



Workshop report

193rd ENMC International workshop
Pathology diagnosis of idiopathic inflammatory myopathies
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Jan L. De Bleeker^{a,*}, Ingrid E. Lundberg^b, Marianne de Visser^c,
for the ENMC Myositis Muscle Biopsy Study Group¹

^a Department of Neurology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium

^b Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, SE-171 76 Stockholm, Sweden

^c Department of Neurology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

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1. Introduction

The 193rd ENMC International Workshop brought together 21 researchers from nine countries: Belgium, Finland, France, Germany, The Netherlands, Spain, Sweden, United Kingdom, and United States of America. The group was joined by a patient representative from the Dutch working group of myositis patients. The participants discussed the idiopathic inflammatory myopathies (IIM), that comprise a number of different entities recognized on clinical, pathological and immunological/serological grounds. Consensus documents on clinical and pathological classification criteria have been issued following previous ENMC and MRC workshops, but there remains a strong need to revise and re-classify. The present workshop aimed, by combining the input from people with diverse background, to draft a set of muscle biopsy diagnostic features and criteria that will gain wide acceptance in the clinical and scientific communities involved in IIM diagnosis. The workshop aimed at identifying crucial variables in muscle biopsies and how these should be evaluated qualitatively and quantitatively in routine histopathological studies, leading to a consensus classification and scoring system to be employed in diagnostic laboratories reading IIM diagnostic muscle biopsies.

Traditionally, adult dermatomyositis (DM), juvenile dermatomyositis (JDM), polymyositis (PM) and sporadic

inclusion body myositis (IBM) have been the main subsets of the IIM [1–3]. The definition of the PM entity has been variable between centers, more particularly between rheumatologic and neurological clinicians and neuropathologists involved in the diagnosis and management of these patients. Recent studies have even cast doubt on the very existence of the PM entity, suggesting that most patients diagnosed with PM either have IBM or an overlap disease between myositis and an identifiable connective tissue disorder, often with an immunopathological profile more akin to DM [4,5].

Depending on the presenting symptoms and signs and local habits, patients suffering from IIM are cared for by rheumatologists or neurologists with special expertise in neuromuscular diseases. These two groups have based their diagnosis and classification on partly different criteria. Rheumatologists have long been using the Bohan and Peter criteria published in the early seventies, mainly for research purposes [6]. Neurologists have based their diagnosis to a far larger extent on muscle biopsy findings. This divergent practice has led some authors to suggest that “neurologists are from Mars and rheumatologists are from Venus” [7]. This different classification has hampered the comparison of clinical and basic research publications and the set-up of international multicenter studies including patients with different presentations of a probable spectrum of disease manifestations.

As research in the field has moved on in the past 10 years, it became clear that (1) the Bohan and Peter criteria, by not using strict muscle biopsy criteria, did not adequately deal with the rather common entity of IBM, and that usage of these criteria led to indiscriminate inclusion of probably different subsets of patients in

* Corresponding author. Tel.: +32 9 3324544; fax: +32 9 3324971.

E-mail address: jan.debleecker@ugent.be (J.L. De Bleecker).

¹ Members of the ENMC Myositis Muscle Biopsy Study Group are listed at the end of the report.

clinical trials [8]; (2) strictly pathologically defined PM represents a rare entity, (3) many patients have mild necrotizing myopathy as the sole biopsy manifestation of their illness; (4) some biopsies lack inflammatory cells but exhibit other changes that indicate a pathology secondary to inflammation, e.g., major histocompatibility class I (MHC-I) expression on muscle fibers; (5) the increased recognition of myositis specific antibodies allows in at least some instances to define certain clinico-pathological subsets of IIM patients [9]. Conversely, the antibody profile may identify a specific disease causing agent, such as in statin induced necrotizing autoimmune myopathy (NAM) [10].

Although consensus documents on classification criteria had been issued on previous ENMC [11] and MRC [12] workshops, there remains a need to revise and re-define the pathological criteria and eventually confront them with the evolving data from the other fields, e.g., serology. By bringing together researchers from different backgrounds, i.e., neurologists, rheumatologists, immunologists and pathologists, the workshop aimed to combine this input in order to draft a set of diagnostic features and criteria that will gain wide acceptance across sub-specialties. Because a recent ENMC workshop dealt with IBM, the focus was on the other IIM. State-of-the-art lectures covering recent developments, a pathological discussion session around the microscope and round-table discussions on methodological aspects were held.

