NON-MOTOR SYMPTOMS IN MULTIPLE SCLEROSIS

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ABBREVIATIONS

ANOVA	Analysis of Variance
BBB	Berg Balance Scale
CBT	Cognitive Behavioural Therapy
CIS	Clinical Isolated Syndrom
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DMT	Disease-modifying treatment
EBV	Epstein Barr Virus
EDSS	Expanded Disability Status Scale
EEG	Electroencephalography
FSS	Fatigue Severity Scale
GA	Glatiramer Acetate
HRQoL	Health-Related Quality of Life
HSCL	Hopkins Symptom Checklist
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSIS-29	Multiple Sclerosis Impact Scale
NAB	Neutralizing Anti-Bodies
NHP	Nottingham Health Profile
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PASAT	Paced Auditory Serial Addition Task
PPMS	Primary Progressive MS
PTS	Painful Tonic Spasms
QoL	Quality of Life
RCT	Randomised placebo Controlled Trials
RRMS	Relapsing Remitting MS
SEM	Standard Error of Mean
SF-36	36-item Short Form Health Survey
SPMS	Secondary Progressive MS
SSRI	Selective Serotonin Re-uptake Inhibitor
TN	Trigeminal Neuralgia
TUG	Timed Up&Go
VAS	Visual Analog Scale
VER	Visually Evoked Respons
6MWT	Six-Minute Walk Test

LIST OF ARTICLES

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ABSTRACT

Multiple Sclerosis is an immune-mediated chronic inflammatory disease of the central nervous system (CNS) in genetically susceptible individuals. Even if disease-modifying treatment was introduced more than a decade ago, symptomatic treatment is as important as previously, as immunomodulatory medications are not curing. Recent years focus on health-related quality of life (HRQoL) has demonstrated the importance of non-motor problems in MS, of which fatigue, depression, anxiety, and pain are amongst the most important.

This thesis shows that *pain* was underdiagnosed amongst patients with MS and that only one-third of the patients were treated for their pain. Pain was independent of demographic and clinical variables. Fourty percent of the patients reported pain as having an important influence on daily activities.

Thirty-one percent of the patients reported symptoms of *depression*, while 19 % reported *anxiety;* both figures being significantly higher than in the general population. Only 16 % of the depressed patients and only 11 % of those suffering from anxiety reported treatment. 18 % of the untreated patients with symptoms expressed the need of treatment.

A total of 60 patients with MS with moderate disability (Expanded Disability Status Scale, EDSS, 4.0-6.5), were included for four weeks of daily individualised physiotherapy based on the Bobath concept. *Fatigue* improved after four weeks with inpatient physiotherapy, but the patients' perception of fatigue was not correlated with improvement in physical performance. After three months, fatigue scores worsened while physical performance was improved. Improvement of fatigue after inpatient physiotherapy may therefore be explained by other factors than physiotherapy treatment alone.

A 30-month follow-up of 318 secondary progressive MS (SPMS) patients showed the *HRQoL* to be lower than for controls, strongly influenced by physical disability, disease progression and fatigue. The HRQoL dimension of pain, sleep and emotional reactions were influenced by MS.

There is a need of optimizing symptomatic treatment and psychosocial patient care to improve patients' function and HRQoL. There is also a need of clinical trials to evaluate interventions for symtopmatic treatment and care. Finally, the patients need regular follow-up evaluations with focus on non-motor problems and to be

offered the best treatment momentary available.

1. INTRODUCTION

Multiple Sclerosis is a chronic immune-mediated inflammatory disease of the central nervous system (CNS) in genetically susceptible individuals. Although the disease was well described and illustrated by Charcot as early as 1868, the aetiology is still enigmatic.

The diagnostic procedures have become more accurate over time, but misinterpretation and over-diagnosis may occur (Herndon 1994). The introduction of disease-modifying treatment (DMT) has made early and correct diagnosis even more important. These immunomodulatory medications reduce disease activity, but are not curing. Thus, symptomatic treatment is still an important part of MS care, and patients need careful evaluation to optimize treatment with the best available therapy.

