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272nd ENMC international workshop: 10 Years of progress - revision of the ENMC 2013 diagnostic criteria for inclusion body myositis and clinical trial readiness. 16–18 June 2023, Hoofddorp, The Netherlands

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ABSTRACT

Since the publication of the 2013 European Neuromuscular Center (ENMC) diagnostic criteria for Inclusion Body Myositis (IBM), several advances have been made regarding IBM epidemiology, pathogenesis, diagnostic tools, and clinical trial readiness. Novel diagnostic tools include muscle imaging techniques such as MRI and ultrasound, and serological testing for cytosolic 5′-nucleotidase-1A antibodies. The 272nd ENMC workshop aimed to develop new diagnostic criteria, discuss clinical outcome measures and clinical trial readiness. The workshop started with patient representatives highlighting several understudied symptoms and the urge for a timely diagnosis. This was followed by presentations from IBM experts highlighting the new developments in the field. This report is composed of two parts, the first part providing new diagnostic criteria on which consensus was achieved. The second part focuses on the use of outcome measures in clinical practice and clinical trials, highlighting current limitations and outlining the goals for future studies.

1. Introduction

Inclusion body myositis (IBM) is a rare age-associated myopathy that generally affects people over the age of 45 years [1]. The incidence and prevalence of IBM is increasing, coincident with the increasing age of the global population. However, prevalence is likely underestimated, due in part to the fact that diagnosis currently relies heavily upon myopathologic criteria. There are no specific therapies that modify the disease course, leaving patients and clinicians with supportive treatment for this disabling disorder.

A consensus statement describing diagnostic criteria for IBM was last published in 2013 after a group of expert clinicians and pathologists met at the European Neuromuscular Centre (ENMC meeting) in 2011 [2]. These are now referred to as the "ENMC criteria for IBM diagnosis" and are used for diagnosis in clinical practice, cohort stratification, and as entry criteria for clinical trials. However, since 2011, several advances in the understanding of IBM have been made. These include studies describing the sensitivity and specificity of imaging techniques such as muscle magnetic resonance imaging (MRI) and ultrasound for the diagnosis of IBM, and the identification of a serum autoantibody, anti-cytosolic nucleotidase 1A (cN1a), that is associated with IBM and may also serve as a prognostic biomarker [3,4].

Since 2011, two multicenter trials in IBM (of bimagrumab and arimoclomol) failed to meet primary endpoints, giving rise to discussions on appropriate clinical trial outcome measures [5,6]. Several studies which better define the natural history of IBM, as well as the publication of retrospective longitudinal studies offer new insight to guide recommendations on this topic [7]. In 2015, a separate ENMC meeting was held which

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Table 1
Terminology.

Previous terminology	Current terminology
Sporadic IBM	IBM ("Sporadic" is misleading)
Familial IBM	IBM ("Familial IBM" should not be used. More than one case in one family can be specified where relevant.)
Hereditary IBM	"Hereditary Inclusion Body Myositis" is misleading. See below for specific terminology.
Inclusion body myopathy 1	Myofibrillary myopathy (AD/AR); OMIM #601,419 (gene: *DES*, desmin)
Inclusion body myopathy 2 (Nonaka distal myopathy, distal myopathy with rimmed vacuoles [DMRV], quadriceps sparing myopathy, HIBM)	GNE myopathy (AR); OMIM #605,820 (gene: *GNE*) UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase
IBMPFD-1 (AD)	MSP-1; OMIM #167,320 (gene: *VCP*, valosin containing protein)
IBMPFD-2 (AD)	MSP-2; OMIM #615,422 (gene: *HNRNPA2B1*; heterogeneous nuclear ribonucleoprotein)
IBMPFD-3 (AD)	MSP-3: OMIM #615,424 (gene: *HNRNPA1*; heterogeneous nuclear ribonucleoprotein)
Distal myopathy with rimmed vacuoles	MSP-4 (AD); OMIM #617,158 (gene: TIA1+*SQSTM1*, sequestosome 1)

AD = autosomal dominant; AR = autosomal recessive; IBM = inclusion body myositis; IBMPFD = IBM with early onset Paget disease with or without frontotemporal dementia; MSP = Multisystem proteinopathy; OMIM = Online Mendelian Inheritance in Man.

focused on outcome measures and clinical trial readiness. However, this meeting was not specific to IBM and included discussion of immune mediated necrotizing myopathy, anti-synthetase syndrome, and dermatomyositis; disorders which have a natural history, prevalence, and treatment strategies very distinct from IBM [8]. Therefore, lessons from recent studies should be shared to support the development of consensus guidelines on trial design and outcome measures for IBM.

Overall it is clear that over 10 years since the original 2013 ENMC publication, there is a need for updated diagnostic criteria for IBM which are more inclusive, and for recommendations regarding clinical trial outcome measures that are specific to the disease. Focusing our task, this ENMC workshop started with presentations from patient representatives, Marie Christine Breeveld (The Netherlands) and Roland Mischke (Germany). Both provided testimonials regarding their diagnostic journey, frustration with limited therapeutic options, and the burden of disease on their physical function, mental health and ability to care for themselves. They emphasized the urgency in making a timely and accurate diagnosis and the limited information on the impact of exercise, nutrition, or alternative therapies in IBM. Finally, they highlighted several understudied symptoms associated with IBM, including fatigue, pain, respiratory infections, dysphagia, and depression.

This report is composed of two parts, the first part focusing on new diagnostic criteria and the second on trial readiness and outcome measures.

2. PART A: formulating new diagnostic criteria

2.1. Background

The previous ENMC criteria for IBM diagnosis, established in 2011 and published in 2013, continued the trajectory of emphasizing the importance of the clinical features of the disease, specifically the classical pattern of weakness. However, they remained restrictive in several aspects. For example, atypical but well recognized presentations of IBM were excluded, including with relation to age of onset, serum creatine kinase activity, and atypical or restricted patterns of muscle weakness [9]. Furthermore, the 2013 ENMC criteria classified patients into probable, clinically defined, and clinopathologically defined IBM, with some overlap between categories [10]. Overall, the need for a simpler and more inclusive diagnostic scheme to enhance access to appropriate care and clinical trials for patients with IBM is clear.

First, muscle imaging, including ultrasound and MRI, is now widely available in clinical practice and is often routinely performed as part of the diagnostic workup of a patient presenting with muscle weakness [11,12,13]. Evidence has accumulated regarding the distinctive pattern of abnormality seen using these imaging modalities in patients with IBM, although large scale validation studies have not yet been performed. Second, the identification of anti-cN1A autoantibodies in patients with IBM, and the ongoing elucidation of the sensitivity and specificity of antibody positivity for a diagnosis of IBM reflects another important milestone [14]. Again, autoantibody testing for a wide repertoire of myositis-related autoantibodies is now widely available in clinical practice, although the lack of standardized test methodologies and a variable performance of the different assays are unresolved issues. The approach of this workshop has been to reach an expert-based consensus on an updated diagnostic scheme. Overall, the workshop attendees agreed that this should include reference to these widely used investigations to support IBM diagnosis.

2.2. Terminology of inclusion body myositis

Jens Schmidt provided an overview of the current terminology of IBM and its history. The term IBM was first coined in 1971 [15]. Before that, two reports had identified a myopathy with inclusions [16] and Myxovirus-like-structures in a case with polymyositis [17].

The historic terminology for IBM had used "hereditary IBM" for inclusion body myopathy, "sporadic IBM" for inclusion body myositis and "familial IBM" for inclusion body myopathy or inclusion body myositis with a positive family history of the disease. In the meantime, several genes have been identified that allow a precise identification of each unique condition: Myofibrillar myopathy, GNE myopathy, multisystem proteinopathy 1–4 etc. The distinction of these different entities will ensure that patients receive best medical care and can be recruited to clinical trials as appropriate. The historic terms "hereditary", "familial" or "sporadic" IBM are misleading and, thus, should no longer be used. Instead, for all hereditary conditions, the exact gene name should be used, as indicated in Table 1. All other cases should simply be named "IBM".

2.3. Clinical features

Marianne de Visser discussed the initial pattern of muscle weakness seen in IBM. Quadriceps muscle weakness and atrophy is the most frequent presenting manifestation (58 %) [18], males more than females. Black people were found to have more weakness of the quadriceps muscles [19]. Asymmetric deep finger flexor weakness is found in 16 % (both sexes equally affected).

Weakness of oropharyngeal muscles causing dysphagia as sole presenting feature has been reported in 4–50 % [9]. However, this is likely an underestimation, as swallowing difficulty often goes unreported.

If a patient presents with deep finger flexor weakness, or quadriceps weakness, or dysphagia in isolation, it is of utmost importance to consider alternative diagnoses. Quadriceps weakness in middle aged people has an extensive differential diagnosis, including limb girdle muscular dystrophies, e.g., anoctaminopathy (may have asymmetrical involvement), myotonic dystrophy type 2, Kennedy's disease, and others. Muscle imaging may be helpful to assess which pelvic girdle and upper leg muscles are preferentially affected, and thus be an aid to distinguish IBM from these other myopathies. Deep finger flexor weakness may also be found in other myopathies [20]. Dysphagia can be the presenting feature in amyotrophic lateral sclerosis (ALS), Kennedy's disease, myasthenia gravis (in particular MuSK autoantibody positive disease), oculopharyngeal muscular dystrophy, myotonic dystrophy type 1, mitochondrial myopathies, and other idiopathic inflammatory myopathies. All clinical and pathologic features of IBM – alone or in combination – can also be mimicked by myofibrillar myopathies.

Pedro Machado presented information on clinical outliers. It is now acknowledged that a subset of patients with IBM may present differently and might be under-recognized in clinical practice. In a retrospective review of 357 patients with IBM, 50 (14 %) had an atypical presentation; of these 50 patients, the group presenting with dysphagia was the most common (n = 25, 50 %), followed by elevated CK (n = 12, 24 %), foot drop (n = 6, 12 %); proximal upper limb-predominant weakness (n = 3, 6 %); axial weakness (n = 2, 4 %, one patient with head drop and another with camptocormia), and facial diplegia (n = 2, 4 %) [9]. Younger patients (e.g., in their thirties) have been reported; a pattern of early facial diplegia followed by marked bulbar impairment and respiratory failure predominantly in middle-aged females has been described; and macroglossia has also been described as a presenting feature in IBM [21].