2. Classification of the inflammatory myopathies

Jan De Bleecker opened the workshop by presenting an overview of the classical pathological subdivision of inflammatory myopathies and the basic immuno pathological features as they have been outlined in studies dating from the mid-eighties to just recent. DM is characterized by a complement-mediated endotheliopathy. The immune effector mechanism in PM and IBM is different and is characterized by cell-mediated cytotoxicity with infiltration of MHC-I expressing nonnecrotic muscle fibers by CD8+ cytotoxic T cells and macrophages. Recent advances in IIM immunopathology, which includes knowledge of the pro-inflammatory factors [13] and their upstream regulators [14], have further revealed the complexity of these autoimmune diseases. In addition, the entity of NAM has been recognized. Unfortunately, many patients do not fit the subcategories and are reported as non-specific or overlap myositis. Pitfalls such as inflammatory responses in muscular dystrophy and the expression of MHC-I in non-inflammatory myopathies was mentioned. It was concluded that the strict use of pathological criteria has significantly advanced our understanding of these diseases, allowed the clear delineation of IBM and increased comparability of studies from various centres. As a negative consequence, it was felt that rigid

adherence to pathological criteria (1) caused too many patient biopsies to be classified as unspecific IIM and their exclusion from further basic research studies; (2) lead to delayed recognition of some entities such as NAM, and (3) probably resulted in publication bias. It was suggested that this might be avoided by analysis of individual muscle biopsy abnormalities (cellular infiltrates, vascular changes, muscle fiber abnormalities, etc.) instead of the pattern recognition that is mostly used in muscle pathology, and that these individual abnormalities could then be introduced in statistical analysis models confronting them with clinical and serological parameters.

Marianne de Visser elaborated on the over-diagnosis of PM. If the ENMC 2004 classification criteria for definite PM are applied, PM is rare and most IIM patients fall into the unspecific myositis group. A third of these patients developed an identifiable connective tissue disorder in the following years. Also, retrospective observations showed that more than half the patients initially diagnosed as typical PM on clinical and morphological grounds actually suffered from IBM, based on the evolving typical clinical picture of IBM, with or without occurrence of rimmed vacuoles on repeat muscle biopsy [4,15,16]. She also stressed that the focal nature of the inflammation in the IIM makes it important to choose the biopsy site wisely, for instance by MRI guidance.

Ingrid Lundberg discussed the International Myositis Classification Criteria Project (IMCCP), a retrospective, multidisciplinary and multicenter project started in 2004 with the aim to develop new criteria based on patient data. Information has been collected from more than 900 patients, and 600 comparators (clinical and myopathological variables) via a web-based questionnaire. Disease controls, such as metabolic diseases and dysferlinopathies, have been included as reliably distinguishing IIM from other diseases is a top priority of the project. Further aims include the development of classification criteria that separate major subgroups of IIM with high specificity and sensitivity, and to validate the reliability of the new classification criteria in a new set of patients. Two models have been developed, one probability score and one classification tree. Preliminary data were presented, indicating superior performance of easy-to-access measurements and symptoms compared to existing criteria. Further analysis and plans for external validation are in progress.

Werner Stenzel discussed the more rare types of IIM. (1) Neuromuscular sarcoidosis may affect the skeletal muscle producing granulomatous myositis and also the peripheral nervous system leading to granulomatous neuritis, and is potentially treatable by immune modulators or immunosuppressants. The molecular mechanism underlying the immune attack of the skeletal muscle remains poorly understood. Alternative activation of M2-subtype macrophages was shown [17]. (2)

