tjärnlund A, Santoni G, et al; International Myositis Classification Criteria Project consortium, the Euromyositis register and the Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDRG) (UK and Ireland). EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups: a methodology report. *RMD Open*. 2017;3(2):e000507. doi:10.1136/rmdopen-2017-000507

29. Suzuki S, Uruha A, Suzuki N, Nishino I. Integrated Diagnosis Project for Inflammatory Myopathies: An association between autoantibodies and muscle pathology [published online May 4, 2017]. *Autoimmun Rev*. 2017;16(7):693-700. doi:10.1016/j.autrev.2017.05.003