A broader impact of MS on the patients, as evaluated by health-related quality of life (HRQoL), has become an important domain in clinical research and treatment of patients with MS (Nordtvedt 2003). This research has clearly demonstrated the importance of the non-motor, clinically invisible problems in MS. Among the most important are pain, fatigue, depression and anxiety.

1.1. Epidemiology

MS is largely a disease of young adults with a mean age of onset at about 30 years (Confavreux 1980, Weinshenker 1989, Myhr 2001). Only 3 % of the patients present before the age of 16 (Duquette 1987), 6 % are older than 50 years (Noseworthy 1983), and less than 1 % older than 60 years at onset (Hooge 1992). More women than men are affected (2:1) (Duquette 1992, 1993).The sex difference is more pronounced among children (3:1) (Duquette 1987) and patients with disease onset > 40 years (Confavreux 1980). The most recent studies have indicated a temporary increase in the sex ratio, due to increased incidence among females (Grytten 2006, Orton 2006).

The disease is unevenly distributed throughout the world. A diminishing north-south gradient for the MS prevalence in the northern hemisphere has been described, as well as a south-north gradient in the southern hemisphere (Ebers 1998). The highest frequencies are seen in northern parts of Europe and America, but variations have also been reported within geographic regions such as Sicily and

Malta (Dean 1979, Vassallo 1979), as well as high prevalence rates in presumed less frequent areas such as Sardinia (Pugliatti 2001).

Norway belongs to a high prevalence area, with an estimated prevalence of about 150 per 100.000 (Torkildsen 2007). Despite some immigration during the past four decades, the native Norwegian population is ethnically homogeneous and probably shares an identical genetic susceptibility to the disease.

A recent update from Oslo County in Eastern Norway showed a prevalence of 148 per 100 000 in the total population, but as high as 170 per 100 000 among native Norwegians (Smestad 2008). Other recent studies from other parts of Norway have shown prevalence rates of 151 per 100.000 in Hordaland County, Western Norway (Grytten 2006), about 180 per 100.000 in Oppland County, inland of Eastern Norway (Risberg 2007), and 164 per 100.000 in Nord-Trøndelag County, Mid Norway (Dahl 2004). The frequency seems to be somewhat lower in the northernmost counties, with 106 per 100.000 in Nordland County (Alstadhaug 2005) and 73 per 100.000 in the counties of Troms and Finnmark (Grønlie 2000). This lower prevalence in the northernmost counties might be related to the higher proportion of Samis who have a different genetic susceptibility (Torkildsen 2005, Harbo 2007).

1.2. Aetiology

The aetiology of MS is still unknown. The disease pathogenesis encompasses multiple inflammatory and degenerative processes in the CNS. Key neuro-pathological findings include the accumulation of inflammatory cells in the CNS, demyelination and oligodendrocyte loss, axonal degeneration as well as a substantial loss of neurons. It seems that demyelination and axonal destruction follow different pathogenetic pathways in different subgroups of patients (Lassman 2001). A specific antigen for the immune attack in the CNS has not been identified, and whether the local immune response represents a primary or secondary event is yet to be determined. The sequence of events that initiate the disease is largely unknown. The pathological process might even start several years before the clinical symptoms emerge, possibly already during childhood.

Epidemiological studies indicate that environmental factors operate on a complex background of genetic susceptibility leading to the development of MS (Kantarci 2006, Pugliatti 2008). The concordance rate among monozygotic twins (25-30 %) versus dizygotic twins (3-5 %) demonstrates the strength of genetic factors. MS is

also 20-40 times more common in first-degree relatives than in the general population (Weinshenker 1996). The previously detected association with human leukocyte antigen (HLA-II) (6p21) (Jersild 1972) was confirmed in a large genetic linkage study of families of northern European descent (Sawcer 2005) and two other genetic associations, with IL7R (5p13) and IL2R (10p15), were recently described (Lundmark 2007, Hafler 2007).

