



Idiopathic inflammatory myopathies: epidemiology, classification, and diagnostic criteria

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The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of immune-mediated disorders, that may present in an isolated form, or in association with another autoimmune or connective tissue disease, a malignancy, or, rarely, an infection or other environmental exposure. This article summarizes recent findings on epidemiologic aspects of the three major varieties of IIM (dermatomyositis, polymyositis and inclusion body myositis) and proposes schemes for the classification and diagnostic criteria for these conditions.

Prevalence and incidence

A number of studies conducted in different countries have reported the incidence and prevalence of inflammatory myopathies and the methodology and results of these studies are summarized in Table 1. The majority of the more recent investigations have used the Bohan and Peter [1] diagnostic criteria for determining inclusion of cases. Two of the studies of inclusion body myositis (IBM) used criteria proposed by Griggs et al [2] and one used the European Neuromuscular Centre criteria [3]. All of the studies were retrospective in de-

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Table 1
Studies of incidence and prevalence (cases/million) of idiopathic inflammatory myopathy

Author (year)	Period	Location	Criteria	Diagnosis ethnicity/gender (N)	Incidence (95% CI)	Prevalence
Patrick et al (1999) [4]	1989–1991	Australia (state of Victoria); Ms	Biopsy + hospital discharge code; Bohan & Peter Def/Prob/Poss	All cases (94)	7.4 (6.1–9.1)	
				Adult PM + IBM (56)	5.5 (4.2–7.1)	
				Adult DM (12)	1.2 (0.7–2.1)	
				Juv PM/DM (7)	2.3 (1.1–4.8)	
				Overlap (11)	0.8 (0.5–1.5)	
Weitof (1997) [53]	1984–1993	Sweden (province of Gävleborg); Ms	Biopsy + hospital/ outpatient code; Bohan & Peter Def/Prob	PM/DM + Malig (8)	0.6 (0.3–1.2)	
				All cases (21)	7.6	
				PM (5)		
				DM (3)		
				Overlap (7)		
Koh et al (1993) [12]	1986–1991	Singapore; Ms	EMG + hospital diagnosis code; Bohan & Peter Def/Prob/Poss	IBM (3)		
				PM/DM + Malig (3)		
				PM/DM (75)	7.7	
Oddis et al (1990) [5]	1963–1982	USA (county of Allegheny); Ms	Hospital discharge code; Bohan & Peter Def/Prob/Poss	All cases (171)	5.5 (0.3–10.7)	
				Adult PM (88)	2.7 (0.07–5.3)	
				Adult DM (27)	0.8 (0.01–1.59)	
				Juv PM/DM (21)	0.8 (0.01–1.59)	
				Overlap (21)	0.7 (0–1.4)	
	PM/DM + Malig (20)	0.7 (0–1.4)				

Benbassat et al (1980) [7]	1960–1976	Israel; Ms	Hospital discharge code; Bohan & Peter Def/Prob/Poss	PM/DM (89)	2.18	
				Western Jew M	2.17	
				F	3.49	
				Non-Western Jew M	0.89	
Medsger et al (1970) [6]	1947–1968	USA (county of Shelby); Ms	Hospital discharge code; Def/Prob/Poss	F	2.03	
				PM/DM (124)	5.0	
				White M	3.7	
				F	2.7	
				Black M	4.6	
Kaipainen-Seppänen & Aho (1996) [54]	1990	Finland (five districts); Ms	Antirheumatic medication supply	F	10.8	
				PM/DM (4)	3.7 (1.1–10.2)	
				IBM (1)	0.9 (0–5.6)	
Araki et al (1983) [13]		Japan (Kumamoto)		PM		2.4
Darin & Tulinius (2000) [55]	1979–1994	Western Sweden Ms	Biopsy + hospital/ outpatient registers; Bohan & Peter Def/Prob/Pss	Juv PM/DM (9)		25.0
				M		27.0
				F		22.9
				Juv DM (48)	1.9 (1.4–2.6)	
Symmons et al (1995) [8]	1992–1993	UK and Ireland; Ms	Surveillance case definition; Bohan & Peter Def/Prob/Poss			
Hanissian et al (1982) [56]		USA		Juv PM/DM	0.6–3.2	
				Black	7.7	

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Table 1 (continued)

Author (year)	Period	Location	Criteria	Diagnosis ethnicity/gender (N)	Incidence (95% CI)	Prevalence
Phillips et al (2000) [9]	1998 (1988–1998)	Australia (state of Western Australia); Ms	Biopsy + hospital/ outpatient centers Griggs et al Def/Poss	IBM (17)		9.3
				M		10.9
				F		7.7
Felice & North (2001) [10]	1992–2000	USA (Connecticut); Ss	EMG + biopsy + hospital records Griggs et al Def/Poss	Age >50 years		35.3
				IBM (35)		10.7
				M (23)		14.5
				F (12)		7.1
				Age >45 years		28.9
Badrising et al (2000) [11]	1999 (1965–1999)	Netherlands; Ms	Biopsy + hospital code; ENC criteria Def/Prob	M		42.1
				F		18.0
				IBM (76)		4.9
				Age >50 years		16
				M		22
Lindberg (1994) [57]		Sweden (Göteborg)		F		10
				IBM	2.2	

Abbreviations: CI, confidence interval; DM, dermatomyositis; Def, definite; ENC, European Neuromuscular Centre; F, female; IBM, inclusion body myositis; Juv, juvenile; M, male; Malig, malignancy; Ms, multiple centers; N, number of cases; Overlap, myositis associated with another connective tissue disorder; PM, polymyositis; Poss, possible; Prob, probable; Ss, single center.

sign and inclusion was based on biopsy reports and medical records. Where incidence rates have been calculated for diagnostic subgroups the results have been given (Table 1). The majority of studies that examine inflammatory myopathy have not distinguished IBM as a separate diagnostic subgroup. The study by Patrick et al [4] was the only investigation to document the inclusion of IBM cases in the polymyositis (PM) subgroup because prolonged fixation time of biopsy material did not allow accurate identification of the characteristic filamentous inclusions.

