Diagnostic criteria for inclusion body myositis

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Inclusion body myositis (IBM) was first identified as a specific disorder about 40 years ago and is now recognized to be the most frequently presenting primary myopathy in middle age and beyond. Initial characterization was based on the observation of specific pathological features distinguishing it from polymyositis. It was soon appreciated that there were also distinguishing clinical features. The earliest diagnostic criteria were heavily biased towards pathological features, but over time revised criteria have given increasing importance to certain clinical features. Until the specific cause of IBM is determined, and the basic pathogenetic mechanisms are better understood, there can be no diagnostic gold-standard against which to compare the sensitivity and specificity of any proposed diagnostic criteria, but such criteria are essential to ensure that patients entering clinical, epidemiological, genetic, pathological or therapeutic studies represent a homogeneous population. It is likely that any currently accepted diagnostic criteria will, once a gold-standard is eventually established, be shown to have ‘missed’ patients with atypical features, but that has to be accepted to make certain that current studies are not contaminated by patients who do not have IBM. In other words, in everyday clinical practice there will be the occasional patient who an experienced myologist strongly suspects has IBM, but does not meet current criteria – the criteria lack sensitivity. But if the criteria are so broad as to include all such atypical cases, they would be likely to include patients who do not in fact have IBM – they would lack specificity. The sensitivity and specificity of existing criteria have been reviewed recently, in so far as it is possible to do so, and found to have high specificity but variable sensitivity.

Keywords: amyloid, inclusion body myositis, partial invasion, vacuoles.

Introduction

The term inclusion body myositis was first used in 1971 [1]. Over the ensuing years, many individual case reports and retrospective case series were published [2–4]. In brief summary, close scrutiny of patients with presumed polymyositis that did not respond to treatment with steroids (‘treatment-resistant polymyositis’) revealed specific pathological and clinical features that distinguished them from patients with polymyositis. It was not until the 1990s that formal diagnostic criteria for inclusion body myositis (IBM) were proposed, and the ‘Griggs criteria’ (although actually developed by Mendell) of 1995 became the established benchmark [5]. As an aside, in the area of myositis in general, the 1975 Bohan and Peter diagnostic criteria [6, 7] had a major influence, and still do to this day particularly in rheumatological circles, but did not recognize IBM as a specific entity and such patients would probably have been classified as having polymyositis.

In this review, the time-honoured Griggs criteria will be considered, with comment on some of the individual pathological features that are a prerequisite for diagnosis using these criteria. More recent pathological observations will be noted, followed by discussion of the highly characteristic clinical features of IBM. The transition from pathologically based diagnostic criteria to predominantly clinically based criteria will be discussed, with comment on sensitivity and specificity, with final thoughts about why further revision of diagnostic criteria is now necessary given new immunological, and possibly imaging, developments.
The Griggs criteria

A consensus meeting of expert clinicians and pathologists in 1995 reviewed existing knowledge and, in a discussion headed by Mendell, proposed diagnostic criteria for IBM [5]. The major elements are summarized in Table 1. The most important point to note is that a diagnosis of definite IBM can only be made if all three pathological features (inflammatory infiltrate with partial invasion, rimmed vacuoles, and either amyloid deposits or 15- to 18-nm tubulofilaments) are present, independent of the clinical features. If characteristic clinical features are present, with partial invasion but without rimmed vacuoles and amyloid or tubulofilaments, then the diagnosis of IBM can only be considered possible. It is widely accepted that if all of the pathological features are present the diagnosis is secure, although more recent diagnostic criteria insist upon appropriate clinical features in addition. However, it is also the case that each individual pathological criterion is certainly not specific for IBM, and may be seen in a wide range of other myopathies. Since the proposal of the Griggs criteria, attempts have been made to identify other pathological features that may help in the diagnosis of IBM.

