

Inclusion body myositis: an underdiagnosed condition?

N D Hopkinson, C Hunt, R J Powell, J Lowe

Abstract

Inclusion body myositis is an increasingly recognised form of inflammatory myopathy with characteristic clinical and histopathological features which has seldom been reported in the United Kingdom. This paper presents the clinicopathological features of a series of patients diagnosed in Nottingham from 1986 to 1990. During this period, 1319 muscle biopsy samples were processed by this laboratory and rimmed vacuoles were seen in 17 patients. Eleven patients had definite or probable inclusion body myositis according to published criteria. The mean age of the group was 69.4 years with a male to female ratio of 8:3. Typical clinical features were a slowly progressive painless, proximal lower limb weakness, with muscle wasting and early loss of reflexes. The median duration of illness from first symptom to presentation was five years (range 2-18 years). Falls were a prominent symptom in six patients and distal weakness occurred in nine patients. Creatine kinase was increased in 10 patients but only one had a level >1000 IU/l; the erythrocyte sedimentation rate was normal in five patients. Treatment with steroids or cytotoxic drugs, or both, did not prevent disease progression. It is confirmed that inclusion body myositis is a distinct cause of inflammatory myopathy which is probably underdiagnosed in the United Kingdom. Clinically, it should be suspected in older patients presenting with muscle weakness of insidious onset. Pathologically, a careful search should be made for rimmed vacuoles and inflammation; ultrastructurally, the presence of inclusions will confirm the diagnosis.

(*Ann Rheum Dis* 1993; 52: 147-151)

The term inclusion body myositis was first used by Yunis and Samaha¹ in 1971 when they described patients with a slowly progressive myopathy and characteristic nuclear and cytoplasmic filamentous inclusions accompanied by vacuoles rimmed by basophilic material in the muscle fibres (fig 1). Electron microscopy of these 'rimmed' or 'lined' vacuoles showed that they contained cytoplasmic degradation products (fig 2). These inclusions were originally observed by Chou² in 1967 in a man with 'chronic polymyositis', and on electron microscopy he observed aggregates of interwoven filaments in the sarcoplasmic matrix (fig 3) which resembled myxovirus nucleocapsids. Since then inclusion body myositis has been increasingly recognised,

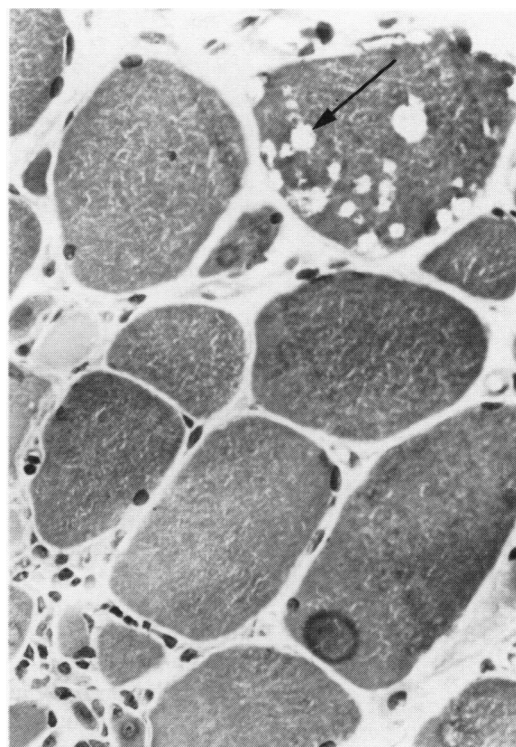


Figure 1 Histological features of inclusion body myositis include fibres containing rimmed vacuoles (arrow) and atrophic fibres associated with a lymphocytic inflammatory infiltrate (bottom left). Haematoxylin and eosin frozen section.