The average overall annual incidence rates for inflammatory myopathy vary from 2.18×10^{-6} to 7.7×10^{-6} . Some studies reported increasing incidence rates over the time period studied. In a study by Oddis et al [5] the incidence rate of 8.9×10^{-6} for 1973–1982 was significantly greater than that of 2.5×10^{-6} for 1963–1972. Medsger et al [6] also reported an increasing incidence rate from 1.2×10^{-6} in 1947–1952 to 8.4×10^{-6} in 1963–1968. Benbasset et al [7] reported incidence rates ranging from 1.3×10^{-6} in 1960–1964 to 2.6×10^{-6} in 1970–1974. This trend may reflect improved diagnostic techniques and completeness of medical records rather than a true increase in the incidence of inflammatory myopathy. The results of studies in which data were collected after the publication of the Bohan and Peter [1] diagnostic criteria in 1975 may have greater certainty of diagnosis, although it is noted that in most studies, cases in the “possible” diagnostic category were included.

Age-specific rates have been reported in some of these studies. Annual incidence rates increased with age, ranging from 2.5×10^{-6} in people under 15 years of age to 10.5×10^{-6} in people over 65 years of age [5]. Medsger et al [6] reported that incidence rates were highest for patients aged 35 to 44 years (18.7×10^{-6}) and 55 to 64 years (38.3×10^{-6}). In children, the age-specific incidence rates ranged from 0.6×10^{-6} for children under 5 years of age to 7.8×10^{-6} for children 10 to 14 years of age. Benbasset et al [7] reported that the incidence rates were 0.7×10^{-6} for children under 9 years of age, 1.8×10^{-6} for children aged 10 to 19 years, 0.5×10^{-6} for those aged 20 to 29 years, and 6.3×10^{-6} for those aged 60 to 69 years. In a study of juvenile dermatomyositis (DM) in the United Kingdom and Ireland, the overall incidence rate for children under 16 years of age ($N = 48$; median age was 6.8 years) was 1.9×10^{-6} [8]. This study found two peaks for the age of onset in girls, one at 6 years and another at 11 years, whereas the eight boys with DM were all under 10 years of age. Studies of IBM [9–11] have reported a much higher prevalence in patients over the age of 50 years, which agrees with clinical experience that the condition is rarely encountered in younger adults.

Few studies have reported gender-specific incidence rates (see Table 1). In general, the incidence rates of PM and DM are higher in women, whereas the prevalence rates of IBM are higher in men. Only a few reports of the incidence rates for nonwhite ethnic groups have been published. Oddis et al [5] found incidence rates for black, male patients of 11.4×10^{-6} compared with 2.9×10^{-6} for white, male patients and 17.1×10^{-6} for black, female patients compared with 6.1×10^{-6} for white, female patients. A higher incidence of PM in black

patients was also reported by Medsger et al [6]; the incidence rate in black men and women was 4.6×10^{-6} and 10.8×10^{-6} , respectively, compared with 3.7×10^{-6} and 2.7×10^{-6} in white patients. See Table 1 for incidence rates for Western and non-Western Jews [7] and for the results of two studies performed in Asia [12,13].

A number of methodologic issues need to be considered when interpreting the results of previous incidence-prevalence studies. The issues relating to diagnostic classification were discussed previously. Total case ascertainment is difficult to achieve regardless of the search methods used; however, many of the reported studies used hospital discharge codes in medical records for case ascertainment. Because it is likely that a significant number of patients with inflammatory myopathy are not hospitalized for diagnosis, the reported rates are probably underestimations. Because inflammatory myopathy is an uncommon disorder, the numbers of cases identified in some studies, particularly in diagnostic subgroups, are quite small. Confidence intervals for rates were not reported in most studies and, therefore, the results need to be interpreted with caution. If tertiary care centers are used to identify cases, then it may be difficult to accurately determine the size of the population at risk.

Associated disorders

Autoimmune diseases

Inflammatory myopathies may occur in association with various types of autoimmune disorders. Myositis has been reported in 5% to 17% of patients with scleroderma, 4% to 16% of patients with systemic lupus erythematosus (SLE), and 16% to 79% of patients with mixed connective tissue disease [14–17]. In some studies, the criteria for myositis were not sufficiently specific for diagnostic certainty.

A few studies have examined in more detail the association of myositis with progressive systemic sclerosis, or scleroderma. In a 29-year retrospective study of 1095 patients with systemic sclerosis without renal involvement, 17% had a myopathy, using criteria which included the presence of proximal muscle weakness, elevated serum CK activity, and EMG or biopsy results consistent with myopathy [18]. In a study of 60 black, South African patients with systemic sclerosis, 37% had myositis (defined as proximal muscle weakness with elevation of muscle enzymes). Fifty-one percent of patients with diffuse cutaneous systemic sclerosis had myositis compared with 12% of patients who had limited cutaneous systemic sclerosis [19]. In an 11-year American study of 397 white women and 117 black women with scleroderma, 21% of the black women had myositis/myopathy, compared with only 12% of the white women [20]. Clements et al [21] reported that of 23 patients with progressive systemic sclerosis, three had inflammatory myositis (termed ‘complicated myopathy’) diagnosed with muscle biopsy, and 19 had a ‘simple myopathy’ Only three patients in the latter

group underwent muscle biopsy which revealed fibrosis and fiber atrophy only without inflammatory changes.