Anti-Synthetase-Syndrome (ASS) associated NAM constitutes an important subgroup of patients. NAM should probably be considered a (clinico) morphological syndrome rather than a circumscribed disease such as DM or IBM. Underlying diseases comprise paraneoplastic necrotizing myopathy, anti-signal recognition particle (SRP)- and hydroxyl-3-methylgluaryl-coenzyme A reductase (HMGCR)-autoantibody associated myopathy [18], and myopathy associated with ASS. Aiming to delineate subgroups of NAM that can be assigned to a specific disease on morphological grounds, his group identified a number of morphological hallmarks of ASS-associated necrotizing myopathy. These comprise predominant myofiber necrosis and myophagocytosis and focal and diffuse lymphocytic infiltrates of the peri- and endomysium. This infiltrate is composed mainly of CD8 and CD4 cells but very few B cells, and there is no invasion of nonnecrotic myofibers by lymphocytes. (3) Shulman Syndrome or eosinophilic (myo) fasciitis displays diffuse fasciitis, perimyositis, blood eosinophilia and hypergammaglobinaemia. In suspected cases it is important to obtain a biopsy from the fascia-muscle interface. Eosinophils are found in only one third of biopsies, but large numbers of macrophages and CD8+ T cells and rare B cells can be detected. (4) Macrophagic myofasciitis has been linked to vaccines containing aluminum hydroxide. Inflammatory lesions are focal and contain round cells located in the perifascicular space. Macrophages and numerous CD8+ T cells are present. CD20+ B cells may occur in clusters. Tissue necrosis or giant cells are typically not detected. (5) Pipestem-capillaries in necrotizing myopathy have been reported as a feature of a distinct type of myopathy. Data support the existence of microangiopathy with pipestem capillaries as a characteristic and distinct histopathological pattern, and indicate that it occurs in the context of a broader variety of muscular disorders than initially suspected. It was shown that the pipestem capillary associated decrease in fiber size is at least in part a result of hypoxic changes [19].

Alan Pestronk presented his alternative classification scheme based on muscle biopsy features, as it is increasingly difficult to classify acquired immune and IIM into the traditional groups DM, PM and IBM. IIM without lymphocytic inflammation fit poorly into any category. DM syndromes comprise at least two clinically and pathologically different IIM. Myositis-specific antibody (e.g. Jo-1) related IIM can include both DM and PM syndromes. Muscle in IBM-like patients often has no inclusion bodies. Myopathologic classification of IIM can provide useful diagnostic specificity. Myopathologic features used in defining IIM types include: (a) muscle fiber changes; (b) immune abnormalities (cellular, humoral); and (c) tissue types involved (connective tissue, vessels, muscle fibers). Some features, like B cell foci and alkaline phosphatase positive capillaries or perimysium, are associated generally with treatable IIM. Myopathologic subtypes of IIM include:

(1) *Immune myopathies with perimysial pathology* (IMPP) have fragmented perimysial connective tissue that contains histiocytic cellularity. Jo-1 antibody associated IIM often have IMPP pathology; (2) *Myovasculopathies* have damaged perimysial or endomysial vessels. Muscle damage may be related to ischemia rather than direct immune attack. Childhood DM syndromes are typically myovasculopathies; (3) *Immune polymyopathies* are active myopathies with necrosis but little inflammation. Serum CK is often very high. Myopathies with SRP antibodies are one example; (4) *Immune myopathies with endomysial pathology* (IM-EP) often have C_{5b-9} complement deposition on endomysial connective tissue, and mononuclear cell foci. Brachio-cervical inflammatory myopathies illustrate IM-EP; (5) *Histiocytic inflammatory myopathies* have granulomas and focal invasion of muscle fibers by mononuclear cells. They include sarcoid myopathy; (6) *Inflammatory myopathies with vacuoles, aggregates and mitochondrial pathology* (IM-VAMP) in muscle fibers often also have diffusely upregulated MHC-I, CD4 and CD8 cell foci and NT5C1A antibodies. IBM is a subgroup. IM-VAMP are poorly treatable [20]. Myopathologic classification of IIM adds diagnostic and prognostic accuracy, and focuses diagnostic testing, treatment and therapeutic trials, and studies of pathogenic mechanisms.

3. Standardization and interpretation of muscle biopsies

Janice Holton and **Lucy Wedderburn** explained how the international scoring system for JDM came to shape [21]. The scoring tool breaks down into the description of four domains to which the myopathologic changes can be localized: muscle fibers, blood vessels, inflammation, and connective tissue. It was stressed that the approach was developed as an assessment tool to score severity of pathological change permitting clinical correlations rather than as a diagnostic tool. The necessity for large cohorts was emphasized: the juvenile DM tool was developed on the basis of 55 biopsies and that did not allow fullsub-typing of patients. The tool was developed for open muscle biopsies and in the future could be adapted to needle biopsies.

