Inclusion body myositis
MRC Centre for Neuromuscular Diseases, IBM workshop, London, 13 June 2008

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1. Introduction

This first MRC workshop on inclusion body myositis assembled 29 clinicians and scientists. The workshop sought to establish a platform upon which an organised international network of neuromuscular specialists could consider a range of important unresolved issues in relation to IBM. The aims of the workshop were as follows: to review current practice regarding clinical and histopathological diagnostic criteria, to assess recent advances in relation to aetiology and basic science with potential for translation into clinical trials, to review current evidence for IBM treatments and lessons applicable to future trial design, to review genetic advances in IBM and to consider an IBM disease-specific prospective database in an electronic network.

2. Clinical and histopathological diagnostic criteria

2.1. Consideration of clinical diagnostic criteria

After a brief discussion of the typical clinical features of IBM [1–4], David Hilton-Jones updated the workshop on the current diagnostic criteria for IBM [5–8]. The widely employed Griggs criteria for ‘definite’ IBM requires fulfilment of several histopathological criteria encompassing degenerative and inflammatory disease processes [5]. According to the Griggs criteria the diagnosis can be considered definite on the basis of fulfilling certain histopathological criteria alone (inflammatory myopathy with mononuclear cell invasion of non-necrotic muscle fibre, and vacuolated muscle fibres, and either intracellular amyloid deposits or 15–18 nm tubulofilaments by EM). It was agreed that in practice there is a group of patients who may be considered on clinical grounds to have IBM, with selective involvement of long finger flexors and quadriceps muscles, but who do not meet the stringent histological requirements of the Griggs criteria. Typically such patients show biopsy features consistent with the diagnosis of IBM (e.g. endomyosial inflammatory cells with partial invasion, increased expression of MHC-I on otherwise normal looking fibres, and sometimes vacuoles (rimmed or unrimmed) but lack the canonical features of amyloid deposition or 15–18 nm tubulofilaments. Such specific pathology may be lacking because of sampling error, because appropriate techniques to look for amyloid, or electron microscopy were not performed routinely, or that the absence of such changes is a feature of an earlier stage of the disease. Further consideration of this group of patients was considered important since it is possible they may represent an earlier stage of the IBM disease process and thus may be more amenable to therapeutic intervention. There should be provision for including such cases in clinical trials provided there could be a clear operational definition. Further support for this view comes from Cahin and Engel who have recently described a cohort of patients in whom IBM was clinically apparent to the neuromuscular specialist but in whom some of the suggested canonical pathological features were lacking. They analysed 107 patients whose biopsies had originally been reported as either polymyositis or IBM [4]. In a detailed retrospective analysis of the muscle biopsies and clinical features three main groups were identified: pure PM in 27, pure IBM in 64 and an overlap of IBM/PM in 16. Importantly, the IBM/PM group had a clinical distribution of muscle weakness considered typical of IBM and although they had pathological features considered consistent with polymyositis (i.e. inflammatory infiltration in the endomysium, with or with out infiltration on non-necrotic fibres and without histological feature of DM) they did not have the canonical feature of IBM as defined by the Griggs criteria to include rimmed vacuoles or congophilic deposits. In all other respects, including in terms of treatment response and disease progression this IBM/PM group were indistinguishable from the IBM group. In such patients even repeated muscle biopsy, although acknowledged to be important, may also fail to contain the canonical histological features. A further confounding factors, discussed in more detail below, is the lack of consensus on histopathological protocols, particularly on how intracellular amyloid and associated proteins are detected.

In order to accommodate the above, modified diagnostic criteria are proposed (Table 1). The suggested categories are:

- Pathologically defined IBM – i.e. meeting the Griggs criteria [5].
- Clinically defined IBM – suggested at this workshop.
- Possible IBM – essentially as defined by Griggs criteria [5].

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- Possible IBM – essentially as defined by Griggs criteria [5].
It was agreed that the criteria for the “clinically defined” group should remain provisional whilst the cause of IBM remains undefined. The first group includes those patients who meet Griggs’ criteria for definite IBM. It was agreed that the time-course required by a clinically defined case should be 12 months (longer than the initial Griggs’ criterion of 6 months) and that the age of onset should be after 35 years (again, slightly later than the Griggs criterion) – these time extensions may add greater security to the clinical diagnosis. There should be no additional clinical or pathological features inconsistent with the diagnosis of sIBM.

