Chapter 1

Introduction and aims

Sporadic inclusion body myositis (IBM) is an acquired myopathy. In 1978, Carpenter and co-workers for the first time described 14 patients with distinct clinical and histopathological features.[1] Sporadic IBM is now recognized as the most common inflammatory myopathy and one of the most important myopathies in individuals over the age of fifty.

Epidemiology

The minimal prevalence of sporadic IBM in 1999 in The Netherlands was estimated at 5 patients per million inhabitants. Corrected for age and gender distribution, the prevalence was 16 per million for inhabitants over the age of 50 years in the Netherlands.[2] However, prevalence figures vary considerably in different populations and racial groups. In Turkey, prevalence was 0.7 per million inhabitants,[3] 9.8 in Japan,[4] 10.7 in the USA,[5] whereas a study in Western Australia reported a prevalence of 14.9.[6] Differences in the worldwide distribution of sporadic IBM may be attributed to different diagnostic criteria, recruitment procedures, and possibly to genetic or environmental factors.

Clinical characteristics

The first symptoms of weakness in sporadic IBM usually start after the age of 40, with an average age at onset of 60 years.[2, 7] Men are 2-4 times more often affected than women.[8, 9] Muscle groups affected early in the course of the disease are the quadriceps muscles, finger flexors and pharyngeal muscles. Weakness of these muscles leads to typical functional disability in patients: quadriceps weakness leads to buckling of the knees, repetitive falls on the knees and difficulty with climbing stairs or rising from a chair. Weakness of the deep finger flexors results in inability to make a tight fist with nails no longer visible (Figure). Pharyngeal weakness causes swallowing dysfunction, leading to social impairment, when shared meals are avoided due to embarrassment. Furthermore, it can lead to weight loss due to decreased caloric intake. Prevalence figures of dysphagia in sporadic IBM differ considerably between reported studies, ranging from 40-80%.[9-13] The wide range in prevalence most likely originates from the lack of a common definition of dysphagia.

In some cases, the onset of symptoms follows an atypical pattern, presenting with extensive finger extensor weakness, ‘scapula alata’ or ‘dropped head syndrome’.

It is not known whether the heart, which is a non-skeletal striated muscle, is affected in sporadic IBM, although it is in the other idiopathic inflammatory myopathies,

polymyositis and dermatomyositis.[14-17] However, data on cardiac involvement in polymyositis should be interpreted with caution, as the criteria used in these studies include the previous Bohan and Peter criteria[18, 19] which may include sporadic IBM patients in the polymyositis category. It is therefore possible that to some extent, the heart in sporadic IBM is involved as well.

Although data on the distribution of muscle weakness in the early phase of the disease are known, this is not the case for the exact course of the disease over a longer period of time. The rate of progression of muscle weakness and the acquired functional disability have not been studied over multiple years. Sporadic IBM is considered to be slowly progressive and is thought not to shorten life-expectancy, but studies confirming these assumptions are lacking so far. It is unknown whether sporadic IBM patients die due to causes related to sporadic IBM.

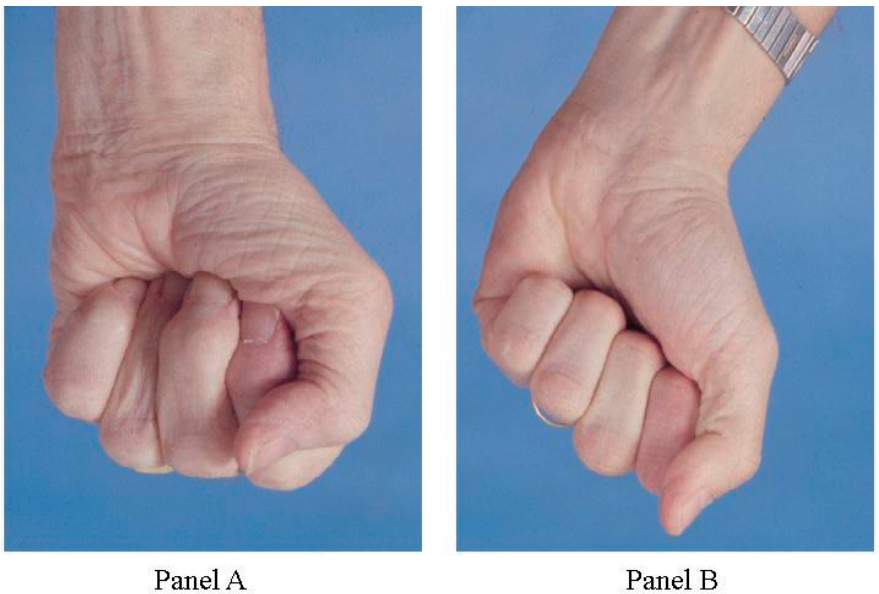

Figure
Panel A showing a sporadic IBM patient unable to make a tight fist in which the nails are no longer visible due to weakness of the deep finger flexor muscles. Panel B shows a healthy subject.