The incidence and prevalence among monozygotic twins seems to vary over time and with geography. This indicates the influence of environmental factors on aetiology (Ebers 2005). Migration studies support the hypothesis that the susceptibility to environmental factors in childhood can alter the risk of developing MS. Migration from low to high incidence areas before the age of 15 increases the risk of MS, compared to migration after the age of 15 (Dean 1997, Cabre 2007). The association between the exposure to different microbial agents in childhood and the later development of MS has so far been contradictory (Compston 2006) with the notable exception of the Epstein-Barr virus (EBV), a member of the herpes virus family. The MS risk is estimated to be 1:10 in patients not infected with EBV when compared to EBV-positive individuals (reviewed by Ascherio et al 2007), and 2.3 times higher if the patient has a history of infectious mononucleosis according to a meta-analysis by Thacker et al (2006). The leading hypothesis of how the virus is associated with the initiation of MS aims at a possible cross reactivity of the immune response to EBV infection with myelin antigens based on presumed molecular mimicry.

Among non-infectious environmental factors associated with MS are the exposure to sunlight and the corresponding synthesis of vitamin D. In two large cohorts of US nurses total vitamin D intake at baseline was found inversely associated with the risk of MS (Munger 2004). Moreover high circulating levels of vitamin D were associated with lower risk of multiple sclerosis in a prospective, nested case-control study among US military personnel (Munger 2006). The underlying mechanisms of vitamin D in the MS pathogenesis are unclear, but tissue-specific immune responses are known to be regulated by Vitamin D (Hayes 2003).

A positive association between smoking and MS was found in a case-control study (Ghadirian 2001), and a survey of the general population in Hordaland County, Norway, also showed that the risk of MS was higher among smokers than among

never-smokers (Riise 2003). Smoking among parents may also increase the risk of childhood MS (Mikaeloff 2007).

A large longitudinal Danish study suggested an increased MS risk after bereavement (Li 2004), indicating influence of psychological factors.

1.3. Clinical characteristics

Neurological manifestations in an individual patient reflect the anatomic location of the lesions, the overall lesion burden and the effectiveness of repair and compensatory mechanisms. Because these lesions may develop anywhere within the CNS, a wide variety of potential neurological manifestations are possible. The marked heterogeneity in the specific manifestations, the time course over which they develop and their severity over time also add to the variation both between patients and within individual patients.

Until recent years, measurements of disability in MS have been heavily weighted towards motor function and especially ambulation. However, symptoms without a clear focal pathology often diagnosed as non-motor symptoms or invisible symptoms, such as pain and fatigue, are also frequently involved. In addition, a wide range of neuropsychiatric symptoms like depression, anxiety and cognitive impairment may occur. As these symptoms are the main focus of this thesis, they will be highlighted in a separate section below. Althoug belonging to non-motor symptoms, cognitive impairment is not focused on in the reseach presented in this thesis. Characteristic symptoms important for the diagnosis will first be summarized.

1.3.1. Motor symptoms

Lesions in the pyramidal tracts (motor system) are associated with spasticity and weakness, clumsiness and slowness in the extremities. Paresis is the most important cause of gait and physical disability. The most common distribution includes para-paresis, usually asymmetrical, followed in decreasing order of frequency by weakness of one lower limb and hemiparesis. Spasticity is estimated to be present in 60 % of MS patients and may fluctuate depending on numerous factors such as pain from any source, fever, infections, bowel impaction as well as changes in medication.

1.3.2. Brainstem and Cerebellum

Brainstem and cerebellar lesions cause ataxia, instability and vertigo, but may also bring about tremor, diplopia, nystagmus, dysarthria, dysphagia and facial weakness (facial paresis). Ataxia and tremor are the most common symptoms due to cerebellar involvement and can be severe and very disruptive to self-care. Vertigo due to pontine lesions at the root entry zone of the vestibular nuclei may mimick acute peripheral vestibulopathy (Gass 1998).