Umesh Badrising gave an overview of dysphagia and respiratory involvement in IBM. Dysphagia is prevalent in IBM and can be a clue to the diagnosis, as it can be the first or most obvious feature in patients. It may lead to life threatening complications, weight loss and social isolation [22]. The prevalence of dysphagia in IBM varies widely in research studies, which can be attributed to differences in the disease stage and various assessment methods used in these studies. Nevertheless, dysphagia is also reported to be common in independently living elderly individuals [23]. Due to a lack of a consistent definition of dysphagia, the reliability, validity, and general applicability of prevalence statistics are affected.

The gold standard for assessing dysphagia is videofluoroscopy (VFS) and fiberoptic endoscopic evaluation of swallowing (FEES). However, there is currently no international consensus on key factors such as patient positioning, bolus volume and consistency, swallowing sequence, the number of swallows during measurements, recording view, recording frames per minute, and assessment criteria. So far, there is insufficient evidence to recommend any specific VFS/FEES measure as both valid and reliable. Other modalities like real-time MRI, 3D-CT scanning, ultrasound, and high-resolution manometry cannot yet routinely replace VFS/FEES, except for centers with distinct research expertise in one of the experimental modalities.

Several questionnaires are available for dysphagia screening, focusing on functional health status (e.g., EAT-10, Sydney Swallow Questionnaire) or health-related quality of life (e.g., SWAL-QOL, Dysphagia Handicap Index, Deglutition Handicap Index, MD Anderson Dysphagia Inventory). However, these tools lack comprehensive evaluation, were not specifically designed for IBM, or exhibit poor psychometric properties.

Treatment options for dysphagia in IBM include the Mendelsohn maneuver, expiratory strength training, balloon dilatation, cricopharyngeal myotomy, laryngeal suspension, and percutaneous endoscopic/radiological gastrostomy. It is essential to identify individuals at risk of aspiration and those who may benefit from an effective (invasive) procedure to address pharyngeal bolus residue. Currently, standards for selecting the most appropriate treatment modality and the optimal timing during the disease progression are unavailable. The efficacy and safety of botulinum toxin treatment remain insufficiently established, with limited evidence suggesting potential efficacy based on a small study [24].

For future high-quality studies, a universally accepted gold standard for assessing dysphagia, along with the development and utilization of validated screening tools and assessments with robust psychometric properties, is necessary. Individuals with dysphagia in IBM may follow a distinct natural course compared to those without, emphasizing the need for prospective long-term studies including those on selection of optimal treatment techniques, timing and approach to optimize patient safety.

Sleep disordered breathing is a common finding in IBM according to 2 studies (n = 7/13 and n = 16/16) [25,26]. The frequency of respiratory insufficiency in IBM is unknown [27]. In a retrospective series, patients with IBM showed a forced vital capacity (FVC) decline of 0.1 liter/year. There was no correlation between muscle strength decline and FVC decline. To address these knowledge gaps, more extensive studies are required to prospectively assess diaphragmatic function and lung function measures. This research is also necessary to determine whether one or more of these measures could serve as potential outcome measure in clinical trials.

2.4. Incidence and prevalence of inclusion body myositis

Elie Naddaf delivered a presentation on IBM epidemiological studies in the United States. The incidence of IBM has been primarily documented in Olmsted county, MN [28]. The most recent population-based study conducted in 2021, utilizing the ENMC 2013 diagnostic criteria, indicated an incidence of 0.32 to 1.22 per 100,000 person-years [7]. Additionally, a prevalence of 182 per million was reported for individuals aged 50 or older [7]. A distinct prevalence rate of 28.9 cases per million among individuals aged 45 or older was recorded at a referral center in Connecticut in 2001, using the more stringent Griggs criteria [29].

A population-based case-control study that encompassed a larger population across Minnesota and Wisconsin revealed that IBM was associated with increased mortality with a 10-year survival rate of 36 % of index compared to 50 % in control patients [30]. Respiratory failure or pneumonia was the most common cause of death. Furthermore, IBM patients were more likely to have peripheral neuropathy, Sjögren's syndrome and hematologic malignancies than population controls. Notably, the presence of T-cell large granular lymphocytic leukemia was exclusively observed in the IBM group. Patients treated with corticosteroids had poorer survival than those who were not, however, a causative relationship between corticosteroid use and survival could not be established with certainty.

Merrilee Needham presented epidemiological studies in Australia. High quality prevalence studies rely on accurate and unbiased complete case ascertainment at a particular point in time, and should follow as best as possible the Methodological Evaluation of Observational Research (MORE) checklist [31]. IBM prevalence studies have had difficulty in obtaining all cases at a

particular point in time due to the slowly progressive nature of the disease leading to significant delays-to-diagnosis from symptom onset, and differences between diagnostic criteria used and their various sensitivities at an earlier disease stage.

In Australia, thus far there have been four prevalence studies; three from West Australia (WA), and one from South Australia (SA) [32–34]. The original WA study by Phillips et al. [32] in 2000 reported a prevalence of 9.3/million and used the Griggs diagnostic criteria on ascertained cases through specialists and correlated this with the central muscle biopsy laboratory. The follow-up prevalence study done by Needham et al. [33] in 2008 using similar methodology for case ascertainment but used the Needham and Mastaglia criteria [35], reported a higher prevalence (14.9/million). It was not certain whether this reflected higher case ascertainment due to improved recognition of the disorder locally, or a true increase in prevalence. Recent figures from the specialist IBM clinic (personal communication) using ENMC 2013 criteria reported an even higher prevalence (31.1/million). There is a male predominance in WA, and the vast majority of cases are Caucasian. The fourth study done in SA by Tan et al. [34] in 2013 showed the highest prevalence reported in Australia (50.5/million), with a slight female predominance. This study ascertained cases by muscle biopsies and used muscle biopsy criteria, and then performed clinical correlation using medical record review. Overall, in Australia, three consecutive studies performed in the same population reported consistently rising prevalence, approaching the prevalence reported in South Australia. These three prevalence studies over 23 years could represent a true increased prevalence in the condition, or could still reflect improved recognition, diagnosis and referral to appropriate specialists.

Ichizo Nishino provided epidemiological data from Japan. His lab functions as a referral center for muscle disease in Japan and is thought to collect more than 70 % of muscle biopsies performed within the country. In his muscle biopsy cohort, the number of IBM cases has been increased since 2002 but this increase is proportional to the increase of total number of myositis cases he receives. In recent years, the number of newly diagnosed IBM cases have been around 100 cases per year. In 1996 through 2001, IBM accounted for 6 % among all myositis cases while it was almost stably around 20 % in 2002 through 2022. This increase may be attributed to the fact that Ikuya Nonaka who used to be responsible for muscle pathology is a pediatric neurologist while Dr. Nishino who became responsible for the diagnosis in 2001 is an adult neurologist. In Japan, the government provides subsidy for medical expenses for 338 designated intractable diseases, including IBM. As of the end of fiscal year 2021 (March 2022), 756 patients are registered. However, this number may well be much lower than the actual number of IBM patients in Japan because not all patients renew the registration every year and most likely a significant number of patients are registered in the category of polymyositis/dermatomyositis.

Ulrika Lindgren presented epidemiological, survival and clinical data from a population-based cohort of 151 patients (99 men and 52 women) with IBM in Western Sweden [18]. The patients were diagnosed according to the ENMC 2013 criteria and their diagnostic muscle biopsies were performed between 1985 and 2017 [2]. Re-examination of muscle biopsy specimens and data from medical records identified 128 patients fulfilling the criteria for clinicopathological IBM (mean follow up time 8 years), and six patients fulfilling the criteria for early-onset IBM defined as <46 years of age at symptom onset and a first muscle biopsy with inflammation <50 years of age (median follow up time 11 years) [18,36]. The mean incidence for clinicopathological IBM was 2.5 patients per million inhabitants and year. The prevalence on December 31, 2017 was 32 patients per million inhabitants (19 per million women and 45 per million men) for clinicopathological IBM, 1.2 patients per million inhabitants for early-onset IBM and 36 patients per million inhabitants when considering all IBM subgroups including early age at onset [18,36].

Regarding clinicopathological IBM, the mean age at symptom onset and diagnosis was 64 and 70 years, respectively. Quadriceps weakness was the most common symptom of onset. Swallowing difficulties affected 77 % of patients during the disease course and were the first symptom in 23 % of women. Wheelchair use was reported in 61 % of patients. Autoimmune diseases were observed in 15 % of men and 36 % of women, but there was no clear association with the prevalence of malignancy. In a cross-sectional study including 50 patients with clinicopathological IBM, 40 % had positive anti-cN1a testing. Cumulative survival was reduced compared to the matched population, and the mean age at death was 80 years (n = 73) [18]. The six patients with early-onset IBM had a median age of 36 years at symptom onset and 43 years at diagnosis. Five patients experienced swallowing difficulties during the disease course, three used ventilation assistance devices and five reported using a wheelchair. The decrease of cumulative survival compared to the matched population was more pronounced than in clinicopathological IBM, with a mean age at death of 61 years (n = 4) [36].

2.5. Pathological considerations

Ichizo Nishino summarized the pathological findings of IBM, including endomysial cytotoxic T cell infiltration surrounding non-necrotic fibers (with or without invasion), and rimmed vacuoles. On immunohistochemistry, aggregates of p62 and TDP-43 are also seen, which are thought to reflect the same pathological process as rimmed vacuoles. Dr. Nishino pointed out that the expression of MHC class I (HLA-ABC) in myofibers is less useful to differentiate IBM from other myositis subtypes as it is seen in virtually all types of myositis, and even in some muscular dystrophies. In contrast, the presence of MHC class II (HLA-DR) expressing myofibers is more useful in the diagnosis of IBM as it is rarely seen in other types of myositis except anti-synthetase syndrome (ASyS), and almost never seen in hereditary muscle diseases. Furthermore, the distribution of MHC-II-expressing fibers is diffuse/patchy in IBM while it is often perifascicular in ASyS. He further pointed out the presence of abundant PD-1 positive cells in IBM muscle, which may also be helpful for the diagnosis of IBM.