Pathological features

Partial invasion

Endomysial inflammatory infiltrates (T cell predominant) are a characteristic feature of polymyositis and IBM (Fig. 1). Partial invasion of non-necrotic muscle fibres (Fig. 2) has been considered a prerequisite for the diagnosis of polymyositis and IBM. The former has been challenged, with an interesting argument concerning literature distortion [8]. Whilst very common in IBM, it is not in our experience invariable. On the basis of the Griggs criteria, many studies only included patients whose biopsies fulfilled the stated criteria, including the presence of partial invasion. With the more recent development of predominantly clinically based criteria, it is evident that many patients do not show all of the canonical pathological features, including partial invasion. In a series reported by Chahin and Engel, 3 of 16 patients with polymyositis (PM)/IBM (clinical features of IBM but pathological features of PM without the specific additional pathological features of IBM) had endomysial inflammatory infiltrates without partial invasion [9]. So, partial invasion is very common in IBM, but probably not invariable.

Rimmed vacuoles

Current evidence suggests that rimmed vacuoles are the result of autophagic degeneration and may be seen in a wide range of myopathies (Fig. 3). There is increasing evidence that they appear relatively late in the evolution of IBM [10] and in recent diagnostic criteria are no longer considered as essential for diagnosis, although their presence in association with typical clinical features strongly supports the diagnosis.

Amyloid and tubulofilaments

Congophilic deposits are common in IBM, particularly if rimmed vacuoles are also present [11]. The nature of the protein deposits has been much debated [12–14]. Many laboratories no longer routinely stain for amyloid, or use electron microscopy for the detection of tubulofilaments (Fig. 4), partly because of inconvenience and technical issues, partly because other staining techniques have been introduced, and partly because revised diagnostic criteria place less emphasis on pathological features.

Table 1 ‘Griggs criteria’ for IBM (simplified from [5])

<table>
<thead>
<tr>
<th>1. Characteristic features</th>
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<tbody>
<tr>
<td><strong>A. Clinical</strong></td>
</tr>
<tr>
<td>1. Duration &gt; 6 months</td>
</tr>
<tr>
<td>2. Age of onset &gt; 30 years</td>
</tr>
<tr>
<td>3. Weakness</td>
</tr>
<tr>
<td>Proximal and distal of arms and legs and must exhibit at least one of:</td>
</tr>
<tr>
<td>a. Finger flexor weakness</td>
</tr>
<tr>
<td>b. Wrist flexor &gt; extensor weakness</td>
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<tr>
<td>c. Quadriceps weakness ≤ Grade 4 MRC</td>
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<tr>
<td><strong>B. Laboratory features</strong></td>
</tr>
<tr>
<td>1. Creatine kinase &lt; 12× normal</td>
</tr>
<tr>
<td>2. Muscle biopsy</td>
</tr>
<tr>
<td>a. Inflammatory myopathy (with partial invasion)</td>
</tr>
<tr>
<td>b. Rimmed vacuoles</td>
</tr>
<tr>
<td>c. Either</td>
</tr>
<tr>
<td>i. Intracellular amyloid deposits, or</td>
</tr>
<tr>
<td>ii. 15- to 18-nm tubulofilaments by EM</td>
</tr>
</tbody>
</table>

Diagnostic criteria: (i) Definite IBM = all muscle biopsy features. None of the clinical/laboratory features are mandatory and (ii) Possible IBM = partial invasion without other pathological features + characteristic clinical and other laboratory features.

IBM, inclusion body myositis; EM, electron microscopy.
MHC I expression
Inflammatory myopathies are defined by the presence of inflammatory cell infiltrates, but in some clinically typical cases, because of the patchy nature of the pathological process, a single biopsy may not show such infiltrates. In these disorders, there is usually generalized upregulation of sarcolemmal MHC I, and its presence, in the absence of cellular infiltrates, may be taken as a surrogate marker of an immune-mediated inflammatory process (Fig. 5). Upregulation of MHC I may also be seen in immune-mediated necrotizing myopathies when inflammatory infiltrates are, by definition, inconspicuous or absent [15]. However, although sensitive, upregulation of MHC I lacks specificity and may be seen, presumably as a secondary phenomenon, in a wide range of noninflammatory myopathies. Possibly, MHC II may have greater specificity [16].