It has been reported that 11% to 40% of patients with PM or DM have an associated connective tissue disease; the female:male ratio in this subgroup is 9:1 [10,15,17]. Connective tissue diseases associated with PM and DM included scleroderma, SLE, rheumatoid arthritis, Sjögren's syndrome, and polyarteritis nodosa. The majority of patients with an overlap syndrome had PM instead than DM. Autoimmune disorders such as SLE, Sjögren's syndrome, scleroderma, and sarcoidosis have been reported in up to 15% of patients with IBM [15].

Malignancy

The association of malignancy with inflammatory myopathy has been investigated in a number of studies. The severity of the inflammatory myopathy is not associated with the occurrence of malignancy [15]. The results of recent studies that reported standardized incidence ratios (SIRs) for malignancy in patients with inflammatory myopathy are summarized in Table 2. The frequency of malignancy varied from 4% to 42%. Except for patients with PM in the study by Airio et al [23], all diagnostic groups had an increased risk of malignancy. The incidence ratio for malignancy was highest for patients with DM, with the exception of the study by Buchbinder et al [24] in which the incidence ratio for juvenile PM/DM was higher than DM. In this study the reported incidence ratio for malignancy in juvenile PM/DM was 29.0×10^{-6} , however, this result needs to be interpreted with some caution as indicated by the wide 95% confidence interval ($3.5-105 \times 10^{-6}$) and the small number of cases with malignancy.

The diagnosis of malignancy can be antecedent, concurrent, or subsequent to the diagnosis of the inflammatory myopathy. Buchbinder et al [24] reported that in 74% ($n = 69$) of cases, the malignant disease occurred concurrently or after diagnosis of the myositis, but the diagnosis of malignancy prior to myositis was most common in DM (53% of DM cases with malignancy). The increased risk of malignancy fell progressively with time after diagnosis; the overall risk was highest in the first 3 years after diagnosis. The SIR was 4.4×10^{-6} for the first year; this steadily decreased to 1.6×10^{-6} over the 5 years following diagnosis. When malignancies detected within the first year after myositis diagnosis were excluded (allowing for the possibility of a more intensive surveillance for malignancy following the myositis diagnosis), the overall incidence rate for malignancy was 2.3×10^{-6} . Two other studies [25,26] also reported that the risk of malignancy was highest within the first year after diagnosis of the myositis. In the study of PM done by Hill et al [25] there was no increased risk of cancer 5 years after myositis diagnosis, whereas in DM the SIR was 1.4×10^{-6} at 5 or more years after diagnosis. Conversely, in the study by Sigurgeirsson et al [27], the relative risk of malignancy in patients with PM increased from 1.8×10^{-6} to 2.4×10^{-6} in men and from 1.7×10^{-6} to 1.8×10^{-6} for women for the first 5-year period after diagnosis. For the same time period the

Table 2
Recent studies of the incidence (cases/million) of malignancy with inflammatory myopathy

Author (year)	Period and location	Duration of follow-up	Occurrence of malignancy ^a	Diagnosis (N)	Standard incidence ratio ^b (95% CI)	No. of malignancies (%)
Buchbinder et al (2001) [24]	1982–1998; Australia	Median 5.3 y	Concurrent, subsequent	All cases (537)	2.6 (2.1–3.3)	116 (22)
				PM (321)	2.0 (1.4–2.7)	58 (18)
				DM (85)	6.2 (3.9–10.0)	36 (42)
				IBM (52)	2.4 (1.2–4.9)	12 (23)
				Overlap (30)	4.6 (1.2–11.7)	8 (27)
				Juv PM/DM (49)	29.0 (3.5–105)	2 (4)
Hill et al (2001) [25]	1964–1985; Sweden, Denmark, Finland	Not given	Subsequent	PM (914)	1.3 (1.0–1.6)	137 (15)
				DM (618)	3.0 (2.5–3.6)	198 (32)
Maoz et al (1998) [58]	1984–1994; Israel	Not given	Concurrent, subsequent	All cases (31)	12.6 (5.7–23.8)	
				PM (15)		4 (27)
				DM (20)		9 (45)
Airio et al (1995) [23]	1969–1985; Sweden	Mean 8.7 y	Subsequent	All cases (311)	2.1 (1.4–2.9)	63 (20)
				PM	1.0 (0.5–1.8)	
				DM	6.5 (3.9–10.0)	
Chow et al (1995) [26]	1977–1989; Denmark	Mean 5.0 y	Subsequent	PM (336)	1.7 (1.1–2.4)	42 (13)
				DM (203)	3.8 (2.6–5.4)	57 (28)
Sigurgeirsson et al (1992) [27]	1963–1983; Sweden	Mean 10.4 y	Concurrent, subsequent	PM (396)		42 (9)
				M	1.8 (1.1–2.7)	
				F	1.7 (1.0–2.5)	
				DM (392)		61 (15)
				M	2.4 (1.6–3.6)	
Bonnetblanc et al (1990) [59]	1981–1985; France	Not given	Antecedent, concurrent, subsequent	F	3.4 (2.4–4.7)	
				DM (118)		36 (31)

Abbreviations: CI, confidence interval; DM, dermatomyositis; F, female; IBM, inclusion body myositis; JUV, juvenile; M, male; N, number of cases; Overlap, myositis associated with another connective tissue disorder; PM, polymyositis.

^a Timing of the occurrence of malignancy in relation to diagnosis of inflammatory myopathy.

