Chapter 7

Summary and discussion

Sporadic IBM is a rare disease, but it is the most common among the myopathies with onset after the age of fifty. Men are more frequently affected than women. Symptoms most frequently start with weakness in the quadriceps muscles, the finger flexors or pharyngeal muscles, the latter resulting in swallowing dysfunction. Diagnostic pitfalls still contribute to a delay in diagnosis. The pathogenesis of sporadic IBM remains an enigma, with uncertainties as to whether a degenerative or an inflammatory pathway causes the disease.

At the start of our studies long term follow-up data were lacking. In the **second chapter** of this thesis the results of such a follow-up study in 64 sporadic IBM patients have been described. The aim was to investigate the rate and distribution of weakness progression over years and the nature of disabilities that develop during the course of the disease. Furthermore, life expectancy and causes of death in sporadic IBM patients were described. Patient characteristics related to the course of the disease were sought for.

As expected, the course of the disease was progressive, with a mean decline on manual muscle testing of 3.5% per year, and 28.8% over a ten-year period. For quantitative muscle testing, these numbers are somewhat higher, 5.4% and 39.4% percent respectively. We cannot be sure regarding the linearity of the decline, as we examined patients at two time points only. However, almost all patients reported their weakness being relentlessly progressive during the course of the disease. Furthermore, a subgroup of patients was indeed examined 50 weeks after baseline as they participated in another study. The degree of decline in strength in these patients after 50 weeks was comparable with our calculated rates. Another recent study describing the rate of muscle decline tested by quantitative muscle testing in 66 sporadic IBM patients reports a strength decline of 0.79% per month.[1] The calculated rate of decline per year would be 9.1%, which seems much higher than the rate we found in our patient group (5.4%). In their study, 4 muscles were tested (biceps, triceps, iliopsoas and quadriceps femoris), in contrast to 14 muscle groups in our study. If we restrict our study to these four muscles, the calculated rate of decline would be 9.4% per year, comparable with Lindberg's findings. Recently, Cortese et al. found a 5.2% decline on manual muscle testing (23 muscle groups) after one year in 23 subjects.[2] No prognostic value could be attributed to a single clinical feature, similar to the findings of Lindberg et al. and Cortese et al.[1, 2] Muscle strength in the lower legs declined most rapidly, followed by that of the forearms and upper legs. In our study the more severe affliction of ventral muscles as compared to the dorsal ones in the early stage of the disease eventually disappeared in the lower legs. The severity of the ongoing strength loss is reflected in the functional grading scale scores, which showed that 40% of patients could be

considered to be completely or severely dependent 20 years after onset. The mean time between the first symptom and the first use of a wheelchair was 16 years in our study, as has been confirmed by two other studies.[2, 3] The assumption that the mild course and slow decline of muscle strength in sporadic IBM does not result in major disabilities is refuted by the findings in our study and is confirmed in a later study of Cortese et al, who also concluded sporadic IBM to be a disabling disease.[2]

Life expectancy was normal in our patient group, and this is supported by two other recently published papers.[1, 3] However, in this chapter we described causes of death in the sporadic IBM population to be significantly different from an age-matched general Dutch population. Patients died more often due to disorders of the respiratory system, in particular (aspiration) pneumonia. This is possibly a reflection of weakness of respiratory and pharyngeal muscles. Inamori et al. performed an autopsy in a sporadic IBM patient and reported inflammatory changes as well as rimmed vacuoles in the diaphragm.[4] Together with possible involvement of the abdominal muscles, impairment of respiration, coughing and swallowing may result in aspiration and pneumonia. A higher rate of aspiration pneumonia in sporadic IBM has been described before.[5] In this study 19 patients were followed during approximately 50 months. Thirteen patients died during follow-up, eight out of these due to aspiration pneumonia. In the other cases, the causes of death were unknown. Cachexia was also seen more frequently in our sporadic IBM patient group, supposedly reflecting the great impact that muscle wasting and dysphagia can have on these patients at end-stage disease. Furthermore, an unexpectedly high number of patients asked for end-of-life care interventions, including euthanasia (6.5%) and continuous deep sedation (6.5%), approximating the rates in amyotrophic lateral sclerosis in the Netherlands.[6] This underlines the high disease burden in the final stage of sporadic IBM.