Protein aggregates
Given the difficulties (lack of sensitivity and technical issues) associated with looking for amyloid and tubulofilaments, many studies have used...
immunohistochemistry techniques to detect protein aggregates, and in particular to determine their sensitivity when rimmed vacuoles are absent [17, 18]. The most studied have been SMI-31, SMI-131, TDP43 and p62. p62 seems to be the most useful (Fig. 6). A combination of rimmed vacuoles, a characteristic pattern of p62 staining, and increased sarcolemmal and sarcoplasmic MHC I expression had a sensitivity of 93%, and a specificity of 100% for IBM. Characteristic p62 staining in the absence of rimmed vacuoles had a specificity of 91% for IBM, but a sensitivity of only 44% [18].

Mitochondrial abnormalities

Cytochrome oxidase (COX)-negative fibres, best shown by combined COX/succinate dehydrogenase (SDH) staining (Fig. 7), are more numerous in IBM than expected for age, and are associated with multiple mitochondrial DNA (mtDNA) deletions; the significance of variants in genes associated with mtDNA maintenance is uncertain [19]. It is very rare for there to be no COX-negative/SDH-positive fibres in IBM; even in the absence of rimmed vacuoles, they were seen in all patients with IBM in one study [18], and in 63 of 64 patients with IBM and 16 of 16 patients with PM/IBM in another [9].

Clinical features

Between the first description of IBM in 1971 and 1987, about 50 case reports concerning IBM appeared, commenting mostly on pathological features. A case report in 1982 noted the presentation with quadriceps weakness, and when reviewing the first 24 published cases commented upon the male predominance and combination of both proximal and distal weakness [20]. The first ‘large’ single-centre study reported on 15 men and four women [21]. It confirmed the male predominance, and emphasized the presence of distal as well as proximal weakness, asymmetry of muscle involvement, and the frequent presence of facial weakness and dysphagia; all these features are unusual for polymyositis. But the terminology, in terms of what was meant specifically by proximal and distal weakness, was not clearly defined and in particular, in the light of subsequent experience, there was no comment on finger flexion weakness, or any
differential involvement between hip flexion and knee extension.

Between 1987 and 1995, the year of the publication of the Griggs criteria, there was a marked increase in the number of publications concerning IBM, many about pathological features, some about therapeutic approaches (mostly failures) and some about clinical presentation oddities (e.g. with dysphagia, or with paraspinal muscle weakness). A few publications describing small series commented on the combination of proximal and distal weakness, but without clearly defining which specific muscle groups were involved. As noted (Table 1), the ‘characteristic’ clinical features required by the Griggs criteria were somewhat loosely defined, but did specifically mention finger flexion weakness and quadriceps weakness, but did not compare the latter with hip flexion weakness. A simple database search reveals nearly 2000 publications concerning IBM since 1995. From this vast literature, a consistent picture emerges concerning the clinical features of IBM, and for the experienced clinician, a confident diagnosis can often be made on the basis of clinical assessment alone. Difficulties can arise at first/early presentation when the characteristic features are not fully established, but they will almost certainly evolve with time. And it is very common experience to see the typical features being missed because of inadequate examination technique.

Onset before ~45 years of age is unusual, and a very wary eye should be kept open to the possibility of other diagnoses in such patients. There is a male predominance, but probably not quite as marked as earlier studies might have suggested, and this feature is of no use in individual diagnosis. Asymmetry of muscle involvement is extremely common and a useful feature in that it is so uncommon in other myopathies. Progression is invariably very slow, and by the time of specialist attention, symptoms have often been present for several years. Natural history studies emphasize the slow progression with major disability developing 10–20 years after first symptom onset [22, 23].

The majority of patients present because of lower limb muscle weakness. A small number present with hand weakness, but many will have asymptomatic weakness of finger flexion demonstrable at presentation if appropriately sought. Asymptomatic facial weakness is fairly common, and rather difficult to quantify. Dysphagia is rarely a presenting symptom, but is common with disease evolution.