1.3.3. Bladder dysfunction

Urgency, frequency, hesitation, incomplete emptying and incontinence are symptoms of bladder dysfunction. Urgency occurs more often during relapses involving the spinal cord, often followed by remission. Persistent urgency leads to occasional incontinence, becoming increasingly disabling with progressive disease. In advanced disease large volumes of urine may be passed without warning, sometimes leading to continuous dribbling. Retention of urine may occur and inadequate emptying of the bladder is a very common finding, often followed by urinary tract infections, which when left untreated may lead to life-threatening sepsis. Hyperreflexia and dyssynergia between contraction and relaxation of the detrusor and sphincter muscles is nearly always the fundamental defect (Betts 1993).

1.3.4. Bowel dysfunction

Constipation, defined as two or fewer bowel movements each week, was reported in 43 % and might be the presenting symptom (Hinds 1990). Prolonged colonic transit time, mainly in the left colon, has been demonstrated (Wiesel 2001). The normal postprandial increase in colonic motility has been shown to be absent in advanced MS (Glick 1982). Constipation may also be secondary to reduced mobility, medication and reduced water intake.

Major nocturnal faecal incontinence may occur, presumably related to the loss of normal cerebral inhibition of bowel function during sleep. General muscle weakness, spasticity, impaired mobility, fatigue and medications can also contribute to continence problems (Wiesel 2001).

1.3.5. Sexual dysfunction

Sexual function both in men and women is often disturbed by MS. In men, common presenting symptoms of sexual dysfunction include erectile dysfunction, delayed ejaculation and loss of libido. In women, altered vaginal sensation, decreased lubrication and anorgasmia can develop (Zorzon 1999). The psychological effect of having MS may reduce potency and libido in both affected persons and their partners. Sexual function is also often adversely affected by other symptoms of the disease, such as weakness and spasticity, fatigue, bladder- and bowel incontinence as well as pain and impaired sensory function, depression and anxiety.

1.3.6. Cardiovascular and other autonomic dysfunction

Cardiovascular and sudomotor autonomic abnormalities in MS patients are likely to be due to plaques distributed throughout the brainstem and spinal cord affecting anatomically widespread autonomic regulatory areas and their connections. Orthostatic intolerance was reported in 50 % of MS patients compared to 14 % of controls (Flachenecker 1999).

1.4. Non-motor symptoms

Until recent years, measurements of disability in MS have been heavily weighted towards motor function and especially ambulation. However, non-motor symptoms, or symptoms without a clear focal pathology, such as pain and fatigue, neuropsychiatric symptoms like depression, anxiety and cognitive impairment are frequently involved, and have major impact on function.

1.4.1. Pain and sensory symptoms

The prevalence of pain in MS patients has been reported to vary from 29-86 % (Clifford 1984, Stenager 1995). This wide range in pain frequencies relates to differences in methodology, study populations, as well as the definition of pain employed.

Pain in MS has been defined by location (most frequently located to the extremities and lower part of the back), by presumed mechanism (continuous or intermittent central neuropathic pain, musculoskeletal pain and mixed neuropathic and non-neuropathic pain) or by duration (ranging from acute paroxysmal to chronic long-standing pain).

Pain in MS may also be classified into four diagnostical and therapeutic relevant categories as proposed by the International Association for the Study of Pain (Merskey 1994); a) pain directly related to MS, b) pain indirectly related to MS, c) treatment-related pain, and d) pain unrelated to MS. A definite classification of a pain is sometimes impossible due to overlapping categories (e.g. back pain).