The effect of use of the immunosuppressant drug methotrexate for 48 weeks on weakness progression in our patient group in a previous study was negligible. Benvensite et al.[3] confirmed that immunosuppressants do not slow down weakness progression. They performed a long-term observational study with 136 sporadic IBM patients. Seventy-one of these patients had received immunosuppressive treatment (most frequently prednisone) for a median time of 41 weeks. At their last visit, patients who had received immunosuppressants were even more severely affected according to several disability scales as compared to patients who did not have used immunotherapy. Contrarily, Lindberg et al[1] conclude that sporadic IBM patients treated with different kinds of immunosuppressive drugs have a smaller decline of muscle strength of the biceps muscle only. However, this conclusion is based on retrospective and un-blinded data collection. Furthermore, weakness progression of the quadriceps muscle was not altered, whereas this muscle showed the largest decline in strength in

our study. In addition, their conclusion is based on treatment with a combination of immunosupressants. The authors also mention that two patients in their study group died due to complications related to immunosuppressive drug use. Therefore, as long as a clear benefit of immunosuppressive drugs has not been shown in a properly conducted clinical trial, their role should be considered with great caution in the treatment of sporadic IBM.

Our study revealed the high impact of the ongoing progression of weakness on patients. While sporadic IBM patients remain ambulant and independent in the initial stage of the disease, the end-stage is characterized by serious disability. Their normal life expectancy goes along with a prolonged disease burden, with disabilities and handicaps having a serious impact on the life of these patients.

In the **third chapter** the frequency and nature of swallowing dysfunction and the way in which dysphagia can be detected best have been described. Fifty-seven patients were interviewed using a questionnaire for dysphagia and 43 of these patients underwent swallowing video fluoroscopy (VFS). We aimed to describe the frequency and symptoms of dysphagia in sporadic IBM patients and to identify questions from a questionnaire predicting swallowing abnormalities on VFS. Furthermore, we tried to determine the mechanism of dysphagia in these patients. Sixty-five percent of 57 patients had symptoms of dysphagia. Remarkably, only a small proportion of patients had ever mentioned their swallowing dysfunction to their physician. Two questions from a structured questionnaire were identified to adequately predict abnormalities on VFS. These questions were: 'Do you have to swallow repeatedly in order to get rid of food' and 'Does food get stuck in your throat'.

The nature of dysphagia was studied using VFS. We found abnormalities on VFS in 79% of 43 patients. Most abnormalities were signs related to impaired propulsion of the bolus, such as cricopharyngeal dysfunction. Aspiration-related signs were found in almost half of the patients, but actual aspiration was rarely observed. Cricopharyngeal dysfunction was a frequent abnormality, as described in another study investigating dysphagia in sporadic IBM.[5] Murata et al[7] investigated 10 sporadic IBM patients with and without dysphagia. They performed VFS and computed pharyngoesophageal manometry. All patients, including the patients without dysphagia, showed cricopharyngeal dysfunction. Additionally, the computed pharyngoesophageal manometry revealed a lack of oropharyngeal peristaltic activity in all patients, with an absence of deglutitive relaxation of the upper esophageal sphincter in patients with dysphagia. Based on current knowledge dysphagia in sporadic IBM is most likely caused by pharyngeal muscle weakness, with the inability to generate sufficient intrabolus pressure to establish relaxation of the cricopharyngeal muscle. This poor synchrony between the contracting

pharynx and the relaxing sphincter causes stasis of the bolus in the pharynx. Treatment of swallowing dysfunction can be invasive or non-invasive. Invasive interventions include cricopharyngeal myotomy, being the most frequently applied therapy, followed by pharyngoesophageal dilatations. Cricopharyngeal myotomy seems to benefit 63% of patients with sporadic IBM, whereas pharyngoesophageal dilatation is reported to be less effective (33%).[5] The reason for treatment failure could be due to a too far advanced pharyngeal weakness. It has been established that prolonged obstruction at the pharyngoesophagal outlet leads to pharyngeal weakness.[8] Therefore, it seems plausible to treat patients before dysfunction is too severe in order to have the optimal result. Treatment effect can possibly be predicted by measurements of the intrabolus pressures, a measurement of pharyngeal strength, but studies investigating this are lacking so far. Another invasive treatment for dysphagia is botulin toxin injections in the cricopharyngeal sphincter, but studies investigating the benefit are lacking. There are some case reports[9, 10] reporting a positive effect on swallowing function following IvIg therapy. Furthermore, one placebo-controlled double-blind study in 19 patients showed a significant improvement of swallowing function measured by ultrasound after the use of IvIg therapy.[11]

Non-invasive interventions include diet modification, compensatory techniques and feeding strategies. In case of failure of above mentioned therapeutic options a percutaneous endoscopic gastrostomy (PEG) tube placement can be required to warrant a sufficient calorie-intake.