2.2. Review of histopathological assessment, diagnostic criteria and application

Janice Holton presented the histopathological features of IBM and outlined a suggested minimum approach to histopathological evaluation Table 2. Typically features include variation in fibre diameter and inflammatory infiltration of intact, non-necrotic myofibres [1]. The endomysial infiltration, predominantly by CD8+ T-cells, in IBM and PM contrasts with the perivascular distribution of predominantly CD4+ lymphocytes seen in DM. In DM there may also be a contribution by CD20+ B lymphocytes to the inflammatory infiltrate. Rimmed vacuoles, surrounded by basophilic material, may be few or frequent but are often multiple within single fibres. These are not specific features and may be seen in other conditions in which the intracellular environment favours the accumulation of misfolded proteins. They might be consequent to lysosomal activity [1] or myonuclear breakdown [9]. It was noted that fibres containing rimmed vacuoles did not tend to be the fibres undergoing inflammatory infiltration. This has led to the suggestion that there may be two parallel pathological processes at play [1].

It was agreed that the widespread upregulation of MHC Class I, whilst sometimes subtle, is a key feature of inflammatory myositis and is expected in pathologically defined IBM. Coincident upregulation of MHC-I seen in regenerating fibres can be distinguished by staining for neonatal myosin. Additional features of IBM include ragged red fibres seen in Gomori trichrome and SDH preparations and cytochrome oxidase deficient fibres, disproportionate to the patient’s age. Features of denervation may also be seen.

Ultrastructurally, abnormal protein deposition manifests as whorled membranous deposits, tubulofilamentous inclusions of 16–20 and 6–10 nm amyloid like filaments. A number of different proteins have been demonstrated to accumulate in muscle fibres in IBM and these are identified as typical neurodegenerative candidates, such as β-amyloid, α and β-synuclein, but others have been detected and are thought to represent overwhelmed cytoprotective mechanisms such as proteasome components, heat shock proteins, valosin-containing peptide, and ubiquitin [3].

Caroline Sewry outlined the histological overlaps between IBM, polymyositis, myofibrillar myopathies, distal myopathy with rimmed vacuoles and statin induced myopathy. The overlaps often presented difficulties in the clinical setting and the importance of correlation with the clinical phenotype, clinical history, and also family history was emphasized. A precise standard definition of the full histological phenotype in these different conditions and an assessment as to whether histological protocols can consistently differentiate them is required. However, achieving this type of definition is compounded by the lack of uniformity or standardization in the range of available techniques that has been used by different workers both routinely and for entry into clinical trials. Many different techniques have been proposed. For example, vacuolated fibres may be examined for phosphorylated tau with SMI-31 or SMI-310, however, a comparison between the two is lacking. SMI-310 immunostaining has been shown to label some nuclei but it is undefined whether this indicates intranuclear inclusions or is non-specific. A peripherally rimmed pattern was seen in other fibres, the significance of which is also unknown.

Reflecting the presence of amyloid, it was agreed that congophilia can be seen without coexisting rimmed vacuoles. Congophilia can be detected using a variety of methods, most of which were established in brain tissue rather than muscle although no standard method is agreed. There is a possibility that thioflavin S might be a further promising such agent to detect amyloid. The frequency of various protein deposits in IBM muscle has not been fully studied. Caroline Sewry outlined a recent audit of 33 IBM cases from Oxford and London and in 21 were positive for ubiquitin inclusions. However β-amyloid and APP were detected less frequently. It was agreed that essential pathological diagnostic features of IBM should include upregulation of MHC Class I. It was noted that MHC-I is upregulated in other classes of myopathy including low grade levels in Duchenne for example emphasizing the importance of clinical correlation. Furthermore one needs to consider the possible impact of steroids or statins in MHC-I and this has not been fully studied. MHC-I staining may be positive in 10–20% IBM fibres but only in invaded fibres but it is unclear if this is specific. The presence of protein deposits in