Lower limbs

One of the most common modes of presentation is ‘unexplained falls’, which can be shown to be due to weakness of the quadriceps and thus loss of stabilization of the knee [10, 24]. Because falls in the elderly are common, and comorbidities such as degenerative changes in the back/hip/knee may be blamed initially, it is not unusual for the patient’s history to date back several years. Examination may show fairly advanced wasting and sometimes profound weakness (Fig. 8). In many patients, and probably most later on in the course of the disease, knee extension (quadriceps) is proportionately weaker than hip flexion (iliopsoas); when present, it is an extremely useful sign as such a pattern is never seen in polymyositis or indeed in most other myopathies. This differential involvement of knee extension/hip flexion has been incorporated into several proposed diagnostic criteria, but its validity has recently been challenged [25]. However, caution is needed in the interpretation of manual muscle testing (MMT) data obtained from retrospective review of case notes, and lack of specific detail with respect to testing methodology. Mild weakness of these very powerful muscles is difficult to assess with MMT (not least if the assessor is of substantially smaller frame than the patient) and the use of MRC scoring may mask the differential. Thus, MRC grade 4 covers...
everything from minimal weakness to residual strength sufficient to overcome little more than gravity. From our experience, it is often possible to say that knee extension is proportionately weaker than hip flexion, even if both fall within the category of MRC grade 4. The sensitivity of this sign needs to be determined through future prospective studies, ideally using quantitative techniques in addition to MMT. What is clear is that dynamometric assessment of knee extension is a sensitive marker of disease progression and is likely to be incorporated in most future therapeutic trials [26].

Another common feature of IBM, and one often missed by inexperienced examiners, is the presence of mild weakness of ankle dorsiflexion. As the condition advances, frank foot drop, requiring use of orthoses, may develop. Such a combination of proximal and distal weakness is relatively unusual in most myopathies (obvious exceptions being myotonic dystrophy and facioscapulohumeral muscular dystrophy) including polymyositis, but can be seen in myofibrillar myopathies which are an important differential diagnosis to IBM.

Upper limbs

Few would argue that finger flexion weakness is a highly characteristic feature of IBM, and together with falls due to quadriceps weakness is for the patient a major cause of disability with respect to everyday activities. The small hand muscles are not involved, and invariably flexor digitorum profundus (FDP) is involved earlier and more markedly than flexor digitorum superficialis, leading to a highly characteristic appearance when patients try to flex their fingers and form a fist (Fig. 9). The only other common disorder in which a similar pattern is seen, with equally severe disabling consequences, is myotonic dystrophy type 1. A difficulty can arise early in the course of the disease, when finger flexion weakness may be asymptomatic or, as is probably quite often the case, inexperienced or inappropriate examination fails to demonstrate it. The simplest method of assessment is to ask the patient to curl his/her fingers around the examiner’s fingers, and for the examiner to then try to uncurl the patient’s fingers. If there is weakness of FDP, there is a highly characteristic feel as the distal interphalangeal joints give way and the fingertips uncurl. Asymptomatic weakness may also be demonstrated by the use of a simple grip dynamometer. There is considerable variability of normal grip strength, so it is not possible to give precise figures, but it is not uncommon to see a patient who does not complain of any difficulties, having a grip strength of only 10 kgN, which is undoubtedly below the normal range. In addition, there may be a substantial difference in strength between the two sides and it has been a consistent observation that the non-dominant side is more severely affected [24].

A very important observation is that, when appropriately assessed, finger flexion is invariably weaker than shoulder abduction, a pattern never seen in polymyositis.

Facial weakness

Facial weakness is difficult to quantify. Mild facial weakness (i.e. incomplete burying of the eyelashes on forceful eye closure) is relatively common, particularly as the disease progresses. Severe weakness is uncommon. It has been reported once as a presenting feature [27] and we have seen incomplete eye closure in a few patients with very advanced disease.

Dysphagia

Some symptoms of dysphagia are not uncommon in the older population, so some reports of an association with IBM may be coincidental. However, there is no doubt that dysphagia is relatively common as the disease progresses, may become severe, and may contribute to significant morbidity and mortality through aspiration. It is rarely a
presenting symptom (2% in one series [24] and 4% in another [22]).

Respiratory muscles

There have been few studies of respiratory muscle function in IBM, which is perhaps surprising given the high incidence of pneumonia as a cause of death. The latter is usually attributed to profound immobility and aspiration secondary to dysphagia. Certainly, overall experience indicates that ventilatory insufficiency is not an early feature of IBM and personal experience is that few require any form of assisted ventilation. However, there have been no systematic studies and some recent data suggest that there may often be features of sleep-disordered breathing over and above any respiratory insufficiency [28].