Inger Nennesmo shared the results of 16 DM and 26 PM patients aged 17–84 years being part of the SweMyoNet cohort. Purpose of the study was to describe the morphological changes in the initial muscle biopsy obtained from patients for the first time between January 2010 and October 2012. The diagnosis was based on Bohan and Peter diagnostic criteria. In both groups (PM and DM) there were 13 patients with definite DM or definite PM. Semi-open muscle biopsies mainly from the vastus lateralis using the conchotome were analyzed. The pathological lesions looked for included presence of inflammatory cells, invasion of inflammatory cells in nonnecrotic fibers, MHC-I expression, perifascicular atrophy, necrotic/regenerating fibers and the presence of COX negative fibers. The microscopic findings were very

variable. Infiltrates of inflammatory cells were not present in all biopsies and if present they varied from just a few cells to large infiltrates. Necrotic fibers and regenerating fibers were more common in patients with PM than DM. Invasion of inflammatory cells in nonnecrotic fibers was only found in the PM group. MHC-I was expressed in most biopsies. In the groups of definite DM and definite PM all patients expressed MHC-I. Inflammatory cells were found in all but one DM patient. In about half of the definite DM patients perifascicular atrophy was present. According to these preliminary results the initial pathology in DM and PM is variable. Some patients have very scarce histopathological findings although clinical and other laboratory data support the diagnosis of an inflammatory myopathy whereas other patients have major changes with both inflammatory infiltrates and muscle fiber abnormalities. For diagnostic purposes, using muscle biopsy findings on their own will underestimate the frequency of DM and PM. Clinical features together with muscle biopsy findings are therefore important for making the correct diagnosis [22].

Hans Goebel presented a comprehensive overview of pathologic information that can be gained from electron microscopy [23]. Excluding IBM, undulating tubules or tubuloreticular structures/profiles in endothelial cells are a hallmark of the IIM. More rarely, cylindrical confronting cisternae are encountered. These ultrastructural abnormalities are derived from rough or smooth endoplasmic reticulum and may also be seen in fibroblasts, satellite cells and blood lymphocytes. Causally, they are related to possible viral infections and effects of interferons and may also be observed in lupus erythematosus and HIV infection. The fine structural pathology of capillaries may encompass degenerating, necrotic, absent or regenerating endothelial cells as well as the absence of entire capillaries, marked by basement membrane loops. Diagnostically valuable ultrastructural pathology may solely consist of identifying blood lymphocytes within structurally intact muscle fibers. A recent observation is the densely packed thin or actin-like filaments within myofiber nuclei, which are regularly seen in the ASS. The intranuclear filaments are of identical size and packing density, and can also be demonstrated by actin immunohistochemistry.

4. Differential tissue changes in inflammatory myopathies

Romain Gherardi summarized the vascular changes associated with IIM. The intramuscular vasculature branches off from the feeding arteries (epimysium) to the arcade arteries (perimysium), to the transverse and subsequently terminal arteries (endomysium). Each terminal artery feeds a muscle microvascular unit, i.e. a group of capillaries. Six to eight capillaries perfuse five muscle fibers. During muscle development, fiber size increases together with capillary density, while the numbers of satellite cells go down. In adult muscle,

muscle satellite cells increase with myofiber capillarization. The capillary destruction associated with DM is presumed to result from a self-antibody response against an endothelial antigen. Ischaemia/reperfusion-induced damage occurs in clusters, displays a distinct 6-by-6 loss pattern and is followed by MAC deposition [24].

Differentiating inflammatory myopathies from hereditary muscle disease is highly important. Given the similarity of the processes of necrosis and regeneration, **Dalia Dimitri** pointed to the peculiar characteristics of the inflammation in some muscular dystrophies [25]. For instance, in calpainopathies the infiltrates contain many eosinophils. Nevertheless, caution should always be taken to prevent misdiagnosis. In fascioscapulohumeral muscular dystrophy, endomysial CD8 + T cells surrounding muscle fibers mimics IBM inflammation. And although hereditary IBM is generally described to lack inflammation, endomysial inflammation has been observed in selected cases. A possible mechanism by which genetic defects lead to chronic muscle inflammation may be that continuous damage results in the exposure of antigens that otherwise remain hidden, which could lead to the formation auto-antibodies.