1.4.1.1. Pain directly related to MS.

Pain related to relapse, such as optic neuritis, is common in MS. The term "retrobulbar neuritis" is often used. This is certainly useful in individual cases with characteristic visual symptoms, but normal optic head (no papilitis). Pain is usually present at some stage, often felt in the eye or it is supraorbital and sometimes accompanied by unilateral or generalised headache. The intensity is varying, often aggravated by movement of the eye. Typically, blurred vision is the initial visual symptom. Spontanous remission will usually occur, and optimal visual acuity is often achieved after a mean of two months from onset. About 14 % of the patients are left with a vision worse than 6/12, and less than 5 % worse than 6/60 (Perkin 1979).

Central neuropathic pain is a broad category of MS-related pain, of which there are several distinct types. Central neuropathic pain has been defined as present if the distribution of pain is regionally consistent with a central nervous system lesion and a thorough evaluation for nociceptive and peripheral neuropathic pain is negative (Osterberg 2005). In a survey of 364 patients nearly all who suffered from central neuropathic pain (27.5 %), had abnormal sensory exams supporting a hypothesis that central neuropathic pain in MS patients often results from lesions in spinothalamocortical pathways (Osterberg 2005).

Svendsen found MS patients with any type of pain to have lower pressure pain thresholds than MS patients without pain on quantitative sensory testing (Svendsen 2005). The most common central neuropathic pain condition in MS patients is extremity pain, trigeminal neuralgia and Lhermitte's sign. Trigeminal neuralgia is also often categorized as a pain with paroxysmal occurrence and Lhermitte's sign as a sensory disturbance.

"Dysesthetic" extremity pain (central extremity pain) is reported to be the most common type of pain associated with MS (Clifford 1984, Vermote 1986, Moulin 1988, Indaco 1994, Solaro 2004, Osterberg 2005). Extremity pain is usually a chronic form of pain in MS (Moulin 1988, Indaco 1994, Osterberg 2005). The pain is described as

“burning” (Clifford 1984), can exacerbate by physical activity (Osterberg 2005) and is usually worst at night (Moulin 1988). This type of pain is mostly bilateral, involving the legs and feet (Moulin 1988, Kalia 2005, Osterberg 2005).

Trigeminal neuralgia (TN) has been reported in 1-2 % of MS patients over a 10-13 year period (Rushton 1965, Hooge 1995), roughly 20-40 times the prevalence in the general population (Soyka 1999). In MS, TN is more often bilateral (Hooge 1995). If the TN was an early MS symptom the patients tend to be younger than patients without MS and TN (Rushton 1965, De Simone 2005).

Lhermitte’s sign or rather symptom, has been defined as a “transient short lasting sensation related to neck movement, felt in the back of the neck, lower back or in other parts of the body” (Al-Araji 2005). The fact that the examiner might be able to provoke the sensory disturbance adds to the objectivity, and for these reasons some authors continue to call it a sign. Patients commonly describe the symptom as “electric” or like an “electric shock” lasting less than two seconds, with immediate relief upon cessation of neck flexion (Al-Araji 2005). The prevalence of Lhermitte’s symptom at the time of evaluation in two recent studies ranged from 9-13 % (Solaro 2004, Al-Araji 2005). Mostly the symptom resolved over 4-6 weeks, in some patients however, it recurred occasionally over time, especially during attacks of MS even when the new lesion clearly localised to some other part of the nervous system (Kanchandani 1982).

1.4.1.2. Pain indirectly related to MS

Painful tonic spasms (PTS) were originally considered to be epileptic in nature resulting in the name “painful tonic seizures” which is still sometimes used. However, electroencephalography (EEG) performed during the episodes did not reveal epileptiform discharges, making ”spasm” or ”dystonia” more an appropriate description (Watson 1979). PTS are not always painful, which likely accounts for the broader terms such as “paroxysmal spasms” or “dystonia”, “muscle” or “tonic spasm”, or “tonic seizures”. PTS usually occur several times a day, lasting less than two minutes each, are stereotypical, may be preceded by an aura, and can be triggered by movement, touch, hyperventilation, sudden noices or emotions. In some patients no precipitating factors can be found (Matthews 1975, Spissu 1999). PTS can be chronic or can remit over days to months, and in some cases the pain precedes the spasms, suggesting that the pain may not be caused by the muscle

spasm itself (Matthews 1975). Symptoms are thought to result from spontaneous discharges generated by demyelinated axons (Maimone 1991).