Bent spine syndrome (camptocormia)

Stooped posture due to paraspinal muscle weakness is a rather common problem in the elderly, and if there are no extra-axial muscle manifestations, a specific cause is rarely identified. A patient has been described with exactly this presentation, and paraspinal muscle biopsy showed the canonical pathological features of IBM [29]. Whether this broadens the clinical presentation of IBM, or challenges diagnosis based on pathological features alone, remains debatable. Perhaps favouring the former, otherwise clinically typical IBM has been associated with camptocormia [30].

Evolution of clinically orientated diagnostic criteria

As discussed above, the first widely accepted diagnostic criteria (Griggs) were biased heavily towards pathological features, which is not surprising given that most of the literature to that date concerned pathology. The criteria stated ‘even without a typical history, a diagnosis of inclusion body myositis can be made solely on the basis of muscle biopsy if all of the pathological features are present [inflammation, vacuoles, amyloid deposits, and 15- to 18-nm tubulofilaments’ [5]. Conversely, they appreciated that diagnostic problems could arise if the patient has ‘typical features of the disease including an inflammatory myopathy [but] does not show vacuolated muscle fibres, intracellular amyloid deposits or 15- to 18-nm tubulofilaments’. They suggested that confirmation of the diagnosis might then require study of additional sections from the biopsy, or repeating the biopsy. However, two decades of clinical experience has clearly shown that the canonical pathological features may indeed be absent, even on repeat study, when long-term follow-up of patients leaves the clinician in no doubt about the correct diagnosis [9, 10].

Since 1995 (the Griggs criteria), there have been several proposals for revised diagnostic criteria, the most recent coming from a European Neuromuscular Centre (ENMC) Workshop in 2011 (Table 2) [31]. The general drift has been for increased importance to be given to specific clinical features, allowing a diagnosis of IBM in the absence of what have previously been considered to be essential pathological features.

A recent evaluation of published criteria summarized that each proposal includes ‘features’ [comprising clinical [demographic characteristics, temporal aspects and patterns of weakness] and pathological [laboratory studies and muscle pathology]] which through Boolean algebraic combination define ‘categories’ [e.g. definite, probable possible] [25]. The authors assessed the sensitivity and specificity of the published criteria by application through medical records review of 200 patients diagnosed as having IBM by neuromuscular specialists. All published IBM diagnostic categories had high specificities (98–100%), but wide-ranging sensitivities (11–84%). It is noteworthy that poor performance of some categories could be attributed to use of highly specific but insensitive pathological criteria; these are easily quantified. It must be added that they also questioned the validity of comparative strength criteria but, as discussed above, there are some concerns about assessment methodology particularly when reviewed retrospectively.

The 2011 ENMC criteria recognize two major categories of patients, those with typical clinical and pathological features (‘clinico-pathologically defined IBM’), and those with typical clinical features but limited pathological changes (‘clinically defined IBM’). A third group (‘probable IBM’) includes patients with a characteristic upper or lower limb pattern of weakness, but not both. Lloyd’s analysis showed sensitivities of 84% for probable, 57% for clinically defined and 15% for clinico-pathologically defined IBM [25]. Using the features recorded at presentation, we applied the Griggs and 2011 ENMC diagnostic criteria to a group of 67 patients who, after long-term review
by a neuromuscular specialist, were considered to have IBM. At presentation, 88% fulfilled ENMC criteria, but only 27% fulfilled the Griggs criteria [10]. Over a long period of review, no differences were noted in clinical features or outcome, leading us to conclude that ‘we are dealing with a clinically homogenous disorder, irrespective of whether patients are diagnosed on the basis of clinical or histopathological criteria and that IBM can be accurately and reliably diagnosed without fulfilling all of the Griggs histopathological features’ [10]. With respect to rimmed vacuoles, sometimes considered a sine qua non for the diagnosis of IBM, we noted no clinical difference between those with and without vacuoles, but those without vacuoles had had their biopsies undertaken sooner after onset, suggesting that vacuoles appear as a later feature of the disease.

In conclusion, clinically orientated diagnostic criteria can be as specific in diagnosing IBM as conventional pathological criteria, and have substantially greater sensitivity at the time of presentation. This negates the need for more specialized pathological tests (e.g. electron microscopy or amyloid staining) that are time-consuming and not part of the diagnostic repertoire of many laboratories and, more importantly, allows inclusion into trials and studies of patients who are at an earlier stage of their disease. With respect to therapeutic trials, such patients may be more likely to respond to treatments than those with more advanced, ‘end-stage’, disease.