<table>
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<th>Table 1</th>
<th>Proposed modified IBM diagnostic criteria.</th>
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<tr>
<td><strong>Pathologically defined IBM</strong></td>
<td>Conforming to the Griggs criteria [5] – invasion of non-necrotic fibres by mononuclear cells, and rimmed vacuoles, and either intracellular amyloid deposits or 15–18 nm filaments</td>
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<tr>
<td><strong>Clinically defined IBM</strong></td>
<td>Clinical features Duration weakness &gt; 12 months Age &gt; 35 years Weakness of finger flexion &gt; shoulder abduction AND of knee extension &gt; hip flexion</td>
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<td>Pathological features Invasion of non-necrotic fibres by mononuclear cells or rimmed vacuoles or increased MHC-I, but no intracellular amyloid deposits or 15–18 nm filaments</td>
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<th>Table 2</th>
<th>Current minimum approach recommended at this workshop.</th>
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<td>Frozen sections</td>
<td>Immunohistochemistry on frozen sections</td>
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<tr>
<td>H&amp;E</td>
<td>MHC Class I, complement MAC</td>
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<td>Gomori trichrome</td>
<td>CD 3/4/8/68(macrophage)/20 (B-cells)</td>
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<td>Oxidative stains</td>
<td>Neonatal myosin</td>
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<td>(SDH, NADH, COX)</td>
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<td>Acid phosphatase</td>
<td>Amyloid β</td>
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<td>Congo Red</td>
<td>Tau</td>
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<td>ATPase</td>
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Electron microscopy may be performed in selected cases.

Please cite this article in press as: Hilton-Jones D et al. Inclusion body myositis. Neuromuscul Disord (2010), doi:10.1016/j.nmd.2009.11.003
the absence of vacuoles might prove important but a systematic study is required. COX negative fibres are frequently reported but not considered essential. Ultrastructural assessment is not essential since other markers exist for light microscopy.

It was concluded that a standard approach regarding the histological techniques employed to diagnose IBM was required. Further studies are needed before a standard approach can be agreed. Such studies should assess the most appropriate method for the detection of amyloid, αB-crystallin, VCP and compare SMI-31 vs. SMI-310. The presence of αB-crystallin in normal fibres may also be important but has not been fully studied. The absence of desmin and myotillin accumulation might prove a useful negative criterion. Correlation with clinical phenotype remains essential. It was agreed that a consensus should be reached on the evaluation of muscle biopsy tissue for features of IBM. Further studies are required to determine the optimal techniques to detect these. Particular attention should be paid to fibres which appear superficially normal. Establishing a network of IBM Reference Centres could facilitate the implementation of agreed protocols to replace the widely differing systems currently employed in different hospitals.

### 3. Current research with potential for translation into clinical trials

#### 3.1. Aetiology of IBM

Adrian Miller summarized the evidence underlying the pathogenesis of IBM.

In sIBM, inflammation is manifested by clonally expanded CD8⁺ T-cells invading fibres expressing MHC Class I. Additional associations with autoimmune-prone haplotypes, paraproteinaemia, and the upregulation of cytokines imply an immunopathogenic component. The coexistence of an IBM-like myopathy with HIV and HTLV-1 infection [10] might imply a viral trigger to autoimmunity in sIBM. Analogous to Alzheimer’s disease, sIBM shows abnormal aggregation and deposition of proteins, including amyloid-β (Aβ), in an aged cellular environment. The soluble Aβ oligomers which preclude aggregate formation may be particularly cytotoxic. Aβ accumulation and toxicity reflect increased production, abnormal processing and impaired breakdown. Proteasomal degradation is significantly impaired in sIBM [11]. Amyloid accumulation may be both consequent and contributory to this, creating a self-perpetuating pathogenic cycle [12]. This may be enhanced by dysfunctional ubiquitin or valosin-containing peptide. In experimental models, mitochondrial abnormality and histological pathology similar to that of human sIBM tissue, including autophagic vacuolization, were induced by Aβ [3,13]. Aged skeletal muscle’s propensity to mitochondrial DNA mutations and reduced inducibility of the cytoprotective heat shock response may confer susceptibility to sIBM. Fast-twitch fibres appear the most vulnerable, particularly to the cytotoxicity of Aβ [14]. Evidence suggests that degenerative and inflammatory mechanisms can potentiate each other. Their interaction is reflected in the correlation between the mRNA expression of βAPP and of chemokines. In a myogenic cell culture study, exposure to the cytokine IL-1β increased intracellular Aβ concentration [15]. Conversely, upregulation of the inflammatory transcription factor NF-κB by endoplasmic reticular stress suggests a self-sustaining process in which MHC upregulation and T-cell recruitment occur secondarily.