In rare occasions, lymphocyte infiltration may be seen in hereditary myopathies pathologically characterized by rimmed vacuoles such as GNE myopathy and myofibrillar myopathies. Even in cases with relatively striking lymphocyte infiltration, they are not invading into non-necrotic fibers and MHC-II positive fibers are not seen, which should differentiate IBM from rimmed vacuolar myopathies. In addition, he presented the myopathological features of Nakajo-Nishimura syndrome (NNS), which is a rare hereditary condition due to defective immunoproteasome caused by a mutation in *PSMB8* gene. Muscle from a 29-year-old patient with NNS showed all the pathological features of IBM, including endomysial cytotoxic T cell infiltration invading into non-necrotic fibers, rimmed vacuoles and MHC-II expressing fibers, suggesting that rare cases with pathologically-typical/definitive IBM may have some other conditions.

Anders Oldfors summarized the current knowledge on mitochondrial alterations in IBM. Ragged-red and cytochrome c oxidase (COX)-deficient muscle fibers were among the first alterations to be described in muscle tissues after the identification of IBM as a distinct entity. These COX-deficient segments of muscle fibers are typically scattered in the tissue. Several studies

using techniques such as Southern blot, in situ hybridization, single fiber PCR analysis, immunohistochemistry and more lately next generation sequencing have demonstrated that there is clonal expansion of mitochondrial DNA (mtDNA) deletions and duplications in muscle fiber segments, which are associated with COX-deficiency (complex IV of the respiratory chain) [37]. Immunohistochemical studies have demonstrated that even more fibers are affected by complex I deficiency [38]. The mtDNA large-scale rearrangements and to some extent also point mutations are increased in relation to age-matched controls. It has also been demonstrated that the COX-deficient fibers are more atrophic than fibers with normal COX-activity. The amount of COX-deficient fibers frequently accounts for 5–15 % of the fibers and rearranged mtDNA species may account for as much as 35 % of the total mtDNA, but there is large variability between different muscle biopsy specimens, also in the same individual. The mtDNA rearrangements and COX-deficient fibers occur early in individuals with onset of IBM before 50 years of age and appear not to be an accelerated aging phenomenon. The clinical importance of the mitochondrial alterations is still not known.

The vacuolated muscle fibers with inclusions giving the name to IBM were also briefly discussed, as were the huge number of proteins accumulated in the vacuolated fibers. These findings in addition to the accumulation of 15 - 20 nm tubulofilaments in IBM nuclei and cytoplasm have been the basis for hypotheses regarding the IBM pathogenesis as a degenerative disease [1]. They have also formed a ground for histopathological identification and definition of IBM with for example the typical, albeit not specific, p62/sequestosome1 positive inclusions [39].

Werner Stenzel discussed the role of immunohistochemistry in IBM diagnosis and research. He emphasized that immunohistochemistry is a routine diagnostic tool that is used worldwide and, in most places, employed in diagnostic laboratories, often with automated pipelines, many of which have official accreditation, meaning that stains are reliable and reproducible. An ENMC workshop in 2019 recommended standards for muscle pathology [40]. The report from this meeting highlighted standards that should be followed in specialized neuromuscular laboratories devoted to high-level quality of skeletal muscle analysis. The recommendations put emphasis on the analysis of frozen tissues and from several levels not to miss focal alterations. He also mentioned that those recommendations reflect the ideal situation of a work-up, which may not be achieved worldwide and that a selection of stains may suffice for many standard conditions, however, the more complete those recommendations are followed the less of rarer conditions will be missed. The necessity of a respectful and close interaction between morphologists, clinicians and radiologists was also highlighted. To ensure comparability of results, a consensus and standardization of all tissue procedures, protocols, including the techniques, stains and antibodies should be achieved.

Pathologic mimickers of IBM were discussed and included toxic myopathies (e.g., Chloroquine-induced) and genetic diseases with vacuoles and inflammation as well as other protein aggregate myopathies such as autosomal dominant pathogenic variants in *hnRNP A1, DES, FLNC,* or *MYOT* genes. Other considerations included the fact that early forms of IBM, which may not yet present the full characteristic clinical picture may be identified as early IBM or PM-Mito with sarcolemmal and sarcoplasmic positivity of MHC class I and II and endomysial lymphocytes and prominently elevated numbers of COX-SDH+ fibers, highlighting the early and constant occurrence of mitochondrial pathology during morphological progression to the full pathological picture of IBM, but without any vacuoles. With these considerations in mind, Dr Stenzel suggested that the minimum of immunohistochemical stains recommended in state-of-the-art IBM diagnosis are: MHC class I, and class II, CD68, CD8, CD45, C5b-9, p62 (or LC3 or TDP43).

2.6. Consensus myopathology

A subcommittee was formed to provide a precise and contemporary description of the characteristic alterations occurring in skeletal muscles of patients with IBM. This committee consisted of **Anders Oldfors, Werner Stenzel, Ichizo Nishino**, as dedicated myopathologists and **Tahseen Mozaffar** and **Tom Lloyd** as neurologists/pathologists with a specific interest in myopathology and classification systems in IBM.

The primary aim was to be as complete as possible, while being precise and excluding most of the possible morphological mimickers. The second aim was to stay as close as possible to the morphological criteria which had been proposed in the previous ENMC criteria, and which, despite the notable limitations described in this meeting report, have proven to perform well over the last 10 years with high specificity and sensitivity [10]. It was agreed that a diagnosis of IBM would not be made by biopsy only and would require supporting clinical features.

The canonical set of myopathological features of IBM (see Fig. 1) are

1. *Inflammation* consisting of endomysial lymphocytes surrounding non-necrotic muscle fibers (with or without invasion), and an IBM-compatible MHC class I (and – if available MHC class II) pattern
2. *Rimmed vacuoles* and/or *cytoplasmic protein aggregates*
3. *Mitochondrial abnormalities* with COX negative and SDH positive fibers (more than one would expect in relation to age)

Inflammation: In comparison to other IIM entities, the lymphocytic infiltrate is predominantly localized in the endomysium of muscle fascicles surrounding individual myofibers (with or without invasion), and not in the perimysium as in anti-synthetase syndrome and dermatomyositis. The quantity of lymphocytes exceeds that in IMNM, where the lymphocytic infiltrate is also localized in the endomysium. MHC class I staining on the sarcolemma of myofibers in IBM is always strong and diffuse throughout the biopsy specimen and does not follow perifascicular patterns. MHC class I negativity is an argument against IBM diagnosis, even if patients are under treatment. Certain genetic neuromuscular diseases with vacuoles such as the myofibrillar myopathies, distal myopathies such as GNE myopathy, but also sometimes Becker and Duchenne muscular dystrophy or FSHD, may also feature some lymphocytic infiltrates but they do not regularly invade healthy appearing myofibers, and usually show only little or no sarcolemmal MHC class I positivity, and they are negative or only very mildly positive for MHC class II. Sarcolemmal MHC class II is strongly positive with focal enhancement. The sarcolemmal and sarcoplasmic MHC class I and class II staining patterns in IBM have a high diagnostic value and reach nearly 100% sensitivity [41].

Rimmed vacuoles (RVs) and cytoplasmic protein aggregates: RVs, (which should be evaluated by Gömöri trichrome) although considered to be typical, may be absent or difficult to identify in IBM muscle. The immunohistochemical staining by p62 has proven a very sensitive tool to identify fibers showing early pathology of the autophagic breakdown of peptides that is characteristic in IBM, featuring aggregates of variable size in the perinuclear region or in sarcoplasmic areas focally. Those fibers are often small but usually do not show signs of lymphocytic invasion or mitochondrial damage. A valid alternative to study the content of RVs is the thioflavin stain or the fluorescent Rhodamine red stain. Congo Red staining is often not sensitive enough to identify them conventionally. A close substitute to highlight the dysfunctional

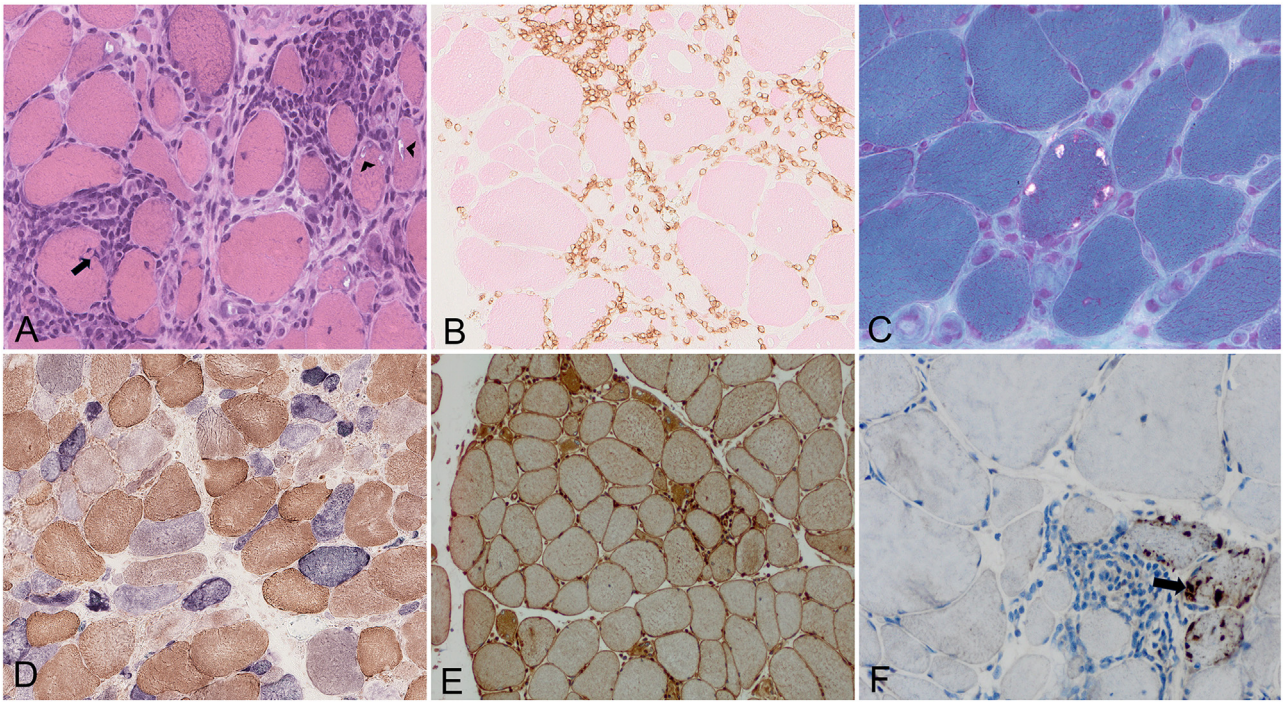

Fig. 1. Histomorphological alterations of skeletal muscles from IBM patients.
A. Hematoxylin and eosin stain demonstrating fiber size variation, endomysial inflammation with regions of focal invasion (arrow) and fibers containing rimmed vacuoles (arrowheads). B. Muscle tissue (same as for A) immunostained with an anti-CD3 antibody denotes that a significant proportion of endomysial inflammatory cells are T-lymphocytes. C. Gömöri-trichrome highlights a fiber with classic red rimmed vacuoles. D. Cytochrome c oxidase-Succinate dehydrogenase (COX-SDH) enzyme histochemical staining demonstrates scattered COX negative and SDH positive (dark blue fibers) consistent with mitochondrial dysfunction. E. MHC class I immunostaining demonstrates sarcolemmal positivity on all fibers with no predilection to perifascicular regions. F. p62/SQSTM1 immunoreactivity is seen as coarse sarcoplasmic aggregates (arrow) consistent with autophagolysosomal remnants.