Eduard Gallardo described the inflammatory component in dysferlinopathies. One of the hallmarks of the muscle biopsy of these patients is the presence of endomysial and perivascular inflammation. Cell infiltrates are mainly composed of macrophages although CD8 + T cells are also observed. Interestingly, MHC-I is restricted to capillaries and necrotic fibers [26] and not on the surface of the muscle fiber as in PM/IBM/NAM. This finding is important because dysferlinopathies can be misdiagnosed as PM and analysis of MHC-I in the muscle biopsy can be of help for the differential diagnosis. In patients with a suspicion of PM in whom the expression of MHC-I in the muscle biopsy is negative, analysis of dysferlin expression through immunohistochemistry or western blot [27], would be recommended before a therapeutic strategy is initiated. In patients with a suspicion of PM in which the muscle biopsy is no longer available or before a muscle biopsy is performed, analysis of dysferlin expression in CD14+ peripheral blood monocytes can be of help.

5. Novel findings on auto-antibodies and immune regulators in the IIM

Myositis-specific auto-antibodies (MSA) are diagnostically and prognostically useful, as they often represent specific clinical subgroups. **Andrew Mammen** shared his views on the clinical relevance of auto-antibody typing in the IIM [28]. Anti-HMGCR antibodies, initially named anti-200/100 kD antibodies, are typically associated with NAM, and 67% of cases with this auto-antibody can be attributed to statin use [18]. The pathology includes capillary damage and MAC deposits

on muscle fibers. The anti-200/100 kD antibodies were found in 16 out of 26 sera diagnosed with NAM. Patients with anti-200/100 auto-antibodies have a typical clinical phenotype and partial or complete response to immunosuppressants. Biopsies show no MAC deposits, no rimmed vacuoles, and no perivascular inflammation. In contrast, anti-SRP antibodies are not IIM specific, but are equally found in systemic immune diseases.

Olivier Benveniste discussed his most recent findings regarding pathology, immunohistochemistry and T cell subsets in biopsies from patients with ASS and myopathy. 90% of patients had interstitial lung disease. Patients with Jo-1 auto-antibodies were scored on H&E, NADH, COX, ORO, PAS and immunostained section. Perifascicular necrosis was predominant and diffuse MHC-I staining was found in 90% of biopsies. Inflammation was largely perimysial and frequency of inflammatory cell subtypes was: CD68 > CD8 > CD4 > CD20 [29].

Statin-induced necrotizing myopathy was discussed by **Lisa Christopher-Stine**. The USAGE study (<http://www.statinusage.com/Pages/>) describing 10,000 persons on statins showed that 62% stopped with therapy due to side effects and 33% reported myalgias. SLC01B1 gene variants have been linked to genetic predisposition for statin myopathy, with homozygotes having 17 times more chance to develop myopathic symptoms [28]. This group elaborated on that sub-group of patients who continued to have symptoms despite statin withdrawal. Their biopsies showed immune mediated damage including diffuse MHC-I upregulation, and most patients were responsive to steroid treatment. They went onto detect auto-antibodies to HMGCR, the rate-limiting enzyme of cholesterol production. Prevalence of statin use in a cohort of anti-HMGCR antibody positive patients (92%) was significantly higher than in age matched IIM patients over the age of 50 including DM (25%), PM (36.8%) and IBM (33.3%). Furthermore, one of the strongest links between an autoimmune disease and HLA allele was demonstrated. NAM patients positive for HMGCR antibodies were overwhelmingly associated with DRB1*11:01 [30].

It has long been recognized that inflammatory disease is characterized by a disturbed cytokine balance, which is caused by down regulation of immunomodulatory and/or upregulation of pro-inflammatory cytokines. **Boel De Paepe** discussed the latter category, describing the possibilities of special stains for cytokines as a strategy for typing biopsies. Their potential for inflammatory myopathy identification, subtyping and prognosis were addressed. An overview of state of the art knowledge on muscle expression of different cytokine families was given, highlighting (1) the strong association of DM with type 1 interferon expression, (2) the general upregulation of many interleukins in inflammatory myopathy, which could develop as a prognostic biomarker for the success of immunosuppressive treatment, (3) the prominent

expression of the tumor necrosis factor family of cytokines, and (4) the abundant muscle expression of chemokines, with similar expression patterns in DM on the one hand and PM/IBM on the other hand. The chemokine patterns support the view that the Th1 immune response is the most active in each of the classical IIM [31]. The advantages and disadvantages of typing pro-inflammatory factors in muscle biopsies in contrast to serum samples were discussed.