Diagnostic pitfalls

Patients often experience a considerable delay in time to diagnosis, illustrated by the following case description.

A 70 year-old man presented with progressive gait unsteadiness for five years. He had to use his arms to climb the stairs or to get up from a chair. There were no pain, sensory symptoms or fatigue. He had pulmonary sarcoidosis at the age of 24 years, which remained in remission after treatment with ACTH and prednisone. There was no family history of autoimmune or muscle diseases. Clinical examination showed muscle weakness of the iliopsoas, quadriceps and biceps brachii muscles. Gait examination was normal. Toe and heel walking were normal, but the patient was unable to squat. Further investigations showed normal laboratory findings, including normal creatine kinase levels. Needle electromyography of the left rectus femoris muscle showed no abnormalities. The soleus muscle showed spontaneous muscle fiber activity and high amplitude, polyphasic motor unit action potentials (MUAPs), more reminiscent of an axonal neuropathy than a myopathy. Biopsy of a symptomatic anterior tibial muscle showed nonspecific myopathic changes. A possible sporadic inclusion body myositis or motor neuron disease was considered as only motor dysfunction was found. Over the following years, his muscle weakness progressed and spread to the distal legs and finger flexors of two fingers of the right hand. Three years later he was partially wheelchair bound. He then reported difficulties with swallowing solid foods. He did not develop fasciculations, cramps, or pyramidal tract signs. A second biopsy of the vastus lateralis muscle showed no muscle fibres but only fatty tissue. A muscle MRI was performed to select an appropriate muscle for a third muscle biopsy. This showed extensive fatty infiltration of the shoulder, limb-girdle and leg-musculature. Muscles in the legs not showing fatty infiltration had a high signal on STIR, indicating inflammation. Eventually, the third biopsy of the anterior tibial muscle showed myopathic changes including mononuclear inflammatory infiltrates with invasion of non-necrotic fibers and rimmed vacuoles, supporting the diagnosis of sporadic inclusion body myositis.

A delay in the diagnosis and a high rate of initial misdiagnosis is not uncommon in sporadic IBM.[2, 7] This may well be due to a failure to recognize the characteristic pattern of muscle weakness described earlier. In addition, diagnostic tests can be incorrectly interpreted or inconclusive.

Serum creatine kinase activity (sCK) levels are usually elevated only 2-5 times, but can be normal as well. It is not likely to find sCK levels elevated more than 10 times in sporadic IBM. Normal or mildly elevated sCK levels can disguise this myopathy.

Electromyography in sporadic IBM patients can reveal positive sharp waves, fibrillation potentials and complex repetitive discharges. Motor unit potentials sometimes show high amplitudes and polyphasy, incorrectly suggesting a neurogenic disorder.

Muscle biopsy plays a crucial role in the diagnostic process. To reach a definite diagnosis of definite sporadic IBM the biopsy must show inflammatory as well as degenerative changes.[20-22] In some cases invasion of T-cells (inflammation) or rimmed vacuoles (degeneration) may be absent in a first muscle biopsy. Unfortunately repeated biopsies, even in patients with a high clinical suspicion for sporadic IBM, may still not demonstrate these features.[23] Implementation of muscle MRI in the diagnostic criteria may appear to be useful in selected cases. A previous study reports that magnetic resonance imaging can be used to distinguish polymyositis from sporadic IBM.[24] Another study showed explicit fatty changes in the flexor digitorum profundus muscle, sometimes preceding clinically detectable weakness in this muscle.[25]

In the future serum biomarkers might assist in the diagnosis, as an autoantibody against a muscle protein was recently identified. [26, 27]