macroautophagic breakdown in IBM is LC3. TDP43 can be useful as well to identify sarcoplasmic accumulation. Less used but with undisputable value are the immunohistochemical stains SMI31 and Ubiquitin. Similarly, electron microscopy shows characteristic tubulofilaments in myonuclei and in the vacuoles most often close to myonuclei and mixed with debris of variable and non-specific appearance.

Mitochondrial pathology: Mitochondrial dysfunction is a known hallmark of IBM and has been thoroughly studied in recent years [38]. The number of COX-negative and SDH-positive fibers is usually above age-related normal numbers but may be approaching or even exceeding numbers of genetic mitochondriopathies, while ragged red fibers are more difficult to ascertain. In addition, ultrastructural analysis can be helpful to identify paracrystalline inclusions or circular cristae in mitochondria, features that are underpinning the mitochondrial damage.

2.7. Genetic considerations

Mridul Johari discussed genetic risks for IBM. Inheritance patterns for IBM are unlikely to adhere to Mendelian principles, and a monogenic pathomechanism is also improbable. Establishing polygenic risk scores necessitates the identification of validated genetic markers from various extensive studies. The 8.1 ancestral haplotype in the HLA region consistently exhibits an association with IBM. While analyzing the DNA sequencing data, the presence of rare variants in genes responsible for myopathy or multisystem proteinopathy should prompt a re-evaluation of the patient's phenotype, with cautious reporting of these variants. Distinct co-existing comorbidities may possess diverse molecular origins that require further investigation. Instances of multiple family members diagnosed with IBM may offer insights into the genetic predisposition of IBM, enhancing our understanding of this disease.

2.8. Pathomechanisms of inclusion body myositis

Jens Schmidt provided an overview of the current understanding of the IBM pathology, which is complex and so far unresolved [1]. It is believed that inflammatory and myodegenerative mechanisms act in concert and that more evidence supports the hypothesis that inflammation may drive the degeneration rather than the reverse [42]. The inflammation centers around cytotoxic T cells that can clonally expand and attack muscle fibers, which have the capacity to over-express non-classical co-stimulatory molecules and thereby may fuel or trigger cellular activation and inflammation. A clonal expansion of B-cells has also been demonstrated in IBM as well as presence of B-cell co-stimulatory factors [43]. The B-cell mechanisms may relate to the fact that anti-cN1a auto-antibodies are present in a subset of IBM patients.

The degenerative mechanisms center around disruptions in protein quality control and protein degradation, which can present as protein accumulations in vacuoles or inclusion bodies. Over-expression of β-amyloid or TDP-43 in muscle cells or skeletal muscle from transgenic mice causes cell stress [44,45], but only little if any inflammation. Skeletal muscle cell stress related to over-expression of MHC class I on myofibers has been demonstrated to be a trigger and continuous driver of muscle inflammation in a myositis mouse model [46]. In a cell culture model of chronic muscle inflammation, the cytokine combination of IFN-γ plus IL-1β was identified as cause of protein accumulation with presence of β-amyloid within 72 h [47]. Mediators between inflammatory and myodegenerative cascades

were identified and included iNOS, LC3, HMGB1 / RAGE and the NLRP3 inflammasome [43].

2.9. Natural history of inclusion body myositis

Tahseen Mozaffar gave an overview of the natural history of IBM. Inclusion body myositis is a slowly progressive condition that causes significant disability and morbidity. The magnitude of decline annually is variable and currently difficult to predict at onset of the disease. The decline is most pronounced in the lower legs and activities of daily life are clearly restricted, with 12–47 % being completely wheelchair-bound [48,49]. There are significant deficits in our knowledge of the natural history of disease progression in IBM and none of the studies to date have evaluated these observations in a standardized fashion or with long enough duration, as the longest study was only 12 months. Furthermore, given the recent discovery of the cN1a antibodies and the presence of variant T-lymphocyte population in IBM, influence of these serum biomarkers on disease phenotype, progression and behavior over a long-term period has not been studied.

There are several important issues that remain unknown in IBM, including optimal outcome measures in IBM to quantitate disease progression (or improvement, in the event of a successful treatment), rates of decline in respiratory function, and muscle pathology differences in anti-cN1a seropositive or seronegative patients. To address all these factors, an NIH-funded natural history study (INSPIRE-IBM; clinicaltrials.gov (NCT) identifier NCT05046821) in 150 IBM subjects over 24 months is currently ongoing (Tahseen Mozaffar, principal investigator) at 13 sites across the US and almost fully enrolled. The study is expected to generate a rich clinical and functional dataset, matched with carefully collected and curated biospecimens, including PBMCs and serum at 5 different time points, DNA, RNA, and fresh muscle biopsies (with concurrently collected PBMCs) in 40 subjects. This biorepository will be available to IBM researchers for future studies.

2.10. New diagnostic tools

Pedro Machado stressed that the role of MRI in outcome assessment in IBM is increasingly recognized [50]. T1-weighted spin echo sequences evaluate chronic/structural changes, while T2-weighted sequences with fat suppression (e.g. Short Tau Inversion Recovery [STIR] or Spectral Attenuated Inversion Recovery [SPAIR]) evaluate acute/hypervascularization/muscle edema changes. Dixon sequences have become popular because they allow for water and fat signal separation. Quantitative MRI measures (e.g., fat fraction, thigh muscle volume, global or remaining/contractile cross-sectional area, water T2 maps) hold great potential as imaging outcome measures in IBM. They have been shown to be valid, reliable, and responsive, and they could be useful as either a primary or secondary outcome measure in early phase clinical trials, or as a secondary outcome measure in late phase clinical trials [51]. Integration of artificial intelligence-based segmentation algorithms has the potential to revolutionize the field by substituting manual segmentation with quick automated segmentation, reducing laborious tasks.

Giorgio Tasca presented muscle MRI findings in IBM. There are about 30 cross-sectional studies available describing muscle MRI involvement patterns in IBM, characterized by signs of fatty replacement in the flexor digitorum profundus in the forearm, in the anterior thigh often with a disto-proximal gradient, and findings pointing towards an increased water mobility likely corresponding to the inflammatory changes seen on muscle pathology. Some case series reported a degree of asymmetry and the sparing of rectus femoris was sporadically observed. Relevantly, one study assessed the accuracy of pattern recognition to diagnose IBM using a standard lower limb imaging protocol [11]. The typical pattern was identified as the “melted” appearance of the distal anterior thigh muscles, accompanied by the hyperintense signal on STIR sequences in the same region, supported by the involvement of the gastrocnemius medialis in the lower leg and relative sparing of the pelvic muscles (Fig. 2) [11].

Independent observers assessed MR images blinded to all other patients’ data, and this yielded high values of diagnostic accuracy to detect IBM - 95 % sensitivity in case of recognition of the typical pattern (with 100 % specificity) and 97 % for both typical and consistent patterns (with 97 % specificity) [11]. Notably, the control group was composed of a large number (>100) of inflammatory and genetic myopathies with clinical or pathological overlap with IBM, and accuracy values were further validated in an independent cohort. These results placed IBM among the muscle disorders in which lower limb MRI is most useful in establishing the correct diagnosis. After the publication, Tasca *et al.* refined the criteria aiming to make them more objective and easily scorable, as already presented in a previous ENMC conference [13].

Christiaan Saris presented the use of muscle ultrasound as a diagnostic modality in IBM. With increased replacement of muscle by fat and muscle fibrosis, there will be an increase in echo intensity with a loss of muscle architecture. This can visually be interpreted as being normal or abnormal or can be graded in a semi quantitative way using Heckmatt grading [52] with a sensitivity of 70 and 76 %, respectively, compared with healthy controls. Edema can be appreciated as increased echointensity (EI) with preserved muscle architecture and with good reflection of the underlying bone giving the muscle a “see-through” appearance. Increased EI is not specific for myopathy and can also occur in neuropathies.

Quantitative muscle ultrasound (QMUS) can be used to better determine abnormal muscle EI in mildly affected muscles. This will improve sensitivity up to 92 %. Average greyscale is calculated in a region of interest within the selected muscle and is compared to age matched healthy controls. This comparison depends on the device and the respective setting. Muscle thickness can be measured and compared to age matched healthy controls.

In IBM, the most prominent findings are increased EI of deep finger flexors, vastus medialis and lateralis and medial head of gastrocnemius (mGC). Increased EI in other muscles, e.g., biceps brachii and radial carpal flexor can be present, especially at later stages. Often involvement is asymmetric. Deep finger flexors can show increased EI when clinically muscles are not affected. The EI is higher in the FDP compared to FCU (Fig. 3) and higher in the mGC compared to the lateral head of gastrocnemius and soleus. Inhomogeneous patterns (also referred to as “moth eaten”) with areas of higher and lower EI can be seen. Compared to healthy controls, increased EI in these muscles show a sensitivity and specificity of 82 % and 98 %, respectively [12,53]. Muscle abnormalities identified on US correspond well with replacement of muscle by fat on MRI in IBM patients [54]. Muscle EI showed significant correlations with serum creatine kinase activity and muscle strength and moderate correlation with quadriceps muscle strength [55]. No follow-up study in IBM has been performed. With the development of higher quality point-of-care ultrasound (POCUS) with better resolution, muscle ultrasound has become an interesting tool in daily practice. Also, the development of shear wave elastography and analysis of ultrasound images with artificial intelligence for muscle tissue are promising and need further validation in IBM.