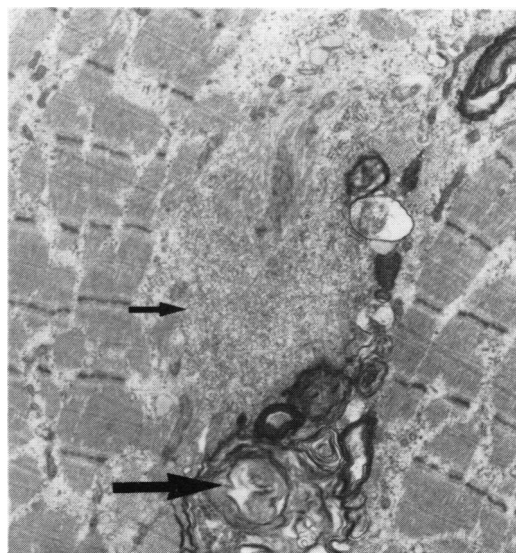


Figure 2 Ultrastructurally, electron microscopy shows that the rimmed vacuoles correspond to vacuolation associated with autophagic debris forming membrane-like whorls (large arrow) adjacent to which is a filamentous inclusion body (small arrow).

Department of
Immunology,
University Hospital,
Queen's Medical Centre,
Nottingham NG7 2UH,
United Kingdom
N D Hopkinson
R J Powell

Department of
Histopathology,
University Hospital,
Queen's Medical Centre,
Nottingham NG7 2UH,
United Kingdom
C Hunt
J Lowe

Correspondence to:
Dr Neil Hopkinson,
Department of Rheumatology,
Derbyshire Royal Infirmary,
Derby DE1 2QY,
United Kingdom.

Accepted for publication
25 July 1992

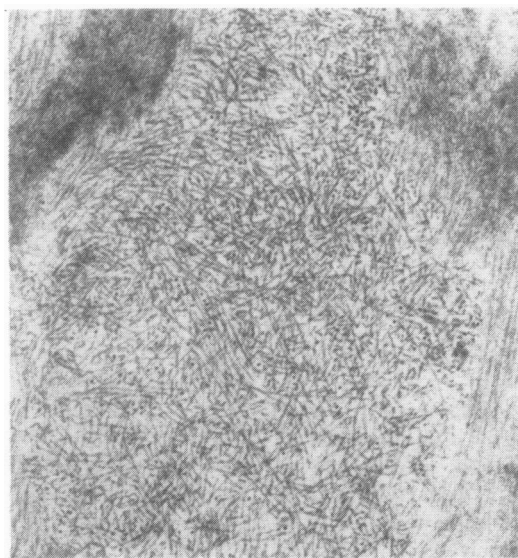


Figure 3 At higher magnification electron microscopy the inclusion bodies are seen to be composed of arrays of filaments.

typically having an insidious onset after the age of 50 years, being more common in men, with the distal muscles often being affected, and a poor response to steroids.³⁻⁷ Most large series of patients with inclusion body myositis have been reported from the USA where, in one paper, it made up 28% of all cases of inflammatory myopathy, the most common cause after polymyositis (31%), and more common than dermatomyositis (18%).⁶ A single series of patients with inclusion body myositis has been reported in Europe,⁷ though it is not clear whether this reflects a genuinely low prevalence or a failure to recognise the disorder. The aim of this study was to quantify the clinical and laboratory findings in a cohort of patients with inclusion body myositis diagnosed in Nottingham.

Patients and methods

During the period 1986-90, 1319 muscle biopsy specimens were examined in the department of histopathology. Because of an interest in muscle pathology, the department receives specimens not only from the whole of Nottingham, but also from neighbouring district hospitals.

Samples of muscle obtained by either open or

closed needle biopsy were orientated under a dissecting microscope and snap frozen in liquid nitrogen cooled isopentane. Serial 8 μm cryostat sections were routinely stained with haematoxylin and eosin, NADH Tr, ATPase, periodic acid-Schiff and diastase, or both, myophosphorylase, and acetylcholinesterase.

During this five year period a diagnosis of inclusion body myositis was pathologically suspected in 17 patients because of the presence of well defined rimmed vacuoles⁸ on light microscopy. Samples from 15 of these patients were available for conventional transmission electron microscopy after fixation in 4% glutaraldehyde.