1.4.1.3. Treatment related pain

DMT might cause pain due to subcutaneous (sc.) or intramuscular (im.) injections. Interferon-beta (IFNβ) is known to cause systemic side effects like myalgia or back-pain which mostly appear 2-8 h after injection and resolve within 24 h during the first months of treatment. Two studies examined the influence of disease modifying treatments on headache in patients with MS. Worsening of pre-existing headaches, or development of de novo headache occurred only in the IFN group (Pollmann 2002, La Mantia 2006). Injections of glatiramer acetate (GA) may also cause local pain at the injection site.

1.4.1.4. Pain unrelated to MS

In many MS patients with back pain, the pain might be musculoskeletal in origin and aggravated by prolonged standing or sitting. Back pain has, however, also in some patients (at least partly) been considered to be central in origin (Osterberg 2005, Svendsen 2005). In one study, 5 % of the patients found the back pain to be the "most distressing" symptom of MS (Stenager 1991).

The frequency of headache has been reported to be higher in MS patients than in the general population (O'Connor 2007). Studies specifically assigned to assess the frequency of headache in MS reported higher prevalence of headache than studies not focusing on headache (Kalia 2005). In a study of newly diagnosed MS patients, 54 % of the patients suffered from headache compared to only 18 % of general neurology patients. They were sex-, age- and disability-matched (Rolak 1990).

Headache, classified as migraine, was found in 21-27 % of the patients with MS in two studies (Rolak 1990, Watkins 1969). Fredman and colleagues reported many of the patients' headaches to appear hours or even days before the onset of neurologic symptoms (Freedman 1989). In complicated migraine it is more typical for neurological complaints to actually precede the development of headache by 10-30 minutes (Edmeads 1983).

1.4.1.5. Pain intensity

Pain intensity has been evaluated in several studies. Using a 0-10 numerical rating scale, the average pain intensity ranged from 4.8 to 5.8 (moderate) in patients with pain symptoms (Warnell 1991, Archibald 1994, Ehde 2003, 2006), whereas two other studies showed that most patients reported milder pain problems (Svendsen 2003, Kalia 2005). Pain might influence the overall quality of life and might affect most dimensions in HRQoL, such as Short Form 36 (SF-36), and this influence increases with pain intensity (Ehde 2003, Kalia 2005, Svendsen 2005, Forbes 2006).

1.4.1.6. Sensory symptoms

Purely sensory symptoms are common at the onset or in early relapses raised from plaques in the sensory pathways. The pinprick may feel “distant”, the tickle sensation normally elicited by cotton wool may be absent, defined as numbness by the patients. Persistent paraesthesia is common, occurring in 84 % of patients in one series (Sanders 1986).

Strange sensations referred to the skin include heat or even burning or, in contrast, the limb feels cold or wet. Loss of position sense accompanied by ataxia is also seen, but is more seldom, and may be associated with the useless hand syndrome. Loss of perineal sensation is the most obtrusive as the normal sensation of micturition or defecation may be lost, although control remains normal. Vaginal sensation is also diminished. Cerebral lesions can also result in more complex abnormalities, including sensory neglect (Graff-Radford 1987).

1.4.2. Depression and anxiety

Depression is much more common among individuals with MS than in the general population (Sadovnick 1996). About 40 % of MS patients report depressive symptoms (Chwastiak 2002) and cross-sectional studies have shown a lifetime risk of depression of 50 % (Sadovnick 1996, Feinstein 2004).

Historically, the origin of depression in MS was thought to be primarily reactive. However, the higher frequency of depressive symptoms in MS compared to other chronic disabling neurological diseases such as motor neuron disease, muscular dystrophy, dystrophica myotonica and temporal lobe epilepsy makes this unlikely (Rabkin 2005, Whitlock 1980, Schiffer 1984).