^b Standardized incidence ratio, calculated using the incidence of malignant disease observed in the myositis cohort and the expected incidence if the cohort developed malignant disease at the same rates as the source population.

relative risk of malignancy in patients with DM increased from 2.4×10^{-6} to 4.4×10^{-6} in men and from 3.4×10^{-6} to 4.8×10^{-6} in women. Airio et al [23] reported that in the first year after diagnosis of DM, the relative risk of malignancy was 26×10^{-6} , the risk decreased to 3.0×10^{-6} for years 2 to 5, and then increased to 4.4×10^{-6} for 5+ years after diagnosis. In patients with PM the SIR was 1.7×10^{-6} for the first year following diagnosis, but there was no increased risk for developing malignancy later. At the time of myositis diagnosis, the prevalence of cancer was significantly higher for patients with DM (standardized prevalence ratio 3.7×10^{-6}), but it was not higher for patients with PM.

In a meta-analysis of four previous studies that reported the association of malignancy with myositis, Zantos et al [28] evaluated the temporal relationship between the onset of malignancy and myositis (excluding the year of myositis diagnosis). For patients with DM, the relative risks for malignancy were 3.6×10^{-6} in the 4 years preceding, and 2.3×10^{-6} for the 4 years following diagnosis. For patients with PM there was an increased relative risk (2.2×10^{-6}) of malignancy only in the period of 1 to 5 years after diagnosis. The reasons for the change in the level of risk for malignancy with increasing time after myositis diagnosis are not clear. Buchbinder et al [24] suggested that some of the excess risk for malignancy evident 5 years after diagnosis may be the result of the long-term effects of immunosuppressant therapy. Airio et al [23] reported that patients with DM who received cytotoxic drugs had a lower incidence ratio (3.8×10^{-6}) for the risk of cancer than those who did not receive the drug (7.6×10^{-6}).

In the studies that reported separate data for men and women, there are different results when comparing the respective risk of malignancy. Higher incidence ratios for women compared with men were reported in two studies. In the study by Sigurgeirsson et al [27], the incidence ratios for malignancy were 1.7×10^{-6} and 3.4×10^{-6} for women with PM or DM respectively, compared with 1.8×10^{-6} and 2.4×10^{-6} for men. Buchbinder et al [24] reported a slightly higher incidence ratio of 2.8×10^{-6} in women compared with 2.5×10^{-6} in men, however, incidence ratios for specific myositis categories were not reported. There was a similar trend of a higher incidence ratio of 2.3×10^{-6} in women compared with 1.8×10^{-6} for men for the total patient group in a third study [30,31], however for patients with DM the incidence ratio for malignancy in men was 8.3×10^{-6} compared with 6.0×10^{-6} for women.

There are a variety of malignancies that are associated with inflammatory myopathy. Because of the small numbers of individual malignancies, it is difficult to determine whether the risk for any particular type of malignant disease is increased compared with the general population. For patients with DM, the types of tumor with the highest risks are ovarian (10.5×10^{-6}), lung (5.9×10^{-6}), pancreatic (3.8×10^{-6}), non-Hodgkin lymphoma (3.6×10^{-6}), stomach (3.5×10^{-6}), and colorectal (2.5×10^{-6}), whereas in patients with PM, the highest risks were non-Hodgkin lymphoma (3.7×10^{-6}), lung (2.8×10^{-6}), and bladder (2.4×10^{-6}) cancers [25]. Chow et al [26] reported that among

patients with DM, ovarian cancer had the highest risk (15.5×10^{-6}), whereas in patients with PM lymphatic and hematopoietic cancers had the highest risk (5.7×10^{-6}). Bronchogenic, colorectal, and nasopharyngeal malignancies were most common in the study done by Koh et al [12].

The frequency of malignancy in patients with amyopathic DM (DM sine myositis) was reported in three studies. In 40 patients with DM studied over an 8-year period by Fung et al [29], malignancy was present in five out of six Chinese patients with amyopathic DM; four of them had nasopharyngeal carcinoma, a common form of malignancy in Asia [30,31]. In a study carried out in Singapore [39], 2 of 13 patients with amyopathic DM had malignancy compared with 10 of 15 patients with DM; half of the patients with malignancy had nasopharyngeal carcinoma. Whitmore et al [33] reported data for 12 cases of DM sine myositis, one third of whom subsequently developed malignancy (three patients with ovarian cancer, one with lung cancer).

In addition to the methodological issues discussed in the section on incidence and prevalence, the effect of increased surveillance for malignancy in patients with inflammatory myopathy needs to be considered. The duration of follow-up is also of particular importance when ascertaining the risk of developing malignancy in patients with inflammatory myopathy; an insufficient follow-up period will lead to an underestimation of the incidence rate. Retrospective analysis of records is an important factor when ascertaining the relative timing of diagnosis of inflammatory myopathy and malignancy, particularly in determining possible causative factors that may link the two diagnoses.

Classification

Although a number of IIM classification schemes have been proposed, none has been prospectively validated or carefully studied to determine its utility in practice. From a clinicopathologic perspective, the IIMs fall into six major categories: (1) dermatomyositis, (2) polymyositis, (3) overlap syndromes, (4) cancer-associated myositis, (5) inclusion body myositis, and (6) other forms including rare focal and diffuse variants (Box 1). Dermatomyositis is the most consistent entity, in terms of its clinical manifestations and myopathology. It occurs during childhood and adult life, and is the form most likely to be associated with malignancy in adults. Polymyositis is a less specific disorder that may occur in an isolated form, but is often associated with other manifestations of a systemic connective tissue disease such as mixed connective tissue disease, progressive systemic sclerosis, or lupus erythematosus (overlap syndrome) and may also complicate HIV or HTLV-I infection [34]. Polymyositis is also heterogeneous pathologically, including eosinophilic and granulomatous forms in addition to the more usual T-cell mediated varieties. Cancer-associated myositis differs from some of the other forms in clinical manifestations, age of onset, frequency of autoantibodies, and prognosis; these data suggest that it may be considered a separate entity [35]. Inclusion body myositis is the most common