We found a high rate of swallowing dysfunction in sporadic IBM patients. Patients however often do not report their dysphagia to their physicians resulting in inadequate treatment. Therefore, physicians should take a proactive approach in detecting swallowing dysfunction. Detection of dysphagia is easy and feasible in a clinical setting, as well as useful as therapeutic interventions are available and life-threatening complications can be prevented.

Whether the heart, a non-skeletal striated muscle, is part of the disease was investigated in 51 sporadic IBM patients and described in **chapter four**. Extensive cardiac evaluation, comprising cardiac history, physical (cardiac) examination, laboratory tests, electrocardiography and echocardiography were performed. As a result, we found sporadic IBM patients not to be more prone for cardiac abnormalities than would be the case in an age-matched population. We did however find a high frequency of elevated troponin-T levels in patients with otherwise normal electrocardiography and echocardiography (79%). Troponin-T is considered to be a marker for cardiac damage. It is expressed in regenerating skeletal muscle fibers as well. Troponin-I is also a marker for cardiac damage, but in contrast to troponin-T, it is not expressed in regenerating

muscle fibers. We found elevation of troponin-I in only one sporadic IBM patient, who did have cardiac abnormalities. This led us to the conclusion that elevation of troponin-T in sporadic IBM patients does not necessarily suggest cardiac pathology. Fisher et al[12] studied the significance of raised troponin-T in eleven patients with different kinds of myositis and normal electrocardiography and echocardiography. This study included one sporadic IBM patient only. In 5 patients, without further specification of diagnosis, they performed gel-filtration chromatography and found that in these patients the troponin-T was comparable with the nature of troponin-T in acute coronary syndromes. They concluded that elevation of troponin-T in myositis patients reflected subclinical myocarditis. However, they did not measure the heart-specific troponin-I levels and it is not clear whether the gel-filtration chromatography was performed in the one participating sporadic IBM patient. Therefore, evidence that elevation of troponin-T in sporadic IBM patients is of cardiac origin and therefore reflects cardiac pathology is not yet available.

In contrast to our findings, Utz et al. do report one atypical case of sporadic IBM with cardiac involvement.[13] This case report describes a 36-year-old female patient with the diagnosis sporadic IBM made in her mid-twenties, based on a muscle biopsy. She presented with acute onset exertional chest pain. Cardiovascular magnetic resonance revealed hypokinetic wall motion of the left ventricular wall. Furthermore, extensive pericardial fat was found. According to the authors this would be the first case description of cardiac involvement in a sporadic IBM patient. This is an unusual age of presentation of sporadic IBM, which casts doubt on the diagnosis.

In conclusion, as no other evidence has been found for cardiac involvement in sporadic IBM it is safe to conclude that it is not necessary to conduct routine cardiac investigations in sporadic IBM patients.

The objective of **chapter five** was to describe the skeletal muscle abnormalities on MR imaging in 32 sporadic IBM patients. The additional value of MR imaging in the diagnostic work-up in sporadic IBM was discussed. A total of 68 muscles in the upper and lower extremity were scored for fatty infiltration, inflammation (edema-like changes) and atrophy. We found a specific pattern in our patient group. The presence of fat was far more pronounced than the presence of inflammation. Asymmetry of abnormalities was present in 44% of patients. Furthermore, a preference of fatty infiltration for certain muscles or muscle groups was seen. We found the quadriceps muscles to be commonly invaded with fat, with a relative sparing of the rectus femoris. Hamstrings and adductor muscles of the upper leg were spared compared to the quadriceps muscles, as well as sparing of the other pelvic girdle muscles. The flexor digitorum profundus (FDP) was the most afflicted muscle in the forearm. This selective pattern of muscle

involvement confirmed the findings of a smaller group of sporadic IBM patients previously described.[14] If the FDP was not invaded with fat, other muscles of the forearm were normal as well. In the lower legs, the medial head of the gastrocnemius muscle was most commonly affected. Selective sparing of the rectus femoris and infliction of the medial head of the gastrocnemius muscle has also been described earlier in Becker muscular dystrophy.[15] However, the same study shows clear affliction of the adductors and hamstring muscles in Becker patients in contrast to sporadic IBM patients. The number of muscles invaded with fat correlated well with disease duration in sporadic IBM. In contrast, inflammation of muscles did not correlate with disease duration and could be prominent even 10 years after onset of the disease. Based on this study we hypothesized inflammation to precede fatty infiltration of muscle, as inflammatory changes were mostly present in muscles which were relatively fat-free. However, as this was a cross-sectional study a follow-up study will be needed to clarify the timeframe in which muscles become inflamed or infiltrated with fat.