The case records of all 17 patients were reviewed and specific information sought on age, sex, duration of symptoms, presenting symptoms, site of muscle disease, clinical signs, associated diseases, drug history, electromyogram and laboratory tests, including erythrocyte sedimentation rate (ESR), creatine kinase, anti-nuclear antibodies (indirect immunofluorescence, rat liver substrate), C reactive protein, and blood glucose. All patients were classified as having definite, probable, or possible inclusion body myositis based on the preliminary diagnostic criteria of Calabrese *et al*⁴ (table 1).

Results

Of the 17 patients with rimmed vacuoles seen in muscle biopsy samples, five had typical filamentous inclusions on electron microscopy and appropriate clinical criteria to satisfy a diagnosis of definite inclusion body myositis (table 1). In addition, an 81 year old man (patient No 4) was found to have increased creatine kinase levels during investigations for an increased ESR and thrombocytosis (platelet count $707 \times 10^9/l$), both discovered during hospital admission for a total hip replacement for osteoarthritis. A muscle biopsy sample showed rimmed vacuoles and filamentous inclusions on electron microscopy. He remains well one year after the biopsy sample was taken, however, with no evidence of muscle weakness. Three patients without filamentous inclusions on electron microscopy, and two whose muscle was not available for electron microscopy, had appropriate criteria to satisfy a diagnosis of probable inclusion body myositis (table 1).

PATIENTS WITH DEFINITE OR PROBABLE INCLUSION BODY MYOSITIS

Table 2 gives details of these 11 patients. Table 3 gives the clinical signs and results of investigations.

The mean age of this group was 69.4 years (range 60-81), with a male to female ratio of 8:3. The median duration of illness, from first symptom to diagnosis, was five years (range 2-18). The most common symptom was progressive muscle weakness, which occurred in 10/11 patients; the distribution of weakness is shown in table 3. All 10 patients with weakness had weakness of their legs, usually greater proximally. In contrast, only 8/10 had arm weakness, which in two patients was purely distal. Muscle wasting was apparent at presentation in all 10

Table 1 Preliminary diagnostic criteria for inclusion body myositis.⁴ Definite inclusion body myositis requires pathological electron microscopy criterion 1 and clinical criterion 1 plus one other clinical criterion. Probable inclusion body myositis requires pathological light microscopy criterion 1 and clinical criterion 1 plus three other clinical criteria. Possible inclusion body myositis requires pathological light microscopy criterion 2 plus any three clinical criteria

Pathological criteria	
Electron microscopy	
1	Microtubular filaments in the inclusions
Light microscopy	
1	Lined vacuoles
2	Intranuclear or intracytoplasmic inclusions, or both
Clinical criteria	
1	Proximal muscle weakness (insidious onset)
2	Distal muscle weakness
3	Electromyographic evidence of a generalised myopathy
4	Increase in muscle enzyme levels
5	Failure of muscle weakness to improve on a high dose regimen of corticosteroids (at least 40-60 mg/day for three to four months)

Table 2 Basic clinical information on patients with definite or probable inclusion body myositis

Patient No	Age (years)	Sex	Past medical history	Drug history	Presenting symptoms	Length of history (years)	Diagnostic criteria
1	73	M	Left hemiparesis; hypertension	Atenolol; nifedipine	Progressive weakness of legs; falls; weak grip; muscle cramps	6	Definite
2	71	M	Gout	Colchicine	Progressive weakness of legs; falls	7	Definite
3	71	M	None	None	Progressive weakness of legs and arms; myalgia; muscle stiffness	3	Definite
4	81	M	Osteoarthritis; hip replacement	Sulindac	None (increased creatine kinase levels on blood test)	—	Probable*
5	73	M	Osteoarthritis: hip replacement	None	Progressive weakness of legs; falls; weight loss	12	Definite
6	72	F	None	None	Progressive weakness of legs; falls	2	Definite
7	70	M	None	None	Progressive weakness of arms and legs; falls	5	Probable
8	60	F	None	None	Progressive weakness of legs; dysarthria	5	Probable
9	67	F	None	None	Progressive weakness of arms and legs	18	Probable
10	63	M	Discoid lupus	None	Progressive weakness of arms and legs	2	Probable
11	60	F	None	None	Progressive weakness of legs; falls	4	Probable

*See text for details.

patients with muscle weakness. Four patients had a loss of knee reflexes, and in a further three they were only present on reinforcement. Loss of ankle jerks was more common, these being completely lost in seven patients and present only on reinforcement in one patient.