Hector Chinoy discussed the use of amyloid imaging in IBM. [18F]florbetapir is an amyloid-imaging tracer that has previously been used in the study of Alzheimer disease [56]. The study of [18F]florbetapir PET/CT in IBM was on the original premise of historical IBM literature implicating amyloid

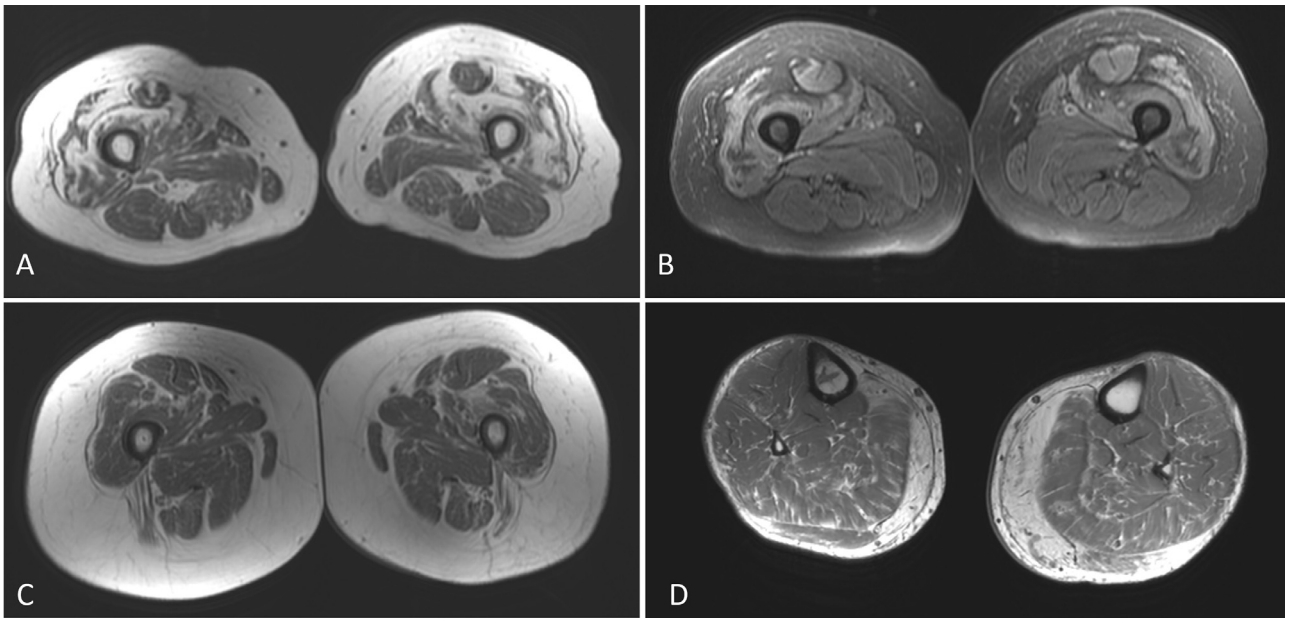

Fig. 2. Lower Limb Muscle Magnetic Resonance Imaging in Inclusion Body Myositis.
Axial T1 (A, C & D) and T2 (B) images. Replacement of muscle by fat is most prominent in the distal anterior thigh compartment (A) with marked involvement of the vastus medialis and vastus lateralis, creating a "melted appearance", and relative sparing of the rectus femoris and posterior thigh compartment. T2-weighted images (B) demonstrate T2 hyperintensity in distal anterior compartments as well. The quadriceps is relatively spared more proximally (C), creating a proximal-to-distal gradient. In the leg, the most severely affected muscle is typically the medial gastrocnemius (D). Additional helpful clues are pelvic muscle sparing, sartorius involvement (if present it adds specificity), and distal STIR hyperintensity in the remaining muscle tissue.

as part of the pathogenesis of disease [57]. By identifying potential pathological hallmarks of IBM, the idea was to improve sensitivity/specificity in the diagnosis of IBM. Ten cases with IBM and six controls with polymyositis were recruited and was subject to a combination of clinical review and whole-body imaging [58]. Whilst visible and statistical differences were present when comparing [18F]florbetapir PET/CT images between IBM and PM, it was felt that further work was required to further validate the findings, and that the current technique was not practical in the clinical setting.

James Lilleker described serum autoantibodies in IBM, focusing on anti-cN1a. In 2005, Greenberg *et al.* [59] used gene expression microarray profiling on IBM muscle to identify immunoglobulin transcripts. In 2011, Salajegheh *et al.* [60] went on to identify autoantibodies against a 43 kDa muscle autoantigen which was present in plasma from 13 of 25 IBM cases and no controls. Thereafter, simultaneous publications in Annals of Neurology in 2013 [3,4] described the definitively identified autoantigenic target as cytosolic 5'nucleotidase 1A using mass spectrometry. Subsequent work by Tawera et al. [61] used passive immunization models to investigate the potential pathogenic effect of anti-cN1a autoantibodies, finding that the injection of purified IgG fractions from patients with IBM who possessed anti-cN1a autoantibodies into mice was associated with the formation of p62 positive sarcoplasmic myofiber aggregates. These findings sparked further interest in the potential role of cN1a immunoreactivity for linking the autoimmune and so-called 'degenerative' aspects of IBM pathology.

Since the identification of anti-cN1a autoantibodies, several studies have examined the diagnostic sensitivity and specificity of antibody positivity [14]. Of note, significant proportions of patients with Sjögren's syndrome and Systemic Lupus Erythematosus have been shown to exhibit antibody positivity. Test methodology also has a significant influence on assay performance, with sensitivity ranging from 33 % to 76 % [62]. It was recommended that consensus should be reached on the optimal anti-cN1a autoantibody testing approach. A recent analysis using hierarchical bivariate and Bayesian approaches questioned the diagnostic usefulness of anti-cN1a autoantibody testing, describing an overall sensitivity of 46 % and specificity of 91 % in the pooled Bayesian analysis [14]. Various studies have attempted to determine whether anti-cN1a autoantibody status has any influence on disease severity or progression, often with conflicting results. No association with malignancy has been found. The ongoing INSPIRE-IBM natural history study (NCT05046821) will hopefully unravel some of these uncertainties. The presence of other autoantibodies in IBM was discussed, including anti-SSA and anti-SSB. Finally, the recent report of the presence of anti-VCP antibodies in 26 % of one IBM cohort was also discussed [63]. The implications of this finding await further clarification.

Jan De Bleecker reviewed the role of other serum biomarkers as a convenient, minimally invasive diagnostic strategy. For analyses of the circulating proteome, many enzyme-linked immunosorbent assays are available, delivering highly specific, straight forward and rapid results. Quantifying serum creatine kinase (CK) in particular, represents the standard blood biomarker for muscle disorders. CK levels are a general indicator of muscle tissue damage, and in a majority of IBM patients normal or mild to moderately increased levels are observed, which remain stable over time. CK quantification is not considered useful as a marker of therapeutic response and, even if CK levels are sometimes seen to decrease with immunotherapy, this is not a good measure for responsiveness and should not be a reason to keep IBM patients on such treatments [64]. Other circulating factors thus would need to be included in the diagnostic workup for IBM.

The conspicuous pattern of mitochondrial damage in muscle tissue warrants exploration of mitochondrial biomarkers in IBM. In this respect, the tissue injury-associated cytokine Growth differentiation factor-15 (GDF-15) recently surfaced as a strong candidate for further exploration. Elevated circulating levels of GDF-15 strongly associated with mitochondrial myopathy, are also found increased in myositis [65] and most particular in

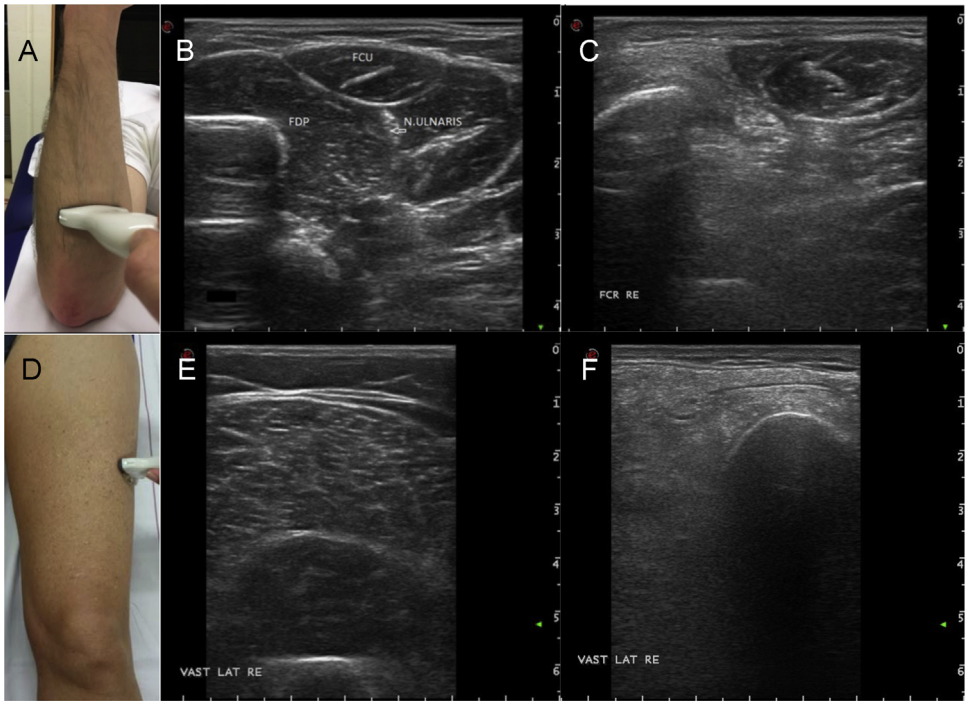

Fig. 3. Ultrasound Imaging in Inclusion Body Myositis.
Ultrasound of deep finger flexors (FDP) at 1/3 of the line between the epicondylar groove of the olecranon and styloid process of the ulna (A). Normal sonoanatomy (B) with FDP around the ulna. Increased echointensity of the deep finger flexors (C) compared to flexor carpi ulnaris (FCU). Ultrasound of vastus lateralis muscle (D) at 2/3 of the lateral line spina iliaca and upper rim of the patella. Normal sonoanatomy (E) with vastus intermedius (VI) and vastus lateralis (VL) on top of the femur (FE). Atrophy and increased echointensity of vastus intermedius and vastus lateralis (F).