Pathogenetic considerations

The pathogenesis of sporadic IBM is as yet unclear, but several findings suggest a primarily immune-mediated pathway. The immune process is thought to be mediated by CD8+ cytotoxic T-cells, which invade non-necrotic muscle fibers that express the MHC-I antigen. The auto-invasive T-cells are most likely antigen-driven and clonally expand in situ within the muscle microenvironment.[28] An upregulation of cytokines and chemokines can further propagate the inflammatory response by facilitating T-cell activity, adhesion and transmigration.[29] Costimulator molecules of the B7 family are present on the muscle fibres that bind to their counterreceptors on the auto invasive T-cells.[30] Apart from T-cells, infiltrates of B-cells (myeloid dendritic cells and plasma cells) are also found. Inflammation is more obvious than other pathological hallmarks of the disease such as the rimmed vacuoles or amyloid depositions.[31] In sporadic IBM patients an overrepresentation of paraproteinemias is present[32] and there is an association with other autoimmune diseases, [9, 33, 34] indicating that these patients might be more prone to autoimmune processes. Furthermore, genetic susceptibility studies have found a strong association between sporadic IBM and the autoimmune prone

8.1 MHC ancestral haplotype in the Caucasian population[35] and the 52.1 ancestral haplotype in the Japanese.[36]

The lack of a long-lasting effect of immunomodulating therapy on the progression of the disease opts for a primary degenerative pathway. Proponents of this theory point at the presence of rimmed vacuoles and accumulation of degenerative proteins, such as β-amyloid en phosphorylated tau protein. It is thought that rimmed vacuoles are derived from the breakdown of myonuclei, as the vast majority of rimmed vacuoles contain nuclear membrane proteins.[37] The discovery of the nucleic protein TDP-43 in the sarcoplasm in sporadic IBM [38-41] supports the theory of nuclear breakdown. Accumulation of degenerative proteins is often associated with other neurodegenerative diseases. It is postulated that protein misfolding leads to the accumulation of aberrant proteins. This accumulation in turn leads to failure of different cell processes, for instance in the lysosomal degradation of autophagosomal material.[42] An inflammatory response is supposed to be secondary to this aberrant protein accumulation. The accumulation of neurodegenerative proteins in muscle fibers is not unique to sporadic IBM, as it is observed in other vacuolar myopathies as well, such as oculopharyngodistal myopathy. However, a feature unique to sporadic IBM is the strong inflammatory response coinciding with the degenerative changes. A possible link between the two mechanisms may be found in the strong correlation between mRNA expression of the amyloid precursor protein with several proinflammatory chemokines and interleukins. Upregulation of the amyloid precursor protein and subsequently accumulation of β-amyloid was seen in human myotubes exposed to IL-1β.[43] This suggests that in a sporadic IBM muscle the presence of pro-inflammatory mediators causes β-amyloid aggregation. Besides an upregulation of the amyloid precursor protein in IL-1β exposed human myotubes, αB-crystalline (a stressor protein) is overexpressed as well.[44] Several normal appearing muscle fibers in sporadic IBM contain αB-crystalline and amyloid precursor protein before amyloid deposits or rimmed vacuoles are detected, suggesting that proinflammatory changes precede degeneration. [44]

Aims of this thesis

The present thesis firstly aims to expand the description of clinical features of sporadic IBM. The natural history study described in **Chapter 2** provides information about the course of the disease over a long time period and might clarify whether sporadic IBM influences life expectancy. The incidence and character of dysphagia, a symptom often present in sporadic IBM, is investigated in a standard manner, using a standardized

questionnaire and by performing a swallowing video fluoroscopy in **Chapter 3**. Possible involvement of the heart in sporadic IBM is studied in a cross sectional setting in **Chapter 4.** MRI of skeletal muscles is described in **Chapter 5** aiming at specific patterns of abnormalities in sporadic IBM compared to other myopathies, hence contributing to a better diagnostic process. Finally, we investigated the role of *TREX1*, a gene strongly associated with autoimmune diseases, in the pathogenesis of sporadic IBM (**Chapter 6**).