Of the nine patients in whom the ESR was measured, four were abnormal (>20 mm/hour); the mean ESR was 23.9 mm/hour (range 2–74 mm/hour). One patient had a normal creatine kinase level and the highest value noted was 1187 IU/l (mean 633 IU/l). C reactive protein was normal in the four patients tested: three of nine patients had positive antinuclear antibodies, none in high titre. No patient had increased blood glucose.

Table 4 gives light and electron microscopy details of muscle samples for these patients. All patients had a lymphocytic inflammatory infiltrate, which was predominantly perimysial.

Electromyography showed a myopathic pattern in six of seven patients, with fibrillation suggesting myositis in four of seven patients. One patient (No 2) showed changes suggestive of chronic denervation with long duration potentials and without any spontaneous activity; one further patient showed an absent sural sensory nerve action potential.

TREATMENT

Five of 11 patients received treatment, all with prednisolone 40 mg/day initially tailing down over at least three months and azathioprine (2.5 mg/kg/day). In all patients weakness progressed and azathioprine was changed to cyclophosphamide (0.5–1.0 g by mouth or intravenously once a week for at least six weeks) in three patients, or chlorambucil (4–6 mg/day) in one patient. No improvement, either clinically or in creatine kinase levels, was seen with this change of treatment. One patient (No 7) died from a widespread bronchopneumonia associated with generalised muscle weakness.

PATIENTS WITHOUT DEFINITE OR PROBABLE INCLUSION BODY MYOSITIS

Six patients with rimmed vacuoles in a muscle biopsy sample did not satisfy diagnostic criteria for either definite or probable inclusion body myositis according to Calabrese *et al*⁴ (table 1). Table 5 details these patients, who had various clinico-pathological features. Two patients including one with active systemic lupus erythematosus (SLE), were considered to have inclusion body myositis even though the criteria were not fulfilled.

Table 3 Clinical signs and investigations in patients with definite or probable inclusion body myositis

	Patient No										
	1	2	3	4	5	6	7	8	9	10	11
Distribution of weakness*	D	P=D	P	None	P=D	None	P=D	D	P>D	P>D	None
Arms	D	P=D	P	None	P=D	None	P=D	D	P>D	P>D	None
Legs	P>D	P>D	P	None	D>P	P>D	P>D	P	P>D	P>D	P>D
Muscle wasting	+	+	+	None	+	+	+	+	+	+	+
Reflexes											
Knee	+	—	(+)	+	+	—	—	(+)	—	+	(+)
Ankle	—	—	—	+	+	—	—	(+)	—	+	—
Erythrocyte sedimentation rate (normal <20 mm/hour)	N/A	7	9	54	2	74	60	9	N/A	25	10
Creatine kinase (normal <210 IU/l)	N/A	760	885	424	745	1187	160	307	444	780	640
C reactive protein (normal <20 mg/l)	N/A	N/A	N/A	<20	<20	<20	N/A	<20	N/A	N/A	N/A
Antinuclear antibodies	N/A	Negative	N/A	Negative	Weakly positive	Negative	Negative	Negative	Weakly positive	Positive	Negative
Glucose (normal <7 mmol/l)	N/A	5.9	N/A	5.1	N/A	7.1	5.3	N/A	7.0	6.1	5.1

*D=Distal; P=proximal; N/A=not available; +=present; -=absent; (+)=present with reinforcement.