To date, several trials of immunosuppressive therapy in IBM, including nine RCTs have not demonstrated clinical benefit [8]. The absence of a response does not itself indicate that IBM is not an immunologically mediated disease. Trials of new, arguably more specific, immunological agents, such as the monoclonal antibody alemtuzumab, are in progress. Nevertheless, the poor efficacy of immunotherapies suggests more effective novel treatments might bridge the degenerative and inflammatory components, for example, by amelioration of endoplasmic reticulum stress. The heat shock response, as an inhibitor of mechanisms leading to aberrant protein deposition, and of NF-κB, might represent a suitable target. In this respect, a pilot study of arimoclomol, a coinducer of heat shock protein expression, is underway.

#### 3.2. Targeting protein misfolding and protein aggregation

Linda Greensmith outlined the increasing evidence to support the hypothesis that in a range of neurodegenerative diseases protein misfolding, protein aggregation, and proteosome dysfunction are implicated in disease pathogenesis. Although it remains unproven that protein aggregation and proteosome dysfunction is central to the pathogenesis IBM, it does seem to be at least a factor in IBM pathology. It is interesting to draw parallels and consider the relevance of progress relating to anti-aggregation strategies in certain neurodegenerative diseases.

In CNS neurodegenerative diseases a considerable amount of work has been undertaken in order to identify agents that may be able to disaggregate abnormal misfolded protein accumulations. Such aggregates are generally thought to be toxic to neurons and there is strong evidence to support this neurotoxicity. Importantly, high throughput systems including cultured cells lines have been developed to rapidly test compounds for potential anti-aggregation activity.

Molecular chaperones act as endogenous markers which co-localize with misfolded protein aggregations such as Aβ amyloid. These chaperones enable the cell to cope with a variety of stresses and tend to minimize abnormal protein aggregation.

The heat shock response is endogenous to all cells and involves the upregulation of a family of chaperones called heat shock proteins (HSPs) in response to a variety of cellular stresses. HSP have the ability to ensure proteins are in the right shape at the right time and in the right place so that they can carry out their normal functions.

Amyotrophic lateral sclerosis (ALS) is a fatal neuromuscular disease for which the aetiology is largely undetermined. Several lines of evidence suggest that oxidative stress, excitotoxicity, and abnormal protein aggregation are all implicated in the premature death of motor neurons which occurs in ALS. HSP inducers have been proposed as possible therapeutic agents in ALS. Arimoclomol is a coinducer of heat shock response, selectively enhancing the response of ‘stressed’ cells by prolonging the activation of the main HSP transcription factor, heat shock factor 1 (HSF-1). HSP inducers can rescue stressed primary motor neurons in culture from oxidative stress generated by exposure to hydrogen peroxide as well as apoptotic death induced by staurosporin. Using this model the most significant cytoprotection was achieved by pre-exposure to a novel HSP-coinducer called arimoclomol, which was more effective than other established HSP inducers such as celastrol. In the SOD1 transgenic mouse model of ALS, 10 mg/kg of arimoclomol resulted in significant benefit. At a late stage of disease, at 120 days, in SOD1 mice treated with arimoclomol there was a significant improvement in EDL motor unit survival and EDL muscle contractile characteristics. For example, in SOD1 mice the normally fast fatigue resistant characteristics of EDL alter dramatically as disease progresses, so that by the later stages of disease EDL in SOD1 mice is fatigue resistant. Treatment with arimoclomol almost completely prevents this disease-dependent alteration in muscle phenotype in SOD1 mice. Video comparison of SOD1 littermates treated with arimoclomol indicates a dramatic improvement in the behaviour of arimoclomol treated SOD1 mice compared to their untreated littermates. This is reflected in a significant improvement in lifespan of arimoclomol treated SOD1 mice, which live for approximately 22% longer than untreated littermates. These improvements in disease characteristics are likely to result from an upregulation in the heat...
4. Review of evidence for IBM treatments and lessons applicable to future trial design