References

1. Carpenter S, Karpati G, Heller I, Eisen A. Inclusion body myositis: a distinct variety of idiopathic inflammatory myopathy. Neurology 1978;28(1):8-17.
2. Badrising UA, Maat-Schieman M, van Duinen SG et al. Epidemiology of inclusion body myositis in the Netherlands: a nationwide study. Neurology 2000;55(9):1385-1387.
3. Oflazer PS, Deymeer F, Parman Y. Sporadic-inclusion body myositis (s-IBM) is not so prevalent in Istanbul/Turkey: a muscle biopsy based survey. Acta Myol 2011;30(1):34-36.
4. Suzuki N, Aoki M, Mori-Yoshimura M, Hayashi YK, Nonaka I, Nishino I. Increase in number of sporadic inclusion body myositis (sIBM) in Japan. J Neurol 2012;259(3):554-556.
5. Felice KJ, North WA. Inclusion body myositis in Connecticut: observations in 35 patients during an 8-year period. Medicine (Baltimore) 2001;80(5):320-327.
6. Needham M, Corbett A, Day T, Christiansen F, Fabian V, Mastaglia FL. Prevalence of sporadic inclusion body myositis and factors contributing to delayed diagnosis. J Clin Neurosci 2008;15(12):1350-1353.
7. Needham M, James I, Corbett A et al. Sporadic inclusion body myositis: Phenotypic variability and influence of HLA-DR3 in a cohort of 57 Australian cases. J Neurol Neurosurg Psychiatry 2008;79:1056-1060.
8. Badrising UA, Maat-Schieman ML, van Duinen SG, van Dijk JG, Verschuuren JJ, Wintzen AR. ['Inclusion body'-myositis]. Ned Tijdschr Geneeskd 1998;142(11):553-557.
9. Lotz BP, Engel AG, Nishino H, Stevens JC, Litchy WJ. Inclusion body myositis. Observations in 40 patients. Brain 1989;112 (Pt 3):727-747.
10. Badrising UA, Maat-Schieman ML, van Houwelingen JC et al. Inclusion body myositis. Clinical features and clinical course of the disease in 64 patients. J Neurol 2005;252(12):1448-1454.
11. Houser SM, Calabrese LH, Strome M. Dysphagia in patients with inclusion body myositis. Laryngoscope 1998;108(7):1001-1005.
12. Lindberg C, Persson LI, Bjorkander J, Oldfors A. Inclusion body myositis: clinical, morphological, physiological and laboratory findings in 18 cases. Acta Neurol Scand 1994;89(2):123-131.
13. Sayers ME, Chou SM, Calabrese LH. Inclusion body myositis: analysis of 32 cases. J Rheumatol 1992;19(9):1385-1389.
14. Gonzalez-Lopez L, Gamez-Nava JI, Sanchez L et al. Cardiac manifestations in dermato-polymyositis. Clin Exp Rheumatol 1996;14(4):373-379.
15. Gottdiener JS, Sherber HS, Hawley RJ, Engel WK. Cardiac manifestations in polymyositis. Am J Cardiol 1978;41(7):1141-1149.
16. Oka M, Raasakka T. Cardiac involvement in polymyositis. Scand J Rheumatol 1978;7(4):203-208.
17. Stern R, Godbold JH, Chess Q, Kagen LJ. ECG abnormalities in polymyositis. Arch Intern Med 1984;144(11):2185-2189.
18. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med 1975;292(8):403-407.
19. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292(7):344-347.
20. Griggs RC, Askanas V, DiMauro S et al. Inclusion body myositis and myopathies. Ann Neurol 1995;38(5):705-713.
21. Needham M, Mastaglia FL. Inclusion body myositis: current pathogenetic concepts and diagnostic and therapeutic approaches. Lancet Neurol 2007;6(7):620-631.
22. Verschuuren JJ, Badrising UA, Wintzen AR, Engelen B, van der Hoeven H, Hoogendijk JE. Inclusion Body Myositis. In: Emery A, editor. Diagnostic Criteria for Neuromuscular Disorders. London: Royal Society of Medicine Press, European Neuromuscular Center; 1997:81-84.
23. Chahin N, Engel AG. Correlation of muscle biopsy, clinical course, and outcome in PM and sporadic IBM. Neurology 2008;70(6):418-424.
24. Dion E, Cherin P, Payan C et al. Magnetic resonance imaging criteria for distinguishing between inclusion body myositis and polymyositis. J Rheumatol 2002;29(9):1897-1906.