**Differential diagnosis**

If the characteristic pattern of weakness (i.e. finger flexion and knee extension) is present, having evolved slowly in a patient over 50 years of age, without any additional features (other than Sjögren’s syndrome), then in everyday clinical practice there is virtually no differential diagnosis. A possible exception, although based on only a single report of four cases, is granulomatous myositis [32]; four patients, presenting with apparently typical clinical features of IBM, where found to have granulomata, but with only one patient having evidence of systemic sarcoidosis. Two showed a response to steroids.

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**Table 2** The ENMC IBM research diagnostic criteria 2011

<table>
<thead>
<tr>
<th>Clinical and Laboratory features</th>
<th>Classification</th>
<th>Pathological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration &gt; 12 months</td>
<td>Clinto-pathologically defined IBM</td>
<td>All of the following:</td>
</tr>
<tr>
<td>Age at onset &gt; 45 years</td>
<td></td>
<td>Endomysial inflammatory infiltrate</td>
</tr>
<tr>
<td>Knee extension weakness ≥ hip flexion weakness and/or finger flexion weakness &gt; shoulder abduction weakness sCK no greater than 15× ULN</td>
<td></td>
<td>Rimmed vacuoles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protein accumulation* or 15- to 18-nm filaments</td>
</tr>
<tr>
<td>Duration &gt; 12 months</td>
<td>Clinically defined IBM</td>
<td>One or more, but not all, of:</td>
</tr>
<tr>
<td>Age at onset &gt; 45 years</td>
<td></td>
<td>Endomysial inflammatory infiltrate</td>
</tr>
<tr>
<td>Knee extension weakness ≥ hip flexion weakness and finger flexion weakness &gt; shoulder abduction weakness sCK no greater than 15× ULN</td>
<td></td>
<td>Upregulation of MHC class I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rimmed vacuoles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protein accumulation* or 15- to 18-nm filaments</td>
</tr>
<tr>
<td>Duration &gt; 12 months</td>
<td>Probable IBM</td>
<td>One or more, but not all, of:</td>
</tr>
<tr>
<td>Age at onset &gt; 45 years</td>
<td></td>
<td>Endomysial inflammatory infiltrate</td>
</tr>
<tr>
<td>Knee extension weakness ≥ hip flexion weakness or finger flexion weakness &gt; shoulder abduction weakness sCK no greater than 15× ULN</td>
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<tr>
<td></td>
<td></td>
<td>Protein accumulation* or 15- to 18-nm filaments</td>
</tr>
</tbody>
</table>

*Demonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). Current evidence favours p62 in terms of sensitivity and specificity, but the literature is limited and further work required. Reproduced, with permission, from: 188th European Neuromuscular Centre International Workshop: Inclusion Body Myositis [31].
The specific pattern of involvement of the long finger flexors in IBM is almost unique. When it is absent, and there is only lower limb involvement at presentation, the differential diagnosis widens. Even so, there are very few other conditions in which the knee extensors are weaker than the hip flexors. The term ‘quadriceps myopathy’ has been used for many decades and encompasses a wide range of conditions, including late-onset Becker dystrophy. Neurogenic causes tend to be of acute onset.

The myofibrillar myopathies are a potential differential diagnosis [33]. Many of them present with late-onset distal weakness, and even if proximal weakness is not evident at presentation, it often appears later. A common presentation is slowly progressive foot drop, a feature that is also seen in IBM, but the proximal weakness inevitably involves primarily the hip flexors and not the quadriceps. Early involvement of the long finger flexors is not a typical feature. An additional source of confusion, and arguably more of an issue than the clinical features, relates to the pathological finding of protein aggregates, which share similarities to those seen in IBM [11].

Hereditary inclusion body myopathy, due to mutations in GNE, causes some confusion because of its similar name, but clinically could not be more different. It is usually of early adult onset, presents with distal weakness (foot drop) and is remarkable for the relative preservation of knee extensor strength, hence its other name of ‘quadriceps-sparing myopathy’ [34].