Box 1. Proposed classification of idiopathic inflammatory myopathies

- I Dermatomyositis
 - Juvenile
 - Adult
- II Polymyositis
 - T-cell mediated (α/β , γ/δ)
 - Eosinophilic
 - Granulomatous
- III Overlap syndromes
 - With polymyositis
 - With dermatomyositis
 - With inclusion body myositis
- IV Cancer-associated myositis
- V Inclusion body myositis
- VI Other forms:
 - Focal: orbital myositis; localized nodular myositis; inflammatory pseudotumor
 - Diffuse: macrophagic myofasciitis; necrotizing myopathy with pipestem capillaries; infantile myositis

IIM in patients over the age of 50 and is more common in men than in women [36]. It differs from the other IIMs by having a selective pattern of muscle involvement, very indolent clinical course, and distinctive histopathologic features [2,37,38]. It usually occurs in isolation, but is sometimes associated with another autoimmune disorder or connective tissue disease [30].

A number of other focal or diffuse IIMs are occasionally encountered in clinical practice (see Box 1) [39]. Because of their rarity, no epidemiologic data are available on these disorders. The focal forms include myositis confined to the extra-ocular muscles (orbital myositis) [40], localized nodular myositis [41], and inflammatory pseudotumor of the limb or trunk muscles [42]. Diffuse varieties include a number of entities characterized by the association of myositis and fasciitis (eg, eosinophilic fasciitis [Shulman's syndrome]) and the recently described condition of macrophagic myofasciitis which has been reported mainly from France [43] and necrotizing myopathy with pipestem capillaries [44].

Diagnostic criteria

Although the diagnosis of an IIM may be suspected on clinical grounds, and is supported by the finding of a raised serum creatine kinase level and abnormal electromyogram, a definitive diagnosis can only be made on the basis of histopathologic changes and requires a muscle biopsy. Although a raised serum CK level supports the diagnosis of an IIM, the test has a low specificity and may be normal, particularly in some patients with DM and IBM. Other serum enzyme

levels, including aldolase, lactate dehydrogenase, or transaminases, are often elevated in patients with IIM when the CK is abnormal and may be elevated when the CK level is normal, but they are also not specific for IIM. Similarly, an abnormal electromyogram lacks specificity and the EMG may also be normal or nondiagnostic because of sampling error. When the muscle biopsy demonstrates the characteristic histologic changes of a necrotizing inflammatory myopathy the diagnosis can be considered as certain. Moreover, in many instances the biopsy will show additional, more specific changes allowing confirmation of the diagnosis of DM, PM, or IBM or of one of the rarer forms of IIM such as eosinophilic or granulomatous myositis.

In some cases the diagnosis of IIM is problematic and it may be appropriate to make a diagnosis of “probable” or “possible” IIM. This occurs particularly when the muscle biopsy is normal or shows only minor nonspecific changes, or when the biopsy specimen fails to demonstrate specific histologic changes such as the typical “rimmed” vacuoles or inclusions of IBM [2] or the perifascicular atrophy and tubulo-reticular endothelial cell inclusions of DM. It becomes necessary to place greater emphasis on clinical criteria and the results of other laboratory investigations in reaching a diagnosis. A number of attempts have been made to develop sets of diagnostic criteria which are applicable to the IIMs as a group and also to individual disorders [1,6]. The best known are the Bohan and Peter criteria which were developed specifically for the diagnosis of PM and DM. These have been widely used since their introduction in 1975 and have a sensitivity ranging from 74% to 100% in several large series of patients with myositis [45]. A number of additional criteria relating to the presence or absence of muscle and joint pain, arthritis, and systemic inflammatory features were added by Tanimoto et al [46]. Others have attempted to define more homogeneous subgroups of patients on the basis of myositis-specific autoantibodies and immunogenetic markers [35,45]. Clinical and pathologic criteria have also been proposed for the diagnosis of IBM [2] but their sensitivity has not been evaluated. More specific diagnostic criteria for PM, DM, and IBM, based upon a synthesis of our current understanding of these disorders, are proposed in Boxes 2, 3, and 4.

Box 2. Proposed diagnostic criteria for dermatomyositis

I. Characteristic features

A. Clinical features

- Subacute onset (weeks to months) from childhood to adult life
- Characteristic skin changes: Gottron’s papules/sign, heliotrope rash
- Subcutaneous calcinosis: especially in juvenile cases
- Muscle weakness: diffuse but with proximal emphasis

- Systemic features in some cases: (eg, dysphagia, synovitis, interstitial lung disease)

B. Laboratory features

- Serum CK and other muscle enzyme levels variably elevated but may be normal in some cases
- EMG: myopathic motor unit potentials, often with spontaneous discharges
- Muscle biopsy:
 - Myofiber necrosis (usually a large group of fibers involved) and regeneration
 - Micro-infarcts
 - Perifascicular atrophy
 - Mononuclear cell infiltrate (perivascular, perimysial): primarily B cells and CD4+ T cells
 - Vascular membrane attack complex and immunoglobulin deposition
 - Capillary depletion; endothelial cell tubuloreticular inclusions
 - MHC Class I expression on muscle fibers

C. Associated disorders

- Overlap features of scleroderma or other connective tissue diseases (eg, mixed connective tissue disease [MCTD], SLE, Sjögren's syndrome)
- Malignancy (especially in patients older than 50 years of age)
- Rare: HIV infection, toxoplasmosis, sarcoidosis

II. Diagnostic categories

A. Definite DM:

- Characteristic skin changes and pattern of muscle weakness with biopsy confirmation. Other clinical features and laboratory findings are not mandatory if the biopsy is confirmatory.