Michael Rose summarized the existing evidence for IBM treatments. The majority of drug treatments have targeted inflammatory and immune mechanisms. Other trials have included antioxidants and mitochondrial impairment (carnitine and ubiquinone). Nine randomized control trials in IBM have been identified for a Cochrane Systematic Review in press. In addition to being relatively few in number, most have recruited small numbers of patients. Other than those studies coordinated by the north American Muscle Study Group all were single centre studies. The nine RCTs in IBM have used the following therapies: IVIG, β-interferon, methotrexate, oxandrolone, methotrexate, and azathioprine ([17–27]). None of these RCTs provided convincing evidence of a definite useful treatment response.

Steroids are commonly employed initially in IBM, reflecting the impression that inflammation may be predominant early in disease course. Consequently, the frequent poor treatment response may reflect the well known delay between onset of symptoms and reaching the diagnosis of IBM [25]. Retrospective studies form the bulk of the evaluation of steroids. One hundred and twelve patients have participated through 15 trials (Cochrane review in press). Doses have ranged from 20 to 100 mg and treatment length has ranged from 2 weeks to 2 years. There was often insufficient information available on dosing regime. In two prospective open label trials of steroids, 8/8 patients deteriorated and 4/16 stabilized or improved although with a clinically significant magnitude. Additionally, the response to steroids difficult to specify as it may reflect response of coexistent illnesses.

In five IVIG open trials disparate results were reported. In three studies there was no benefit, in one some improvement but no functional benefit and one showed ¼ patients improved. However, three RCTs of IVIG failed to show significant changes in strength. Different lengths of treatment weaken meta-analysis but this also shows no improvement [17–22].

There have been two trials examining the impact of exercise on IBM [28,29]. Spector et al. followed five patients over 12 weeks and found no evidence of harm with improvement of dynamic performance [28]. Arnardottir et al. did not detect such benefits in a study of seven patients over 12 weeks but reported an absence of muscle damage [29]. The potential psychological impact of exercise in IBM has not been studied. Mike Rose indicated that his review of the expert approach to IBM patients confirmed that it is common practice that no drug treatment is prescribed. Steroids are widely used, most commonly in cases of diagnostic doubt, rapid progression or pronounced inflammation. Additional co-enzyme Q10 and exercise or methotrexate or azathioprine occasion-ally accompanied steroids. Intravenous immunoglobulin tended to be reserved for rapidly deteriorating cases or those exhibiting significant dysphagia. It was agreed that quality of life in IBM is not related purely to disease severity but includes psychosocial and social support. This outcome measure has been absent from all but one IBM treatment trial.

4.1. Lessons to apply to further IBM trials

It was agreed that the evidence base for IBM treatments is poor. In most trials in IBM the primary endpoint has been proof of concept or safety and tolerability studies rather than efficacy. Although efficacy has often been examined in such studies interpretation is difficult. RCTs have generally been insufficiently powered with variable protocols and variable outcome measures. The required length of IBM trials will depend on the number of participants. Significant difference can probably be measured over 6 months but will require more complicated outcome measures, making multicentre studies more challenging. Demonstrating stabilization is likely to require as long as 2 years follow-up. Improved natural history data are required to determine realistic treatment responses in IBM. This should be the primary initial goal of prospective cohort studies such as IBM-net proposed below. It was agreed that caution should be applied if the placebo arm of an RCT was proposed to represent natural history data due to the potential impact of additional clinical assessments among trial participants over patients undergoing routine clinical follow-up. Ideally, a standard of care could be established to minimize such discrepancies. It is intended that such data and standards would be an achievable outcome of the IBM-net database.

Arrest of progression might be more realistic than improvement. Small changes over short length of time may extrapolate to large differences in a disease of slow progression. Nevertheless, it was agreed that treatment trials must exceed 6 months duration.

There is a diverse population of potential and previously applied trial outcome measures in IBM. These include markers of pathology (e.g. biopsy, gene markers, CK/EMG/MRI/muscle mass), clinical impairment (MMT, QMT), disability (walking, staining, functional assessments), handicap, and quality of life. The selection of measures depends on the purpose and phase of the trial. The importance of developing a disease-specific patient reported outcome measures in line with recent FDA guidance was noted. It was agreed that since grip strength is simple to measure and is commonly impaired in IBM and carries significant functional importance, it is an attractive target for evaluation and outcome measures. Furthermore, it was proposed that the impact of potential drug candidates on grip could be ‘screened’ prior to instigating larger efficacy trials.