Antibodies
Myositis-associated and myositis-specific antibodies have long been recognized in the serum of patients with a wide range of idiopathic inflammatory myopathies and are used to subclassify these disorders (e.g. antisynthetase syndrome), as well as sometimes offering predictive value (e.g. Mi2 and a mild phenotype in dermatomyositis) [35]. The recent identification of anticytosolic 5′-nucleotidase 1A [36, 37] antibodies in IBM offers a potentially useful diagnostic tool that may need to be added to diagnostic criteria. Initial studies suggested a sensitivity of ~33% and specificity of ~95%. Diagnostic performance may be enhanced by looking at multiple immunoglobulin isotypes [38]. Further studies are needed in a wider range of disease controls to confirm specificity.

Imaging
Broadly speaking, muscle imaging may (i) identify specific individual muscle involvement not apparent clinically, (ii) demonstrate a characteristic overall pattern of muscle involvement, which again may not be evident on clinical assessment, and (iii) show focal areas of muscle involvement, suggesting a potentially more productive site for muscle biopsy.

Magnetic resonance imaging (MRI) may demonstrate the characteristic involvement of the forearm flexor muscles in IBM, but in the majority of cases reported, there was also evident clinical involvement, so the contribution of MRI might be considered to be rather limited [39]. Prospective studies including patients without clinically weak finger flexion are required. Similarly, several studies have shown the often clinically evident selective involvement of quadriceps [40–42].

Tasca et al. [41] have recently proposed a qualitative (‘pattern recognition’) approach using MRI, suggesting sensitivity and specificity both in excess of 90%. This was based on retrospective evaluation of scans in confirmed cases of IBM and the positive predictive value needs to be verified by further prospective studies.

Targeting muscle biopsy from an area of muscle shown to be abnormal on MRI may seem logical, but perhaps not surprisingly there have been no prospective studies biopsying normal and abnormal areas in the same patient, and demonstrating a greater diagnostic yield from abnormal areas.

Future diagnostic criteria
The recent review by Lloyd et al. [25] shows that the more recently proposed diagnostic criteria, emphasizing clinical rather than pathological features, are all serviceable with high specificity. They have superseded the pathologically based Griggs criteria. Since the publication of the most recent (ENMC 2011) criteria [31], the major development has been with respect to the identification of anticytosolic 5′-nucleotidase 1A antibodies. Their limited sensitivity makes them unsuitable for sole diagnostic use, but their apparent high specificity may be of value, although further studies of specificity, especially in diseases that may mimic IBM, are required. They could be considered as an additional optional ‘pathological feature’ within the framework of the ENMC criteria (Table 2).
Responding to the devil

Whilst many experienced myologists might consider IBM to be an ‘end-of-the-bed’ diagnosis, most advise muscle biopsy except in a few specific circumstances. But there is some support for the devil’s creed. In a small series of 21 patients, muscle biopsy confirmed the diagnosis (as defined by the Griggs criteria) in only 15 and the authors concluded that ‘the clinical diagnosis of IBM remains superior to the muscle biopsy’, without actually stating that biopsy is unnecessary [43].

As noted above, even the combination of a classical presentation, assessed by an experienced clinician, can mislead (vide supra, granulomatous myositis). In reality, the majority of patients are assessed by clinicians who may not have extensive experience of IBM, greatly increasing the possibility of diagnostic error, and biopsy may reduce that risk (but also acknowledging the fact that the interpretation of an inexperienced pathologist may confuse matters further).

In the authors’ experience, there are two situations when biopsy may not be pursued, particularly when there is a confident clinical diagnosis: (i) when the patient is anticoagulated, and there are anxieties about even brief discontinuation, and (ii) when the patient has previously had a biopsy which was nondiagnostic (e.g. end-stage muscle showing only fatty/fibrous tissue) and may not be keen for a repeat.

Given our continuing uncertainties about the cause of IBM, and the nature of the pathogenic processes, there is an also argument in favour of continuing to study pathological material, and to build a biobank to be used in future studies, in the hope of furthering our knowledge of this enigmatic condition.

Conflict of interest statement

No conflicts of interest to declare.

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Dr Monika Hofer for pathological illustrations. Elsevier for permission to reproduce Table 2.

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