MRI studies have indicated a correlation between the development of depression and frontotemporal lesions and/or ventricular enlargement. Autoimmune and endocrine dysregulation has also been correlated to depression in MS patients (Mohr 2001, Fassbender 1998).

Depression in MS has been associated with other factors like lower education, limited social support and cognitive difficulties (Chwastiack 2002). Age seems also to influence the presence of depression, as older adults with MS reported significantly fewer depressive symptoms than younger adults with MS (Kneebone 2003). This is consistent with findings from studies of general community samples, and may be related to decreased emotional responsiveness among the older adults. It has also been shown that patients with acute relapses report a higher level of uncertainty and increased risk of depression, compared to those during the remission phase (Kroenecke 2001). Others have reported female gender and family history of major depression as risk factors for developing depression in MS (Patten 2000).

Studies on association between depression and disability levels in MS have however, been inconsistent (Chwastiak 2002, Fruehwald 2001, Figved 2005, Møller 1994, Gottberg 2006, Janssens 2006), as well as associations with other non-motor symptoms like fatigue and pain (Møller 1994, Chwastiak 2005, Forbes 2006, Stenager 1995). An earlier study found no correlation between depression and cognitive impairment (Rao 1995). A more recent study, however, suggested that cognitive impairment was likely to be worsened by moderate or severe depression, and primarily in relation to information processing speed and working memory (Demaree 2003).

Anxiety has been less studied, and no association between MRI brain lesions and anxiety has been found (Zoron 2001). One study reported that 25 % of MS patients exhibited clinically significant signs of anxiety (Feinstein 1999). The prevalence of anxiety among MS patients in more recent studies has varied from 14-36 % (Korostil 2007, Janssens 2003), and was in one study associated with chronic pain in females (Kalia 2005). In a study of 101 newly diagnosed MS patients and their partners, the prevalence of anxiety was high for both (patients 34 %, partners 40 %) possibly indicating a psychological reaction to be confronted with the disease (Janssens 2003). A recent large cross-sectional study of 580 patients with confirmed MS found anxiety to be more prevalent than depression, but depression had a greater impact on reducing function in most domains of SF-36 (Spain 2007).

Both depression and anxiety are known to be among the most disabling symptoms in patients with MS, due to the negative influence on general health and quality of life (QoL), (Lobentanz 2004, Fruehwald 2001).

1.4.3. Fatigue

There is no universally accepted definition of fatigue, but it may be defined as an overwhelming sense of tiredness, lack of energy or feeling of exhaustion. It can be distinguished from depression in which lack of self-esteem, despair or feelings of hopelessness are prominent features, and also muscle weakness (Krupp 1996). Others have defined fatigue as a subjective lack of physical and/or mental energy, perceived by the individual or caregiver to interfere with usual and desired activities (Clinical Practice Guideline 1998). A more recent definition is “a reversible motor and cognitive impairment, with reduced motivation and desire to rest. It can appear spontaneously or may be brought on by mental or physical activity, humidity, acute infection and food ingestion. It is further relieved by daytime sleep or rest without sleep and can occur at any time, but is usually worse in the afternoon” (Mills 2008).

It is likely that fatigue results from multifactorial causes related to disturbances in the CNS, as well as immunological and neuroendocrine factors (Kos 2008). Leocani et al summarized in an update on the pathophysiology of fatigue in MS that a “dysfunction of the circuits between thalamus, basal ganglia and frontal cortex, affected by the MS lesions or/and disturbed in their function by the products of inflammation, could be the main substrate for fatigue” (Leocani 2008). Tartaglia and colleages found mental fatigue to alter the pattern and increase the volum of cerebral activation required for a motor task in patients with fatigue and MS. The hypothesis that a substrate for MS fatigue could be a generally elevated demand placed on functioning neural circuits was supported by these findings (Tartaglia 2008).