IBM. GDF-15 may be classified as a myokine, since upregulated expression can be observed in IBM muscle tissues associated with the characteristic protein aggregates within affected muscle fibers [65].

Selective involvement of chemotactic cytokines termed chemokines is continuously being characterized in IBM. It has long been known that monocyte chemoattractant protein-1 or CCL2 associates with myositis in general and active invasion of nonnecrotic muscle fibers in IBM in particular [66]. CCL2 is among the ten cytokines and chemokines determined as good to excellent serum markers for differentiating IBM from healthy controls [67]. This set of ten IBM biomarkers identified by Badrising et al. also includes the IFN-γ-induced chemokines CXCL9 and CXCL10, and levels of the latter change significantly upon methotrexate treatment as compared with the natural clinical course [67]. The IFN signature of the different subtypes of myositis is distinct, and IBM muscle tissue exhibits prominent IFN-γ-driven immunoregulation [68]. CXCL10 also featured among the nine cytokines found increased in sera from patients with IBM compared to other neurological disorders, but this study could not find different CCL2 levels [69]. Circulating levels of cytokines and chemokines might be fitted into a multi-biomarker strategy for IBM, alongside standard clinical blood biomarkers and myositis autoantibody profiling.

Tom Lloyd showed an overview on tissue biomarkers. Ever since IBM was determined to be a TDP-43 proteinopathy [70,71], potentially sharing a common underlying pathophysiology with Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), efforts have been made to apply advances in biomarker assay development in ALS/FTD towards IBM. While plasma TDP-43 levels are not elevated beyond what is observed in other inflammatory myopathies [72], detection of cytoplasmic TDP-43 protein aggregates has proven to be a sensitive and specific biomarker for IBM amongst inflammatory myopathies [73]. Interestingly, cytoplasmic TDP-43 accumulation is common in protein aggregate and rimmed vacuole myopathies, suggesting this pathological finding may be a consequence of impaired proteostasis.

Recently, loss of nuclear TDP-43-mediated splicing regulation has been suggested to be a primary risk factor for sporadic ALS [74]. Loss of TDP-43 splicing repression of "cryptic exons" can be detected using RT-PCR from patient tissue, and using this approach in IBM muscle, Britson et al. found that cryptic exon detection has an 84 % sensitivity and 99 % specificity for IBM diagnosis in a large myositis cohort [75]. Although most cryptic exons result in nonsense-mediated-decay, some missplicing events lead to generation of "cryptic peptides" that can serve as potential diagnostic and prognostic biomarkers. An antibody generated against a cryptic peptide resulting from missplicing of the HDGFL2 gene was recently shown to have prognostic value in patients with ALS caused by the C9orf72 mutation [76]. This same antibody detects cryptic HDGFL2 peptides in myonuclei with immunostaining of muscle biopsies in IBM but not in controls, suggesting utility as a diagnostic biomarker for IBM (unpublished).

2.11. The 2024 ENMC diagnostic criteria for inclusion body myositis

The workshop participants worked diligently to develop a revision to the previously published 2013 ENMC diagnostic criteria for IBM. The creation of new diagnostic criteria required a consensus decision about what does, and what does not constitute a diagnosis of IBM. This is a complex task, as integration of information from different domains, each with varying weight according to their diagnostic specificity, is required.

The participants of this workshop agreed to move away from a hierarchical system of diagnostic categories (e.g., “probable IBM”), and towards a simpler dichotomous system. This decision was made for two reasons; Firstly, from the patient and caregiver

Table 2
2024 ENMC Criteria for the Diagnosis of Inclusion Body Myositis.

Diagnosing IBM should involve consultation of a neuromuscular specialist. These criteria should be applied where clinicians suspect a diagnosis of IBM and where there is no better explanation for the clinical presentation.

STEP 1: Presentation Type		
Common Presentation	**Uncommon Presentation** *Patient may have IBM, but search for alternative diagnosis is mandatory.*	**Considerations for alternative diagnoses** *Where present, alternative diagnosis is likely. Alternative diagnosis should be stringently evaluated.*
All three of: • Age ≥ 45 years at symptom onset, *AND* • ≥ 12-month history of progressive weakness, *AND* • CK ≤ 15x ULN **With** common IBM muscle involvement pattern *at presentation* (often asymmetric and accompanied by dysphagia): • Deep finger flexor (FF) weakness *AND/OR* • Knee extensor (KE) weakness	Patient with suspected IBM, but with any of: • Age <45 years at symptom onset, *OR* • <12 months of progressive weakness, *OR* • CK > 15x ULN, *OR* • Uncommon muscle involvement pattern and the absence of FF *AND/OR* KE weakness *at presentation*: • Axial weakness, • Isolated dysphagia, • Foot drop, • Facial diplegia, • Proximal limb weakness	Presence of any of the following suggests that an alternative diagnosis is more likely than IBM: • Positive family history of neuromuscular disease, • EMG not consistent with IBM (e.g., signs of severe axonal loss or fasciculations), • Myositis *specific* autoantibody positive (e.g., Jo-1)

STEP 2: Investigations	
Mandatory	**Supportive**
Myopathology*: • Inflammation consisting of endomysial lymphocytes surrounding non-necrotic muscle fibers (with or without invasion) *see pathology section in main text for additional details	**Myopathology*:** 1. Rimmed vacuoles *and/or* cytoplasmic protein aggregates 2. Mitochondrial abnormalities (COX- SDH+ fibers > age-related) *see pathology section in main text for additional details **Lab tests:** 3. Anti-cN1a autoantibody positive **Imaging:** 4. Typical muscle MRI appearance *and/or* typical muscle ultrasound pattern

Diagnosis of IBM is confirmed when there is:
1. **Common** presentation with FF **and** KE weakness, **and** mandatory investigation finding, OR
2. **Common** presentation with FF **or** KE weakness, **and** mandatory investigation, **and** at least one supportive investigation finding(s) (1–4), OR
3. **Uncommon** presentation **and** mandatory investigation, **and** at least two supportive investigation findings (1–4)

CK = serum total creatine kinase; cN1a = cytosolic nucleotidase 1A; COX = cytochrome oxidase; EMG = electromyogram; FF = deep finger flexor; IBM = inclusion body myositis; KE = knee extensor; MRI = magnetic resonance imaging; SDH = succinate dehydrogenase; ULN = upper limit of normal.

perspective, it can be difficult to conceptualize the implications of a "probable" or "possible" diagnosis. Secondly, having multiple diagnostic categories can create complexity with regards to eligibility for certain treatments or inclusion in clinical trials, especially when these categories overlap or when a patient may move from one category to another over time. We feel that a system where a patient is defined as either meeting the diagnostic criteria for IBM or not is warranted and simpler.

In setting the minimum number of features required for a patient to meet the diagnostic criteria for IBM, this ENMC working group aimed to ensure that patients in any category of the previous diagnostic criteria continue to meet the revised criteria. However, we were mindful that the revised criteria would not include a small number of patients included in ENMC 2013 "probable" diagnostic category as only one biopsy feature was required in addition to the typical IBM pattern of weakness in upper *or* lower limbs [2]. We feel that we have mitigated this potential issue whilst maintaining high diagnostic specificity by:

1. No longer including the requirement to compare finger flexion with shoulder abduction power, or compare knee extension with hip flexion power, now simply referring to (deep) finger flexion or knee extension weakness
2. Inclusion of mitochondrial abnormalities as a new muscle biopsy feature to support diagnosis
3. Inclusion of two new investigational modalities to support diagnosis, i.e., muscle imaging (by MRI or US), and serology (for anti-cN1a autoantibodies).

Overall, we trust that these changes will enhance the sensitivity and specificity of the diagnostic criteria for IBM, give a clear message to patients about their diagnosis, and facilitate access to clinical trials and hopefully new treatments for this disorder in the future. Future validation and refinement of revised criteria from this report will be necessary over time.

The revised 2024 ENMC diagnostic criteria for inclusion body myositis (Table 2) consist of a two-step approach: determining the clinical presentation type first, followed by confirmatory investigations. IBM most commonly occurs in individuals 45 years of age or older, presenting with at least 12 months of progressive muscle weakness, predominantly affecting deep finger flexors and/or knee extensors and/or deep finger flexors. However, as highlighted during this meeting, it has become widely recognized that IBM may affect younger individuals and may present with weakness beyond finger flexors and knee extensors. Patients with these atypical or less common presentations demonstrate a similar, slowly progressive course, with the majority fulfilling the ENMC 2013 diagnostic criteria at a later stage [9]. Furthermore, despite not being included in previous criteria, dysphagia is a canonical feature of IBM. Aspiration pneumonia, along with respiratory failure, is the leading cause of death in patients with IBM [30]. Isolated dysphagia is the third most common presentation after knee extensors or finger flexors weakness [9] and the majority of IBM patients develop dysphagia at some stage during the disease course.

With all these factors in mind, due regard was given to making the revised criteria more inclusive, which is of utmost importance for clinical trial readiness. Although the diagnosis may be established clinically without following any published diagnostic criteria, diagnostic criteria could offer a framework for diagnosis even in the clinical setting, as deemed appropriate.

From a clinical standpoint, establishing a diagnosis in a timely manner is important to monitor for complications and offer disease modifying treatments, once available, sooner in the disease course, while avoiding treatments not deemed effective in IBM.