Table 4 Light and electron microscopy findings in patients with definite or probable inclusion body myositis

Abnormality	Patient No											Percentage of specimens
	1	2	3	4	5	6	7	8	9	10	11	
Fibres with rimmed vacuoles	+	+	+	+	+	+	+	+	+	+	+	100
Groups of atrophic fibres	+	+	+	-	-	-	-	-	-	-	-	45
Type I fibre atrophy	+	-	+	-	+	-	-	-	-	+	+	45
Type II fibre atrophy	+	+	-	-	+	+	+	+	+	+	+	82
Necrotic fibres	+	-	-	-	+	+	-	-	+	-	-	36
Eosinophilic inclusions	-	-	-	-	-	-	-	-	-	-	+	9
Lymphocytic inflammatory infiltrate	+	+	+	+	+	+	+	+	+	+	+	100
Filamentous inclusions on electron microscopy	+	+	+	+	+	+	-	-	-	-	-	55

Table 5 Details of patients with rimmed vacuoles on muscle biopsy who did not fulfil criteria for inclusion body myositis (IBM)

Patient No	Age (yrs)	Sex	Presenting symptoms	Creatine kinase (IU/l)	Clinical signs	Muscle biopsy findings	Diagnostic label
12	87	M	Collapse; weakness of legs	21	Quadriceps weak and wasted; knee and ankle reflexes absent	Atrophic fibres; lymphocytic infiltrate; rimmed vacuoles; eosinophilic inclusions	IBM
13	81	M	Collapse due to hemiparesis; muscle biopsy taken because of high erythrocyte sedimentation rate	12	Signs of hemiparesis only	Atrophic fibres; rimmed vacuoles	Hemiparesis secondary to cerebrovascular accident, not IBM
14	72	M	None; muscle examined after above knee amputation	22	No wasting or weakness; reflexes normal	Active fibre necrosis; lymphocytic infiltrate; rimmed vacuoles	Peripheral vascular disease; no clinical evidence of IBM
15	75	F	Right footdrop following hip replacement for osteoarthritis	N/A	Right footdrop; absent R ankle jerk	No inflammation; atrophic fibres; severe type II atrophy; rimmed vacuoles	Sciatic nerve lesion possibly resulting from hip replacement; no clinical evidence of IBM
16	59	M	Polyarthralgia; weight loss; muscle biopsy sample taken to look for vasculitis	31	Generalised wasting; reflexes normal	Lymphocytic infiltrate; atrophic fibres; rimmed vacuoles	Non-Hodgkin's lymphoma seen on lymph node biopsy sample; not IBM
17	49	F	Active systemic lupus erythematosus; muscle biopsy taken to look for vasculitis	47	Abnormal gait; quadriceps weakness	Severe type II atrophy; no inflammation (taking steroids); rimmed vacuoles; eosinophilic inclusions	IBM associated with systemic lupus erythematosus

Discussion

This series of 11 patients with definite or probable inclusion body myositis confirms previous observations which suggest that inclusion body myositis is a distinct cause of inflammatory myopathy. Characteristic features include: rimmed vacuoles on light microscopy and filamentous inclusions on electron microscopy; onset in elderly patients; more common in men; insidious onset of muscle weakness, usually proximal but with some distal disease, especially in the arms; marked muscle wasting with early loss of reflexes and a generally poor response to treatment. The frequency of clinical or probable inclusion body myositis in our laboratory (11/1319 biopsy samples: 0.8%) is similar to that reported elsewhere in Europe⁷ (5/850: 0.6%) and the USA³ (7/525: 1.3%).

The criteria for definite inclusion body myositis (see table 1) are microtubular filaments on electron microscopy, proximal muscle weakness, and one other clinical criterion. These criteria would be satisfied by three previously reported patients who had a hereditary distal myopathy or oculopharyngeal muscular dystrophy.⁹⁻¹⁰ The main differences between the latter case reports and our own series are the patient's age and the family history of muscle disease. Our patients all presented when over 60 years old, whereas the patients with hereditary myopathy were 9, 22, and 23 years old at the time of their first symptom. Moreover, a family history of muscle disease was absent in the patients with inclusion body myositis. For probable inclusion body myositis, Calabrese *et*