25. Sekul EA, Chow C, Dalakas MC. Magnetic resonance imaging of the forearm as a diagnostic aid in patients with sporadic inclusion body myositis. Neurology 1997;48(4):863-866.
26. Salajegheh M, Lam T, Greenberg SA. Autoantibodies against a 43 KDa muscle protein in inclusion body myositis. PLoS One 2011;6(5):e20266.
27. Pluk H, van Hoeve BJ, van Dooren SH et al. Autoantibodies to cytosolic 5'-nucleotidase 1A in inclusion body myositis. Ann Neurol 2013;73(3):397-407.
28. Salajegheh M, Rakocevic G, Raju R, Shatunov A, Goldfarb LG, Dalakas MC. T cell receptor profiling in muscle and blood lymphocytes in sporadic inclusion body myositis. Neurology 2007;69(17):1672-1679.
29. Dalakas MC. Inflammatory muscle diseases: a critical review on pathogenesis and therapies. Curr Opin Pharmacol 2010;10(3):346-352.
30. Wiendl H, Mitsdoerffer M, Schneider D et al. Muscle fibres and cultured muscle cells express the B7.1/2-related inducible co-stimulatory molecule, ICOSL: implications for the pathogenesis of inflammatory myopathies. Brain 2003;126(Pt 5):1026-1035.
31. Pruitt JN, Showalter CJ, Engel AG. Sporadic inclusion body myositis: counts of different types of abnormal fibers. Ann Neurol 1996;39(1):139-143.
32. Dalakas MC, Illa I, Gallardo E, Juarez C. Inclusion body myositis and paraproteinemia: incidence and immunopathologic correlations. Ann Neurol 1997;41(1):100-104.
33. Badrising UA, Schreuder GM, Giphart MJ et al. Associations with autoimmune disorders and HLA class I and II antigens in inclusion body myositis. Neurology 2004;63(12):2396-2398.
34. Dalakas MC. Inflammatory, immune, and viral aspects of inclusion-body myositis. Neurology 2006;66(2 Suppl 1):S33-S38.
35. Needham M, Mastaglia FL, Garlepp MJ. Genetics of inclusion-body myositis. Muscle Nerve 2007;35(5):549-561.
36. Scott AP, Allcock RJ, Mastaglia F, Nishino I, Nonaka I, Laing N. Sporadic inclusion body myositis in Japanese is associated with the MHC ancestral haplotype 52.1. Neuromuscul Disord 2006;16(5):311-315.
37. Greenberg SA, Pinkus JL, Amato AA. Nuclear membrane proteins are present within rimmed vacuoles in inclusion-body myositis. Muscle Nerve 2006;34(4):406-416.
38. Kusters B, van Hoeve BJ, Schelhaas HJ, Ter LH, van Engelen BG, Lammens M. TDP-43 accumulation is common in myopathies with rimmed vacuoles. Acta Neuropathol 2009;117(2):209-211.
39. Olive M, Janue A, Moreno D, Gamez J, Torrejon-Escribano B, Ferrer I. TAR DNA-Binding protein 43 accumulation in protein aggregate myopathies. J Neuropathol Exp Neurol 2009;68(3):262-273.
40. Salajegheh M, Pinkus JL, Taylor JP et al. Sarcoplasmic redistribution of nuclear TDP-43 in inclusion body myositis. Muscle Nerve 2009;40(1):19-31.
41. Weihl CC, Temiz P, Miller SE et al. TDP-43 accumulation in inclusion body myopathy muscle suggests a common pathogenic mechanism with frontotemporal dementia. J Neurol Neurosurg Psychiatry 2008;79(10):1186-1189.
42. Nogalska A, D'Agostino C, Terracciano C, Engel WK, Askanas V. Impaired autophagy in sporadic inclusion-body myositis and in endoplasmic reticulum stress-provoked cultured human muscle fibers. Am J Pathol 2010;177(3):1377-1387.
43. Schmidt J, Barthel K, Wrede A, Salajegheh M, Bahr M, Dalakas MC. Interrelation of inflammation and APP in sIBM: IL-1 beta induces accumulation of beta-amyloid in skeletal muscle. Brain 2008;131(Pt 5):1228-1240.
44. Muth IE, Barthel K, Bahr M, Dalakas MC, Schmidt J. Proinflammatory cell stress in sporadic inclusion body myositis muscle: overexpression of alphaB-crystallin is associated with amyloid precursor protein and accumulation of beta-amyloid. J Neurol Neurosurg Psychiatry 2009;80(12):1344-1349.