From an investigational standpoint, the mandatory requirement is to satisfy the myopathologic feature of endomysial inflammation (this does not preclude the identification of further supporting myopathologic features for IBM and an exhaustive evaluation for features supporting an alternative diagnosis). Although some patients may display the classical pattern of weakness at presentation, with prominent involvement of finger flexors in the upper limb and knee extensors in the lower limb, this pattern is not pathognomonic of IBM. Myotonic dystrophies, myofibrillar myopathies, multisystem proteinopathies, filaminopathies, dystrophinopathies, dysferlinopathies, anoctaminopathies, amyloid myopathy and others may have similar distribution of weakness [20]. Many of these disorders may also present later in life and without positive family history. Hence, the importance of combining the clinical presentation with the histopathological findings. However, the level of needed supportive evidence depends on the level of certainty in the diagnosis. We also acknowledge that in some patients obtaining a muscle biopsy may not be feasible and the clinician may opt to base their diagnosis solely on clinical grounds in addition to supportive investigations such as muscle imaging and serological testing for cN1a autoantibodies, when available.

In patients with a common presentation displaying prominent deep finger flexor AND knee extensor weakness, demonstrating endomysial inflammation on biopsy is sufficient to establish the diagnosis of IBM. In patients with a common presentation displaying prominent deep finger flexor OR knee extensor weakness, at least one supportive investigation result is needed in addition to demonstrating endomysial inflammation on biopsy. The supportive investigation could still be derived from myopathological findings (accumulation of rimmed vacuoles or cytoplasmic protein aggregates, or mitochondrial abnormalities). Cytoplasmic protein aggregates could be demonstrated by immunostaining (e.g., p62 or TDP43), by electron microscopy (15/18 nm tubulofilaments), or by thioflavin or Congo Red staining (congophilic inclusions).

Alternatively, anti-cN1a autoantibodies and muscle imaging could also be used as supportive investigations. These are integrated in the revised criteria and would require demonstrating typical muscle involvement pattern on MRI and/or ultrasound. The inclusion of these modalities to support the diagnosis represents an important new development in the diagnostic strategy for IBM. Lastly, in patients with an uncommon presentation, additional evidence is needed to establish the diagnosis as the differential diagnosis in this group is wider and varies depending on the respective phenotype. Therefore, this type of presentation requires at least two supportive investigations, in addition to the mandatory demonstration of endomysial inflammation on muscle biopsy.

It is important to highlight that these criteria should be applied in the appropriate setting where IBM is suspected. Hence, the diagnosis should be established by a specialist familiar with IBM and its mimickers. Although IBM can very rarely affect other family members, a positive family history of neuromuscular disease should prompt consideration of an inherited muscle disorder instead. Regarding the use of electrodiagnostic testing, EMG can help confirming the presence of a myopathy and assist with the exclusion of alternative etiologies such as a motor neuron disease, multifocal motor neuropathy, entrapment neuropathy (e.g., anterior interosseus neuropathy), or radiculopathy (e.g., L3/4 lumbar radiculopathy). It is noteworthy that patients with IBM commonly display mixed short (myopathic) and long (neuropathic) duration motor unit potentials on EMG and the neuropathic changes may be more prominent in some [77]. This may lead to an erroneous diagnosis of a neuropathic process or motor neuron disorder [64]. Lastly, a positive myositis specific autoantibody would also warrant further investigation to determine whether it is false positive, or if the patient has another form of myositis.

In summary, we propose these criteria as a guide to IBM diagnosis. We emphasize an integrative approach that begins with the clinical phenotype and is supported by myopathologic features, laboratory testing and imaging. Further investigations may be necessary to establish a diagnosis. For example, panel based genetic testing in the setting of an absent family history, which is not a mandatory feature of our flow chart, maybe appropriate. Alternatively, further analysis of myopathology using immunohistochemical stains may prove beneficial. For example, when endomysial inflammation is absent or difficult to see using routine stains, immunohistochemical stains for MHCI, MHCII, CD8 or other T-cell markers may be used to support the mandatory biopsy feature of inflammation. Finally, the clinical phenotype or even anti-cN1a serotype may evolve over time as the disease progresses. Thus, the fulfillment of the criteria may require re-evaluation over time.

3. PART B: clinical outcome measures and clinical trial readiness

3.1. Background

The second part of the workshop focused on the use of outcome measures in clinical practice and their utility in clinical trials. A wide variety of clinician assessed and patient reported outcome measures are available for the determination of extent and severity of disease in IBM, but an optimal set of measures to use in clinical practice has not been agreed. Similarly, selection of the optimal outcome measures to use in interventional clinical trials in IBM remains controversial, especially given the slowly progressive nature of the disorder and the variable patterns of muscle involvement and progression.

3.2. Lessons from prior trials

Mazen Dimachkie reviewed lessons from prior trials. Initial reports were limited to observational studies. Earlier controlled trials spanned a few months and had a modest number of subjects. Exercise intervention may have been a limitation to data interpretation of the intramuscular follistatin gene transfer pilot study [78]. Despite encouraging pilot study data, the phase 3 study of bimagrumab did not improve the 6-minute walk distance [5]. The randomized, double-blind, placebo-controlled study of arimoclomol in IBM (NCT02753530) showed no benefit at 20 months as assessed by the IBMFRS. The IBMFRS progression rate in the placebo arm was slower than expected. In the monocentric 12-month study of sirolimus, the primary outcome was not met (stabilization of quadriceps strength measured by myometry), though some of secondary outcome measures showed a benefit (6MWD, FVC, HAQ-DI, and thigh MRI global fat fraction) [79]. While there is a lack of universal consensus on trial design, we are getting closer to that goal in terms of number of subjects, study duration, inclusion/exclusion criteria, outcome measures, and biomarkers (depending on drug mechanism of action - MOA) to demonstrate early target engagement. It is important not to heavily rely on extrapolation from natural history studies and to consider in the trial planning outcome measure variability. Outcome measures may not perform similarly across clinical trials given improvement in supportive care and difference in enrolled patient characteristic. The placebo effect is not to be underestimated as it may compromise the ability to detect benefit.

3.3. Current and upcoming treatments

Olivier Benveniste discussed trials in IBM. Prior to 2002, there were only 7 randomised controlled trials in IBM [80–86] with relatively short observation times (3–12 months) and diverse and unvalidated outcomes. None of these trials demonstrated efficacy of the different molecules evaluated (corticosteroids, IVIG, IFN-β, methotrexate). In the late 2000s, a first large-scale industrial trial was set up to block the myostatin pathway in IBM patients with a mAb (bimagrumab) to induce an increase in muscle mass and possibly muscle function. This first, multicentre, randomized, Phase II/III controlled trial comparing 3 doses of bimagrumab vs. placebo in 240 patients failed on its primary outcome (6MWD) and the majority of secondary endpoints [5]. Recently a trial using arimoclomol which is believed to function by stimulating a normal cellular protein repair pathway through the activation of molecular chaperones, was conducted in 152 patients. Again, the trial failed on both its primary outcome criterion (IBMFRS) and all secondary endpoints (data was not published at the time of the meeting) [6].

At the same time, several teams have described the immunological abnormalities found in patients and in particular the accumulation in the intramuscular inflammatory infiltrates of T effector memory (EM) and T effector memory re-expressing CD45RA (TEMRA) cells [87]. However, these EM and TEMRA cells, which are key effector cells in the pathophysiology of IBM, are not very sensitive to conventional immunosuppressants including corticosteroids, potentially explaining their lack of efficacy. Two approaches targeting specifically these EM and TEMRA cells are ongoing. The first one tests rapamycin (sirolimus, a well-established immunosuppressant licensed to prevent kidney graft rejection) and is based on the results of a Phase II, monocentric trial, in 44 patients treated with sirolimus vs. placebo in a double-blind manner for one year [79]. The primary outcome was based on the myometric measurement of knee extension force (quadriceps). This measure, like all other muscle groups assessed by myometry, did not show a significant difference between patients treated with sirolimus or placebo, probably due to lack of power of the trial and/or too great interindividual variability of the measurements. On the other hand, many secondary criteria showed a significant effect in favour of stabilization under sirolimus, such as 6MWD, fat muscle replacement in quantitative MRI, HAQ or FVC. These encouraging results motivated the initiation of a multicentre Phase III trial for 140 patients (NCT04789070), which is now underway. Even more targeted on EM and TEMRA cells, a mAb directed against a canonical membrane marker of EM and TEMRA T cells (KLRG1) has been developed. The Phase I trial (NCT0465903) is complete and the Phase II/III pivotal trial (201 patients, NCT05721573) is underway (see below).

However, these immunosuppressive molecules will have no direct effect on the restoration of muscle strength. To overcome this medical need, two phase I trials of regenerative medicine by cell therapy are underway. One is promoted by the “Assistance Publique, Hôpitaux de Paris” (NCT05032131) and the other by “University of Kansas Medical Center” (NCT04975841). They both aim to isolate the stromal vascular fraction from the adipose tissue (by slightly different methods) and re-inject this cell mixture (rich in stem cells) into a muscle group in order to increase its mass and function.

Steven Greenberg discussed the development of ulviprubart (ABC008) for IBM. Ulviprubart is a monoclonal antibody therapeutic with enhanced effector function designed to deplete KLRG1+ cytotoxic T cells. KLRG1 marks the most cytotoxic subpopulation of CD8+ T cells. These T cells have been identified as expanded in blood and muscle of patients with IBM, and within muscle can be seen to be invading myofibers [87–91]. Targeting KLRG1+ cells provides a selective approach to spare autoimmune disease helpful regulatory T cells and protective T cell memory responses, while eliminating harmful cytotoxic T cells. A non-invasive PET-CT biomarker of the broader muscle CD8+ T cell population has been developed as a research tool to assess CD8 T cell muscle invasion in IBM [92]. A key aspect for IBM clinical therapeutic development is endpoint selection. The effect size of a therapeutic on a specific endpoint (its mean change/standard deviation of changes) is a key parameter. Some endpoints have such large variability that their comparative effect sizes make them impractical for clinical development. For a therapeutic that might stabilize IBM disease progression, some endpoints such as 6MWD and handgrip dynamometry in large placebo-controlled trials have had such small effect sizes that >2000 patients would be required to detect their statistical significance. The IBMFRS at 76 weeks was selected as the primary endpoint for the development of ulviprubart after these considerations in order to detect disease stabilization (NCT05721573).