B. Probable DM:

- Mild or atypical skin changes with clinical and laboratory evidence of myositis and biopsy confirmation

C. Possible DM:

- Skin changes suggestive of DM with clinical and EMG evidence of myopathy but normal or nonspecific biopsy findings

D. Amyopathic DM:

- Characteristic skin changes without clinical or laboratory evidence of myositis

Box 3. Proposed diagnostic criteria for polymyositis

I. Characteristic features

A. Clinical features

- Subacute onset in adult life (rarely earlier)
- Muscle weakness: diffuse with proximal emphasis but nonselective
- Systemic features in some cases (eg, dysphagia, interstitial lung disease)

B. Laboratory features

- Serum CK and other muscle enzyme levels variably elevated
- EMG: myopathic motor unit potentials with or without spontaneous discharges
- Muscle biopsy:
 - Myofiber necrosis (single fiber pattern) and regeneration; polyphasic and polyfocal.
 - Mononuclear cell infiltrate mainly endomysial: CD8+ T cells
 - Mononuclear cell invasion of non-necrotic fibers: primarily CD8+ T cells and macrophages
 - MHC Class I expression on muscle fibers

II. Associated disorders

- Connective tissue diseases (eg, MCTD, systemic sclerosis, SLE, RA, Sjögren's syndrome)
- Other autoimmune disorders
- Occasional HIV or HTLV-I infection
- Malignancy (weaker association than in DM)

III. Diagnostic categories

A. Definite polymyositis

- Characteristic clinical features with biopsy confirmation. Other laboratory findings are not mandatory if the biopsy is confirmatory.

B. Probable polymyositis

- Characteristic clinical features, EMG findings, elevated muscle enzymes but incomplete biopsy criteria (eg, minor or inconspicuous inflammatory changes)
- or*
- Atypical clinical features, elevated enzymes, and compatible EMG findings with biopsy evidence of inflammatory necrotizing myopathy

C. Possible polymyositis

- Compatible clinical features, EMG findings with elevated muscle enzymes, but normal or nonspecific biopsy findings (eg, myofiber necrosis and regeneration without inflammatory changes; or interstitial inflammatory changes without other histologic features).

Box 4. Proposed diagnostic criteria for inclusion body myositis*I. Characteristic features**A. Clinical features*

- Duration of illness is more than 6 months
- Age at onset is older than 30 years
- Slowly progressive muscle weakness and atrophy: selective pattern with early involvement of quadriceps femoris and finger flexors, may be asymmetric
- Dysphagia common

B. Laboratory features

- Serum CK and other muscle enzyme levels variably elevated but may be normal
- EMG: myopathic or "mixed" pattern with short and long duration motor unit potentials
- Muscle biopsy:
 - Myofiber necrosis and regeneration
 - Mononuclear cell invasion of non-necrotic fibers: primarily CD8+ T cells
 - Endomysial mononuclear cell infiltrate (variable)
 - Vacuolated muscle fibers ("rimmed" vacuoles)
 - COX-negative fibers (excessive for age)
 - Ubiquitin-positive inclusions and amyloid deposits in muscle fibers
 - Nuclear or cytoplasmic 15–18 nm tubulofilamentous inclusions (TFIs)
 - MHC Class I expression on muscle fibers

II. Associated disorders

IBM usually occurs in isolation, but may be associated with:

- Other autoimmune disorders, connective tissue diseases, sarcoidosis
- Occasional HIV or HTLV-I infection
- Malignancy (weaker association than with DM)
- Rare: toxoplasmosis, sarcoidosis

*III. Diagnostic categories**A. Definite IBM:*

- Characteristic clinical features with biopsy confirmation: inflammatory myopathy with autoaggressive T cells, "rimmed" vacuoles, COX-negative fibers, TFIs or amyloid deposits in muscle fibers. Other laboratory features are not mandatory if the biopsy features are diagnostic.
- Atypical pattern of weakness and atrophy with diagnostic biopsy features

B. Probable IBM:

- Characteristic clinical and laboratory features but incomplete biopsy criteria (eg, features of necrotizing inflammatory myopathy with T-cell invasion of muscle fibers but absence of 'rimmed' vacuoles, TFIs, COX-negative fibers, or amyloid deposits).

C. Possible IBM:

- Atypical pattern of weakness and incomplete biopsy criteria

Summary

Epidemiologic studies have helped to define the prevalence and incidence of PM, DM, and IBM and have highlighted differences in risk between men and women and in the age at onset for the different forms of myositis. Additionally, these studies have shown that there is a substantially higher risk of PM and DM in certain racial groups which is likely to be genetically determined. These differences are all likely to be fundamental in terms of the pathogenesis of these diseases but, as yet, their full significance remains uncertain. They do, however, suggest that the interplay between genetic and environmental initiating factors is different in the three disorders. Additional population-based studies in homogeneous racial groups, in parallel with studies of susceptibility genes for autoimmune disease, such as those encoding the MHC and inflammatory cytokines, are needed to throw further light on the role of genetic factors in the pathogenesis of the IIMs [47].

Because of the paucity of epidemiologic data on IBM, further studies are required to determine the degree of variation in prevalence in different populations and racial groups, as well as the consistency of the male association and age spectrum of manifestations of the disease. The particularly strong association with DR3 in this form of IIM [48] clearly points to the importance of genetic factors in pathogenesis, but further studies of DR3-associated genes in the MHC and of other candidate genes are needed to define more precisely the genes that convey susceptibility to the disease in different racial groups.

Epidemiologic studies also have the potential to identify environmental factors that may play a part in disease initiation in genetically susceptible individuals. Seasonal patterns of disease onset have been reported, particularly in patients with DM [49–51] as well as seasonal variation in the frequency of relapses [52], pointing to the probable involvement of intercurrent infections, ultraviolet light exposure, or other environmental factors in disease initiation and reactivation. Further prospective studies are required to determine the contribution of environmental exposures and how they interact with genetic susceptibility factors to lead to myositis.