*al*⁴ propose as criteria the presence of rimmed (lined) vacuoles, proximal muscle weakness, and three of the other four clinical criteria. In this study, only 65% of patients with rimmed vacuoles had a diagnosis of inclusion body myositis, confirming their non-specificity; previously they have been described in some familial distal myopathies,¹¹ denervated muscle,¹² and in oculopharyngeal dystrophy.¹³ For a diagnosis of probable inclusion body myositis, it would therefore seem reasonable to include further criteria of a myopathy with a poor response to treatment. In the clinical setting the diagnosis of inclusion body myositis should be strongly suspected on clinical grounds in elderly patients with muscle weakness, especially when this is of insidious onset and associated with muscle wasting and loss of reflexes. This should then prompt a careful search for rimmed vacuoles on light microscopy which may, in our experience, require examination of the biopsy sample at many levels. Although a diagnosis of definite inclusion body myositis depends on the presence of filamentous inclusions on electron microscopy it is clear from this and earlier studies that they are not always found, possibly because of sampling errors. Patient No 4 in our series is notable in having an increased creatine kinase level, muscle biopsy findings of rimmed vacuoles, lymphocytic infiltrates, and filamentous inclusions on electron microscopy but remaining symptom free. Whether he develops muscle weakness with time remains to be seen.

It is likely that inclusion body myositis

remains an underdiagnosed disorder. During the five year study period, 25 patients were diagnosed histologically as having polymyositis, compared with 11 with definite or probable inclusion body myositis. Rimmed vacuoles may be missed on light microscopy and facilities for electron microscopy may be limited, leading to a misdiagnosis. We have seen patients with a diagnosis of polymyositis who remain unresponsive to treatment; review of their initial muscle biopsy sample, often performed many years earlier, has then showed typical rimmed vacuoles leading to a revised diagnosis. An accurate diagnosis of inclusion body myositis is important because of treatment and prognostic implications. Unlike the generally good response of polymyositis to treatment with steroids and immunosuppressive drugs,¹⁴ the present study is in agreement with others in showing that treatment is disappointing. All five patients treated in this study deteriorated despite cytotoxic drugs and steroids. Likewise, 25 patients followed up for two or more years in the series of Lotz *et al*⁶ showed progression of weakness despite treatment. Treatment intervention is still advocated according to some workers, however,¹⁵ because occasionally a response is seen, particularly when inclusion body myositis is in association with a connective tissue disease. A pragmatic approach to treatment would be to stop treatment with cytotoxic drugs if a therapeutic response is not seen shortly after beginning steroid treatment.¹⁵

Although inclusion body myositis has been associated with a variety of autoimmune diseases,¹⁶ these have usually been single case reports and may represent a reporting bias due to the underlying illness being closely monitored. In the largest series of patients with inclusion body myositis reported to date,⁶ a single case of SLE was seen in 40 patients; there were 13 other autoimmune diseases associated with inclusion body myositis, including eight patients with diabetes. No patients with diabetes were seen in the present series and the relevance of such an association remains unclear.

We did not characterise the mononuclear cell infiltrate in our patients; however, Arahata and Engel have previously reported that the predominantly endomysial inflammation in inclusion body myositis is composed of CD8+ T cells and macrophages in a 2:1 ratio.¹⁷

Historically the involvement of viral agents, such as paramyxovirus, has been implicated. Two studies have provided other possible clues to the aetiology of this poorly understood disorder. Mendell *et al*¹⁸ identified Congo red apple green birefringent deposits in vacuolated muscle fibres in inclusion body myositis characteristic of amyloid. The distribution of the amyloid collections corresponded to the typical filaments of inclusion body myositis. Further-

more, Askanas *et al*¹⁹ have identified the type of amyloid as β -(A4) amyloid protein, which is central to the pathogenesis of Alzheimer's disease. This suggests that these β -(A4) amyloid deposits in muscle in inclusion body myositis and the brain deposits in Alzheimer's disease may follow similar cellular events.