6. Group evaluation of biopsies

The practical session was held at the pathology department of the Amsterdam Medical Centre and led by **Marianne de Visser** and **Anthony Amato**. Participants brought typical and less typical biopsies suspected to be IIM, from which it quickly became clear that there was strong agreement on the pathological hallmarks to be evaluated. There was a strong consensus regarding definitions of the various myositis-related tissue alterations. The evaluation of atypical muscle biopsies alerted the participants to the diversity of the diseases, and the difficulties that can be encountered in differentiating IIM from non-inflammatory muscle diseases associated with inflammation.

7. Consensus building through Delphi phase I

Although not pre-planned, the individual viewpoints of the participants on how a biopsy diagnostic workup of suspected IIM patients should be organized was polled. The answers of a brief list of questions were discussed, and under the experienced leadership of **Lucy Wedderburn** and **Janice Holton** a preliminary effort was made to build consensus through the nominal group technique, with 80% being the cut off for agreement to retain a given item within the consensus.

7.1. Biopsy material

Most participants agreed that muscle biopsy is mandatory for IIM diagnosis, with the exception of some cases of DM. The group was unanimous on the necessity for frozen skeletal muscle material. A small minority of participants wanted additional paraffin embedded tissue and material fixed for electron microscopy to be included for proper diagnosis.

7.2. Biopsy stains

The group was unanimous on the necessity of H&E, COX/SDH, and MHC-I staining. High scores were reached for trichrome, PAS, ATPases, NADH, MAC and CD8 and macrophage inflammatory cell markers. Many participants worried that doing only a limited set of stains with high yield in IIM may not sufficiently exclude other neuromuscular diseases, and suggested that

a basic panel of stains should be done in each biopsy anyway.

7.3. Biopsy scoring

Consensus was reached on dividing the pathological features into four domains, being (1) inflammatory, (2) vascular, (3) muscle fiber, and (4) connective tissue. It was generally felt that much more preparatory work was needed to use the nominal group technique or other decision making techniques to arrive at a robust and widely agreed upon scoring system.

8. Conclusions

After exchange of state-of-the-art knowledge regarding classical and alternative classification criteria, new developments, and a preview of possible methodological ways to arrive at a uniform and valid pathological classification and scoring system for IIM biopsies, the views of the participants were tested via a microscopy session and through a short open-answer list of questions. A contrast was noted between the largely unanimous ideas on the interpretation of the specimens under the microscope, and the difficulty of translating this apparent consensus into a workable tool that is widely accepted and applicable in the major medical specialties where IIM patients are diagnosed. Participants agreed unanimously to continue work on a standardized diagnostic work up and to reconvene in the near future.

9. Participants²

Anthony Amato, Brigham and Women's Hospital, Harvard Medical School, Boston, USA.

Olivier Benveniste, Hopital Pitié-Salpêtrière, Paris, France.

Lisa Christopher-Stine, Johns Hopkins University Hospital, Baltimore, USA.

Jan De Bleecker, Ghent University Hospital, Belgium.

Boel De Paepe, Ghent University Hospital, Belgium.

Marianne de Visser, Academic Medical Centre, Amsterdam, The Netherlands.

Mazen Dimachkie, Kansas University Medical Centre, Kansas City, USA.

Dalia Dimitri, Mondor Institute for Biomedical Research, Creteil, France.

Eduard Gallardo, Hospital de la Santa Creu i San Pau, Barcelona, Spain.

Romain Gherardi, Université Paris Est, Creteil, France.

Hans Hilmar Goebel, Mainz University Medical Centre, Mainz, Germany.

Patrick Gordon, King's College, London, United Kingdom.

Janice Holton, University College London, London, United Kingdom.

Ingrid E. Lundberg, Karolinska Institutet, Stockholm, Sweden.

Andrew Mammen, Johns Hopkins University, Baltimore, USA.

Inger Nennesmo, Huddinge University Hospital, Stockholm, Sweden.

Alan Pestronk, Washington University, St Louis, USA.

Joke Piron, representative of the Dutch patient organization for muscular diseases: Spierziekten Nederland, The Netherlands.

Werner Stenzel, Charité University, Berlin, Germany.

Bjarne Udd, Tampere University Hospital, Tampere, Finland.

Lucy Wedderburn, UCL Institute of Child Health, University College London, London, United Kingdom.

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² *ENMC Myositis Muscle Biopsy Study Group.

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