One of the major limitations of a number of the previous epidemiologic studies is the lack of precision in the diagnostic criteria used and the classification of cases of IIM. The Bohan and Peter criteria [1] which were used in most studies after 1975, were introduced before IBM was recognized as an entity distinct from PM; most of the published incidence and prevalence figures for PM are therefore likely to be inaccurate. Multicentered, interdisciplinary, prospective studies, incorporating comprehensive clinical, laboratory, and pathologic information, are needed to develop and validate better diagnostic and classification criteria and to determine the true prevalence and incidence of the many forms of IIM.

References

- [1] Bohan A, Peter JB. Polymyositis and dermatomyositis. I. *N Engl J Med* 1975;292:344–7.
- [2] Griggs RC, Askanas V, DiMauro S, et al. Inclusion body myositis and myopathies. *Ann Neurol* 1995;38:705–13.

- [3] Verschuuren JJ, Badrising UA, Wintzen AR, et al. Inclusion body myositis. In: Emery AEH, editor. Diagnostic criteria for neuromuscular disorders. London: Royal Society of Medicine; 1997. p. 81–4.
- [4] Patrick M, Buchbinder R, Jolley D, et al. Incidence of inflammatory myopathies in Victoria, Australia and evidence of spatial clustering. *J Rheumatol* 1999;26:1094–100. 1997;26:104–6.
- [5] Oddis CV, Conte CG, Steen VD, et al. Incidence of polymyositis-dermatomyositis: a 20-year study of hospital diagnosed cases in Allegheny County, PA 1963–1982. *J Rheumatol* 1990; 17:1329–34.
- [6] Medsger TA, Dawson WN, Masi AT. The epidemiology of polymyositis. *Am J Med* 1970; 48:715–23.
- [7] Benbassat J, Geffel D, Zlotnick A. Epidemiology of polymyositis-dermatomyositis in Israel, 1960–76. *Isr J Med Sci* 1980;16:197–200.
- [8] Symmons DPM, Sills JA, Davis SM. The incidence of juvenile dermatomyositis: results from a nation-wide study. *Br J Rheumatol* 1995;34:732–6.
- [9] Phillips BA, Zilko PJ, Mastaglia FL. Prevalence of sporadic inclusion body myositis in Western Australia. *Muscle Nerve* 2000;23:970–2.
- [10] Felice KJ, North WA. Inclusion body myositis in Connecticut: observations in 35 patients during an 8-year period. *Medicine* 2001;80:320–7.
- [11] Badrising UA, Maat-Schieman M, van Duinen SG, et al. Epidemiology of inclusion body myositis in the Netherlands: a nationwide study. *Neurology* 2000;55:1385–7.
- [12] Koh ET, Seow A, Ong B, et al. Adult onset polymyositis/dermatomyositis: clinical and laboratory features and treatment response in 75 patients. *Ann Rheum Dis* 1993;52:857–61.
- [13] Araki S, Uchino M, Yoshida O. Epidemiologic study of multiple sclerosis, myasthenia gravis, and polymyositis in the city of Kumamoto, Japan. *Clin Neurol* 1983;23:838–41.
- [14] Iannou Y, Sultan S, Isenberg DA. Myositis overlap syndromes. *Curr Opin Rheumatol* 1999; 11:468–74.
- [15] Amato AA, Barohn RJ. Idiopathic inflammatory myopathies. *Neurologic Clinics* 1997;15: 615–48.
- [16] Medsger KA. Systemic sclerosis (scleroderma), eosinophilic fasciitis and calcinosis. In: McCarty DJ, editor. Arthritis and allied conditions. 10th edition. Philadelphia: Lea & Febiger; 1985. p. 994–1036.
- [17] Foote RA, Kimbrough SM, Stevens JC. Lupus myositis. *Muscle Nerve* 1982;5:65–8.
- [18] Follansbee WP, Zerve TR, Medsger TA. Cardiac and skeletal muscle disease in systemic sclerosis (scleroderma): a high risk association. *Am Heart J* 1993;125(1):194–203.
- [19] Tager RE, Tikly M. Clinical and laboratory manifestations of systemic sclerosis (scleroderma) in Black South Africans. *Rheumatol* 1999;38:397–400.
- [20] Laing TJ, Gillespie BW, Toth MB, et al. Racial differences in scleroderma among women in Michigan. *Arthritis Rheum* 1997;40:734–42.
- [21] Clements PJ, Furst DE, Campion DS, et al. Muscle disease in progressive systemic sclerosis: diagnostic and therapeutic considerations. *Arth Rheum* 1978;21(1):62–71.
- [22] Reference deleted in proof.
- [23] Airio A, Pukkala A, Isomäki H. Elevated cancer incidence in patients with dermatomyositis: a population based study. *J Rheumatol* 1995;22:1300–3.
- [24] Buchbinder R, Forbes A, Hall S, et al. Incidence of malignant disease in biopsy-proven inflammatory myopathy. *Ann Intern Med* 2001;134:1087–95.
- [25] Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet* 2001;357:96–100.
- [26] Chow W, Gridley G, Mellekjær L, et al. Cancer risk following polymyositis and dermatomyositis: a nationwide cohort study in Denmark. *Cancer Causes Control* 1995;6:9–13.
- [27] Sigurgeirsson B, Lindelöf B, Edhag O, et al. Risk of cancer in patients with dermatomyositis or polymyositis: a population-based study. *N Engl J Med* 1992;326:363–7.
- [28] Zantos D, Zhang Y, Felson D. The overall and temporal association of cancer with polymyositis and dermatomyositis. *J Rheumatol* 1994;21:1855–9.