5. Genetic studies in IBM

5.1. Genome-wide studies in IBM

Nick Wood described the options for a genetic approach to complex traits such as sporadic IBM. Whilst associations have been demonstrated between IBM and HLA alleles [30–34], it remains undetermined whether the predilection of IBM for certain muscle groups or the apparent deficiencies of cytoprotective machinery reflects genetic susceptibility. Possible genetic studies include linkage based or candidate gene studies and more modern techniques such as a genome wide association study. The latter has the possibility to determine points of interest, is robust and cost-effective and is now generally considered superior to the others. Sample sizes are considerable and depend upon the odds ratio conferred by a given allele. As case controls will be publicly available, only disease cases would be required but such numbers would...
undoubtedly require multicentre collaborations such as the IBM-net database. Mike Hanna described the IBM genetic biobank facility at the MRC Centre in London and the potential for collecting a large IBM DNA bank.

5.2. Hereditary forms of IBM (single gene)

Hanns Lochmuller described that there are several forms of hereditary IBM (hIBM) that are due to defects in single genes and inherited in recessive or dominant traits. Clinically and morphologically there is overlap of hIBM both with sIBM and myofibrillar myopathies. This is illustrated by the case of a 30-year-old patient with clear and prominent findings of muscle inflammation resembling sIBM whilst found to carry a homozygous GNE mutation proving hIBM [35]. The two most frequently found forms of monogenetic IBM in the UK are caused by mutations in GNE and in VCP. GNE mutations are associated with the recessive form of hIBM, characterized clinically by an early-adult onset with foot drop and sparing of the quadriceps muscle. GNE consists of 12 exons and codes for a bifunctional enzyme which has a key role in sialic acid biosynthesis [36]. A complete knock-out of GNE in mice is lethal and knock-in mutants are currently under investigation in several laboratories. GNE mutations in humans are distributed across the gene, some populations (Near East, Japan) show founder mutations. Staining for the GNE protein does not differentiate between sIBM and hIBM, and is therefore not a good diagnostic marker. Gene testing is currently available in Europe (Antwerp, Munich).

VCP mutations cause an autosomal dominant form of IBM that is often associated with Paget’s Disease and with FrontoTemporal Dementia (IBMPFD). In a series of patients with VCP mutations, IBM was found in 90%, Paget’s Disease in 43% and FTD in 37%. Interestingly, affected members within a family with the same VCP mutation may demonstrate different combinations and different sequence of manifestation of these three main symptoms. The VCP protein is an ATPase that plays a role in the proteasomal pathway and may be involved in myosin assembly [37]. Mutated VCP promotes aggregates and co-stains with ubiquitin in muscle [38]. The VCP gene shows several hot spots for mutations in humans and a limited number of mutations. VCP genetic testing is routinely available for NHS patients at the Institute of Human Genetics in Newcastle.

Myofibrillar myopathies (MFM) are characterized by specific morphological changes and caused by mutations in several genes (such as the desmin and the myotilin-encoding genes), most of them Z-disc related. In addition, MFM frequently present rimmed vacuoles. Moreover, the onset of symptoms is usually in the same age range as for IBM. Therefore, MFM may show clinical and pathological features reminiscent of IBM. A larger series of patients previously labeled as possible IBM showed pathogenic mutations in the genes encoding desmin (12%), myotilin (10%) or even rare cases of FSHD (S. Krause, unpublished results).

6. IBM prospective cohort database

Matt Parton described the full details of the new ‘IBM-net’ database which will represent a structured collection of clinical records and a means to prospectively collect store and retrieve patient data according to agreed protocol. The protocol was presented outlining how to establish a prospective patient database. Adnan Manzur described the process by which North Star created a collaboration between 17 UK neuromuscular centres and successfully collects patient data on DMD.

List of participants

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Acknowledgement

This IBM workshop was supported by the MRC Centre for Neuromuscular Diseases (Centre Grant G0601943).

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