3.4. Clinical outcome measures

Mazen Dimachkie reviewed limitations of available outcome measures with focus on psychometric properties. Validity (face, content, and construct), reliability (inter-rater, intra-rater, test-retest, in-person vs. phone) and responsiveness to change are critically important features of a robust outcome measure. Candidate IBM clinician- or patient-reported outcome measures (ClinRO and PRO) were reviewed including IBM Functional Rating Scale (IBMFRS), Sporadic IBM Functional Assessment (sIFA), Upper Extremity PROMIS, and the IBM Health Index (IBM-HI) (personal communication courtesy by Chad Heatwole, MD) as a measure of multifactorial disease burden. Most outcomes with few exceptions (sIFA and IBM-HI) were not derived using FDA guidance for PRO development specifically for IBM and nearly all lack longitudinal data. Physical outcome measures such as MMT, QMT, TUG, and timed-walk tests have not performed well in the context of large IBM efficacy clinical trials while the sIFA, a secondary outcome measure, revealed a statistically significant difference in the higher dose bimagrumab cohort [5]. The advantages of the IBMFRS, which was derived from the ALSFRS are the recent demonstration of content validity, inter and intra-rater reliability and equivalence between different face-to-face vs phone administration [93]. The ultimate validation of primary outcome measure is through demonstrating its success in clinical trials and that is lacking so far in IBM. It is important to define the minimal clinically important difference (MCID) for improvement and for worsening as they may not be the same. The optimal outcome measure in IBM clinical trials may be further clarified by the ongoing natural history INSPIRE-IBM (NCT05046821) and by analysis of data from placebo groups of large multicenter studies with homogenous enrollment criteria.

Lindsay Alfano presented a variety of methods for testing muscle strength and evaluating functional abilities that have been validated for clinical or research purposes in cohorts of patients with neuromuscular disorders. Several cross-sectional and observational, longitudinal studies have also examined feasibility and validity of these tools in cohorts of patients with inclusion body myositis. Most studies to date have characterized progression of disease through inclusion of demographic information of onset of systems, age at diagnosis, etc. Similarly, evaluation of function using broad functional scales categorizing general disease progression, monitoring progression of weakness in key muscle groups (i.e., quadriceps, deep finger flexors), and ambulatory outcomes have been the focus to date. Much work is needed to further understand optimal tools to measure meaningful function, including identifying outcomes to measure upper extremity

function and to better understand dysphagia and dysarthria in IBM. There is no 'one size fits all' approach to selection of outcome measures as each has more or less utility in a specific context of use. Discussion included a strong recommendation of a validated toolbox of recommended outcomes including quantification of muscle strength, gross motor or ambulatory ability, upper extremity function, and dysphagia/dysarthria, among others.

Louise Diederichsen gave an overview of dysphagia, present in up to 80 % of patients with IBM. In addition, dysphagia has quite substantial life-threatening consequences in IBM as it is the primary contributor to early mortality due to aspiration pneumonia, which is three times more frequent in IBM than in other IIMs [22,94]. Unfortunately, the evidence of how to diagnose and quantify dysphagia in patients with IBM is limited. As for now, assessment procedures/tools and swallowing-related outcome measures used to evaluate swallowing in intervention trials in IBM have only partly been validated for IBM [95] (and see below).

Most former trials have used more than one swallow assessment tool, most often videofluoroscopic swallow studies in conjunction with another instrumental tool including barium swallow, esophageal manometry, oropharyngeal scintigraphy and MRI. Regarding swallowing-related outcome measures, various patient-reported outcome measures (PROM) have been used; some validated and some non-validated. The only validated PROM specifically for IBM is The Inclusion Body Myositis Functional Rating Scale (IBMFRS), which includes one single question regarding swallowing. In conclusion, current evidence that examined swallowing as an outcome measure in interventional trials in IBM is of limited quality. Further work is needed to better define swallowing pathophysiology in IBM using validated assessment methods including PROMs.

Lindsay Alfano and **Jens Schmidt** provided insight in the swallowing function and its dysfunction in IBM. Impairment of swallowing is often overlooked in IBM as patients may not realize their dysphagia or think that their symptoms are caused by other factors than IBM. To identify a possible dysphagia, subjects with suspected IBM as well as patients with an established diagnosis of IBM should be routinely asked specific questions related to the swallowing function:

- Do you experience difficulty chewing solid or liquid food?
- Are there any food residues in your mouth after swallowing?
- Do you have to swallow multiple times and/or in small portions?
- Do you choke or cough during eating?
- Do you have to clear your throat after swallowing?
- Does food "get stuck" in your throat?
- Does eating take longer than normal or previously?
- Did you change your eating habits (e.g., avoid certain food)?

Once dysphagia has been identified in IBM and confirmation by appropriate tests has been achieved, monitoring of the symptoms can be achieved by several scales – albeit they have not been specifically designed for or validated in IBM. These scales include the questionnaires Swallowing quality of life (Swal-QoL; 13 questions, mostly scored 1–5); Sydney swallow questionnaire (SSQ; 17 questions with visual analogue scale); functional oral intake scale (FOIS; 7 levels); Eating Assessment Tool (EAT-10); M.D. Anderson dysphagia inventory (19 questions scored 1–5).

Helene Alexanderson discussed one of the most used patient-reported outcome measures (PROM) in IBM, the Inclusion Body Functional Rating Scale (IBMFRS). It was derived from the ALS Functional Rating Scale and developed as a questionnaire to be completed together with the physician with satisfactory construct validity, test-retest reliability, and sensitivity to change with moderate to large effect size. However, its content validity for IBM has not been established. The IBMFRS performs equally well when obtained by the physician compared to an online survey. The Sporadic Inclusion Body Myositis Functional Assessment (sIFA) was developed with extensive input from patients supporting very good content validity. sIFA also has satisfactory construct validity and test-retest reliability but revealed small effect size. The Upper Extremity Functional Scale for IBM is a PROM focusing on hand and upper extremity function that correlates well to grip and pinch grip strength.

Yves Allenbach provided an overview on available wearables to measure physical activity and function. In the absence of biomarkers, measuring the functional impact of IBM is certainly one of the best approaches because it can be both objective and clinically meaningful. Quantitative or semi-quantitative measurements of muscle strength or endurance require good patient participation and medical expertise. The questionnaires are also interesting but collect information about motor functions that are not linearly correlated with the strength [96]. Moreover, patients overestimate their physical activity when using appropriate questionnaires [97].

Physical activity is usually defined as any body movement produced by skeletal muscles that results in energy expenditure. Portable and wearable technological devices permit continuous monitoring of physical activity. Body-worn inertial sensors (e.g., accelerometers) are differentiated by the site of attachment (wrist-, hip-, ankle-worn).

In myositis patients (excluding IBM), accelerometers showed that physical activity is decreased compared to the general population [98]. In addition, significant relationships between changes in physical activity and changes in other variables at follow-up were observed, including physician global activity, muscle enzymes, manual muscle testing score or Health Assessment Questionnaire [98]. In the absence of data, it is not known whether the performance of accelerometers in IBM is as good. Indeed, the force variations are less intense and slower in IBM than in other myositis subtypes. Nevertheless, in other neuromuscular pathologies (e.g., Charcot-Marie-Tooth disease, Duchenne Muscular Dystrophy or Amyotrophic Lateral Sclerosis), wearable devices are able to detect a decline in walking or in physical activity, but over a long period. Detecting physical activity changes in IBM seems feasible with wearable devices and a possible clinically meaningful outcome but other outcome measures are probably necessary to detect early changes.

3.5. Recommendations for clinical trial endpoints for IBM

Mazen Dimachkie discussed the creation of guidelines for clinical trial endpoints for IBM. There was a general agreement to be parsimonious in selecting patient assessment to minimize participant fatigue. A variety of primary outcome measures were reviewed including Patient- and Clinician-Reported Outcomes (PRO/ClinRO), quantitative muscle strength testing, timed performance tests, and biomarkers. There was agreement that a PRO/ClinRO are the preferred primary outcome measure for large efficacy trials. To reach expert consensus, there was a brief overview of the IBMFRS, sIFA, PROMIS UE and the IBM-HI that led to open deliberation and a vote. Though derived using FDA PRO guidance, the sIFA was not deemed by the group to be the primary outcome measure of choice despite its performance as a secondary outcome measure in the bimagrumab study [5]. The IBM-HI (personal communication – Chad Heatwole) and PROMIS UE, which is limited to the upper extremity, have yet to undergo longitudinal validation studies to determine the MCID for change.

The overwhelming majority of experts voted in favor of using the IBMFRS as the primary outcome measure given its acceptability to US regulators and data presented from the recent validation

study [93], while at the same time acknowledging its limitations. For example, the IBMFRS does not address fatigue or the degree of adaptation or difficulty it takes to successfully complete one of 4 categories of its 10 items. Furthermore, the ultimate validation of an outcome measure is based on its ability to demonstrate a clinically meaningful benefit in the context of a positive clinical trial, but that was lacking for IBM. As far as inclusion and exclusion criteria and secondary outcome measures, there were similarities across the IBM4809 study (NCT02753530) Optimism in IBM (NCT04789070) and ABC008 (NCT05721573). The duration of phase 2/3 studies ranging between 18 and 20 months was appropriate given slow disease progression in IBM. Shorter duration proof-of-concept studies may use a biomarker to gauge early on for target engagement, such as thigh muscle quantitative MRI or an outcome measure (e.g., blood based biomarker) specific to drug mechanism of action. The number of subjects may be upward of 60 per treatment arm in a controlled large-scale phase 3 efficacy trial. Capturing exercise diary and maintaining a stable level of physical activity / exercise level is important during clinical trials. Lessons learned from the completed IBM4809 and both ongoing phase 2/3 studies are likely to expand knowledge about optimal IBM study design.

Participants

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James B. Lilleker: Writing – review & editing, Writing – original draft. **Elie Naddaf:** Writing – review & editing, Writing – original draft. **Christiaan G.J. Saris:** Writing – review & editing, Writing – original draft. **Jens Schmidt:** Writing – review & editing, Writing – original draft. **Marianne de Visser:** Writing – review & editing, Writing – original draft. **Conrad C. Weihl:** Writing – review & editing, Writing – original draft.

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