We concluded that MR imaging of skeletal muscles in sporadic IBM showed a distinct pattern, which could be helpful for its diagnosis, especially in patients with a high clinical suspicion, but lacking the mandatory set of muscle biopsy features. However, MR imaging series of patients with other myopathies evaluated in a systematic way and compared to IBM patients are still lacking, and imaging of the forearm is not standard practice in other myopathies. Therefore, at the moment MR imaging cannot be decisive for the diagnosis of sporadic IBM.

In the **sixth chapter**, we investigated whether *TREX1*, a gene associated with a number of autoimmune diseases, was associated with sporadic IBM. If so, it could be a clue in finding a pathway that contributes to the pathophysiology. TREX1 is a protein which is involved in repair of damaged DNA. Research in mice showed that TREX1 deficiency led to accumulation of ssDNA in the cytoplasm, triggering an autoimmune response. We screened 54 sporadic IBM patients for presence of mutations in the *TREX1* gene by direct sequencing. All patients tested negative for pathogenic mutations in the *TREX1* gene. Therefore, an important role of *TREX1* mutations in the pathogenesis of sporadic IBM seems highly unlikely.

Perspectives for the future

During the natural history study, it became clear that a significant part of the patients did not visit their own neurologist for follow-up, but rather consulted their general

practitioner. They regarded a visit to a neurologist physically challenging, and reasoned that there was no treatment available anyway. Our studies, however, indicate that there are complications in the course of sporadic IBM that can be treated, but are easily overlooked, especially by those not familiar with the disease. Dysphagia is a frequent and socially invalidating symptom that can be easily detected and sometimes treated successfully. If not specifically asked for it can be overlooked. Furthermore, the severe disability which can be present at the end stage of the disease must be recognized in order to offer appropriate palliative care. Some patients mentioned that they had asked their general practitioner about end-of-life care interventions, but that they felt misunderstood. Therefore, it seems desirable to organize care for patients with sporadic IBM in neuromuscular centers, where these topics can be discussed in an appropriate manner. Furthermore, respiratory disorders are a common cause of death in sporadic IBM. A few small studies report hypoventilation in sporadic IBM patients due to weakness of respiratory musculature. Whether disease burden is actually increased by hypoventilation is not yet known. Additionally, whether non-invasive ventilation can improve quality of life in these patients, as in patients with amyotrophic lateral sclerosis[16] needs to be investigated.

At this moment, MR imaging of muscles can be of additional value in the diagnostic process in sporadic IBM patients with muscle weakness for several years. It is unclear however whether a specific pattern is present at disease onset. It would be important to analyze MR images of muscles in the early phase of the disease, to find out if inflammation is more prominent in the beginning and whether the specific pattern of fatty infiltration is already present. Furthermore, information about the degree of inflammation and fatty infiltration on MR imaging in the beginning of the disease could provide insight into the usefulness of MRI as an outcome measure in future clinical trials. Information about the rate of fatty infiltration could also be useful in patient selection for clinical trials, as patients early in the disease process, with the least fat infiltrated muscles, are most amenable candidates for these trials.

Another outcome measure for clinical trials could be the measurement of weakness progression in the quadriceps femoris muscle by quantitative muscle testing. This muscle is frequently affected in the early stages of the disease, the progression of weakness is one of the fastest and weakness of this muscle results evidently in a decline of functional status.

The greatest challenge for clinical trials would be to include patients in the early phase of the disease. The degree of fatty infiltration in these patients is not prominent and therefore a clinically significant effect of therapy is more likely to be found in these patients than in patients with extensive weakness due to fatty replacement of muscles

To include patients earlier, diagnosis of sporadic IBM must be made earlier. Whether MR imaging guided biopsies in sporadic IBM can be of additional value is not known yet. Furthermore, whether sporadic IBM biomarkers, such as the recently discovered biomarker anti-Mup-44,[17] will facilitate early diagnosis in the future needs to be awaited.

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