- [29] Fung WKJ, Chang HLH, Lam WMW. Amyopathic dermatomyositis in Hong Kong – association with nasopharyngeal carcinoma. *Int J Dermatol* 1998;37:659–63.
- [30] Engel AG, Hohlfeld R, Banker BQ. Inflammatory myopathies: the polymyositis and dermatomyositis syndromes. In: Engel AG, Franzini-Armstrong C, editors. *Myology*. 2nd edition. New York: McGraw-Hill; 1994. p. 1335–83.
- [31] Bernard P, Bonnetblanc J. Dermatomyositis and malignancy. *J Invest Dermatol* 1993;100:128S–32S.
- [32] Reference deleted in proof.
- [33] Whitmore SE, Watson R, Rosenshein NB. Dermatomyositis sine myositis: association with malignancy. *J Rheumatol* 1996;23:101–5.
- [34] Dalakas MC. Retrovirus and inflammatory myopathies in humans and primates. *Bailliere's Clinical Neurology* 1993;2:659–91.
- [35] Love LA, Leff RL, Fraser DD, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. *Medicine* 1991;70:360–74.
- [36] Oldfors A, Lindberg C. Inclusion body myositis. *Curr Opin Neurol* 1999;12:527–33.
- [37] Amato AA, Gronseth GS, Jackson CE, et al. Inclusion body myositis: clinical and pathological boundaries. *Ann Neurol* 1996;40:581–6.
- [38] Phillips BA, Cala LA, Thickbroom GW, et al. Patterns of muscle involvement in sporadic inclusion body myositis. A clinical and MRI study. *Muscle Nerve* 2001;24:1526–34.
- [39] Ojeda VJ, Mastaglia FL. Miscellaneous conditions. In: *Inflammatory diseases of muscle*. Mastaglia FL, editor. Oxford (UK): Blackwell Scientific Publications; 1988. p. 185–195.
- [40] Slavin ML, Glaser JS. Idiopathic orbital myositis. Report of six cases. *Arch Ophthalmol* 1982;100:1261–5.
- [41] Cumming WJK, Weiser R, Teoh R, et al. Localized nodular myositis: a clinical and pathological variant of polymyositis. *Q J Med* 1977;46:531–46.
- [42] Heffner RR, Armbrustmacher VW, Earlie KM. Focal myositis. *Cancer* 1977;40:301–6.
- [43] Gherardi RK, Coquet M, Cherin P, et al. Macrophagic myofasciitis: an emerging entity. *Lancet* 1998;352:347–52.
- [44] Emslie-Smith AM, Engel AG. Necrotizing myopathy with pipe-stem capillaries microvascular deposition of the complement membrane attack complex (MAC) and minimal cellular infiltration. *Neurology* 1991;41:936–9.
- [45] Targoff IN, Miller FW, Medsger TA, et al. Classification criteria for the idiopathic inflammatory myopathies. *Curr Opin Rheumatol* 1997;9:527–35.
- [46] Tanimoto K, Nakano K, Kano S, et al. Classification criteria for polymyositis and dermatomyositis. *J Rheumatol* 1995;22:668–74.
- [47] Shamim EA, Rider LG, Miller FW. Update on the genetics of the idiopathic inflammatory myopathies. *Curr Opin Rheumatol* 2000;12:482–91.
- [48] Garlepp MJ, Laing B, Zilko PJ, et al. HLA associations with inclusion body myositis. *Clin Exp Immunol* 1994;98:40–5.
- [49] Leff FL, Burgess SH, Miller FW, et al. Distinct patterns in the onset of adult idiopathic inflammatory myopathy in patients with anti-Jo-1 and anti-signal recognition particle autoantibodies. *Arthritis Rheum* 1991;34:1391–6.
- [50] Manta P, Kalfakis N, Vassilopoulos D. Evidence for seasonal variation in polymyositis. *Neuroepidemiology* 1989;8:262–5.
- [51] Pachman LM, Hayford JR, Chung A, et al. Juvenile dermatomyositis at diagnosis: clinical characteristics of 79 children. *J Rheumatol* 1998;25:1198–204.
- [52] Phillips BA, Zilko PJ, Garlepp MJ, et al. Seasonal occurrence of relapses in inflammatory myopathies: a preliminary study. *J Neurol* 2002;249:441–4.
- [53] Weitoft T. Occurrence of polymyositis in the county of Gävleborg, Sweden. *Scand J Rheumatol* 1997;26:104–6.
- [54] Kaipiainen-Seppänen O, Aho K. Incidence of rare systemic rheumatic and connective tissue diseases in Finland. *J Intern Med* 1996;240:81–4.

- [55] Darin M, Tulinius M. Neuromuscular disorders in childhood: a descriptive epidemiological study from western Sweden. *Neuromusc Disord* 2000;10:1–9.
- [56] Hanissian AS, Masi AT, Pitner SE, et al. Polymyositis and dermatomyositis in children: an epidemiologic and clinical comparative analysis. *J Rheumatol* 1982;9:390–4.
- [57] Lindberg C, Persson LI, Bjorkander J, et al. Inclusion body myositis: clinical, morphological, physiological and laboratory findings in 18 cases. *Acta Neurol Scand* 1994;89:123–31.
- [58] Maoz CR, Langevitz P, Livneh A, et al. High incidence of malignancies in patients with dermatomyositis and polymyositis: an 11-year analysis. *Semin Arthritis Rheum* 1998;27(5): 319–24.
- [59] Bonnetblanc JM, Bernard P, Fayol J. Dermatomyositis and malignancy: a multicentre cooperative study. *Dermatologica* 1990;180:212–6.