We conclude that inclusion body myositis does represent a distinct clinical and histopathological entity that is probably underdiagnosed in the United Kingdom. Evaluation of previous muscle biopsy or repeat biopsy samples are invaluable in the confirmation of the diagnosis and thereby targeting therapeutic approaches. Confirmation of the diagnosis relies on identification of often subtle features within the muscle biopsy sample and electron microscopy remains essential.

The authors thank Janet Palmer for expert preparation of muscle samples for histology, Trevor Gray for electron microscopy, and Bill Brackenbury for the photomicrographs.

- 1 Yunis E, Samaha F. Inclusion body myositis. *Lab Invest* 1971; 25: 240-8.
- 2 Chou S-M. Myxovirus-like structures in a case of human chronic polymyositis. *Science* 1967; 158: 1453-5.
- 3 Danon M, Reyes M, Perurena O, Masdeu J, Manaligod J. Inclusion body myositis. A corticosteroid resistant idiopathic inflammatory myopathy. *Arch Neurol* 1982; 39: 760-4.
- 4 Calabrese L, Mitsumoto H, Chou S. Inclusion body myositis presenting as treatment resistant polymyositis. *Arthritis Rheum* 1987; 30: 397-403.
- 5 Ringel S, Kenny C, Neville H, Giorno R, Carry M. Spectrum of inclusion body myositis. *Arch Neurol* 1987; 44: 1154-7.
- 6 Lotz B, Engel A, Nishino H, Stevens J, Litchy W. Inclusion body myositis. Observations in 40 patients. *Brain* 1989; 112: 727-47.
- 7 Mhiri C, Gherardi R. Inclusion body myositis in French patients. A clinicopathological evaluation. *Neuropathol Appl Neurobiol* 1990; 16: 333-44.
- 8 Carpenter S, Karpati G, Heller I, Eisen A. Inclusion body myositis: a distinct variety of idiopathic inflammatory myopathy. *Neurology* 1978; 28: 8-17.
- 9 Fukuhara N, Kumamoto T, Tsubaki I, Mayuzumi T, Nitta H. Oculopharyngeal muscular dystrophy and distal myopathy: intrafamilial difference in the onset and distribution of muscular involvement. *Acta Neurol Scand* 1982; 65: 458-67.
- 10 Matsubara S, Tanabe H. Hereditary distal myopathy with filamentous inclusions. *Acta Neurol Scand* 1982; 65: 363-8.
- 11 Nonaka I, Sunohara N, Ishiura S, Satoyoshi E. Familial distal myopathy with rimmed vacuole and lamella (myeloid) body formation. *J Neurol Sci* 1981; 51: 141-55.
- 12 Fukuhara N, Kumamoto T, Tsubaki T. Rimmed vacuoles. *Acta Neuropathol (Berl)* 1980; 51: 229-35.
- 13 Tome F, Fardeau M. Nuclear inclusions in oculopharyngeal dystrophy. *Acta Neuropathol (Berl)* 1980; 49: 85-7.
- 14 Henriksson K, Sandstedt P. Polymyositis-treatment and prognosis: a study of 107 patients. *Acta Neurol Scand* 1982; 65: 280-300.
- 15 Richter Cohen M, Sulaiman A, Garancis J, Wortmann R. Clinical heterogeneity and treatment response in inclusion body myositis. *Arthritis Rheum* 1989; 32: 734-9.
- 16 Chad D, Good P, Adelman L, Bradley W, Mills J. Inclusion body myositis associated with Sjögren's syndrome. *Arch Neurol* 1982; 39: 186-8.
- 17 Arahata K, Engel A. Monoclonal antibody analysis of mononuclear cells in myopathies. I: quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibres invaded by T cells. *Ann Neurol* 1984; 16: 193-208.
- 18 Mendell J, Sahenk Z, Gales T, Paul L. Amyloid filaments in inclusion body myositis: novel findings provide insight into nature of filaments. *Arch Neurol* 1991; 48: 1229-34.
- 19 Askanas V, Engel W, Alvarez R, Glenner G. β -Amyloid protein immunoreactivity in muscle of patients with inclusion-body myositis. *Lancet* 1992; 339: 560-1.