However, fatigue may also be secondary to sleep disorders, reduced activity, depression, and side effects of medication. The physical dimension of fatigue has also been reported to be associated with increased disability over time (Debouverie 2008).

Fatigue appears to be present in about 75 % MS patients (Iriarte 2000, Hadjimichael 2008), figures higher than 90 % have also been reported (Wynia 2008). It was experienced almost daily by 40-66 % (Fisk 1994, Freal 1984). A recent two years longitudinal study showed that 27 % of the patients were persistently fatigued,

19 % had no fatigue, and the rest (54 %) reported variable fatigue categories several times during the observation period (Johansson 2008). Independent predictors of fatigue in this study were depressive symptoms, weak/moderate sense of coherence, living with a partner and unemployment.

An association between fatigue and depressive symptoms has frequently been reported (Bakhsi 2000, Scheurs 2002, Strober 2005, Chwastiak 2005, Koch 2008), but the association with gender, age, disease severity, disease course and duration appears to be inconsistent (Krupp 1988, Lerdal 2003, Chwastiak 2005, Ford 1998).

The negative impact of fatigue on the patients' daily activities, QoL and ability to work and socialize was underlined in several studies (Vercoulen 1996, Amato 2001, Bakshi 2003, Janhardan 2002, Pittion-Vouyovitch 2006).

1.4.4. Cognitive dysfunction

Impairment of cognitive function on at least one neuropsychological test was demonstrated in about 50 % of MS patients assessed in clinical settings or in community-based studies (McIntosch-Michaelis 1991, Rao 1991). Klonof and colleagues found that cognitive impairment could be present as an early isolated symptom of MS, or could be minimal in an otherwise severely affected patient (Klonoff 1991). By including patients within the whole range of disability levels (EDSS ≤9.5), others reported a strong correlation between physical disability and cognitive defect (McIntosch-Michaelis 1991).

Rao and collegues showed that patients with MS performed normally or with relatively minor impairment on tests of short-term memory capacity and implicit memory, general intelligence and language (Rao 1995).

A mild cognitive deficit in an effortful learning situation was observed in one third of 127 early MS patients. Mood disorders, fatigue, handicap and reduced QoL were associated with cognitive dysfunction (Simioni 2007), supporting results from a previous study were cognitive dysfunction was found to impaire the patients quality of life (Benito-Leon 2002). It has also been shown that difficulties with patient care are greatly increased with cognitive dysfunction (McCabe 2002).

1.5. Diagnosis

Since the publication of Schumacher's criteria more than 40 years ago, the core of all MS diagnostic requirements has been the demonstration of dissemination in space and time of demyelinating lesions in the CNS (Schumacher 1965). This reflects the nature of MS involving numerous areas of the CNS over time (Poser 1983, McDonald 2001, Polman 2005). As no clinical or paraclinical finding is pathognomonic of MS, a further requirement has always been the exclusion of an alternative explanation for the presenting symptom.

In 1983 the Washington Conference criteria (Poser criteria) included both clinical and paraclinical investigations. To diagnose a clinically definite MS (Poser 1983), paraclinical abnormalities indicating disseminated disease within the CNS were allowed to replace the clinical evidence of the disease. Imaging, electrophysiology (especially visually evoked respons, VER) and cerebrospinal fluid (CSF) examinations for oliogoclonal immunoglobulin G (IgG) bands were used as supplement when the clinical criteria were not met (Table 1). A positive CSF is defined as the presence of IgG, preferably based on isoelectric focusing with immunofixation and differing from those in serum or an increased IgG Index: >0.7 (CSFIgG/Serum IgG)/(CSF albumin/Serum albumin) (Andersson 1994).

An abnormal VER can be used as an objective evidence of a second lesion provided that the only clinically expressed lesion did not affect the visual pathways. An abnormal VER typical for MS is a delayed wave, but with well-preserved form (Chiappa 1988).

With the inclusion of magnetic resonance imaging (MRI) for defining dissemination in space and in time (Table 2), the McDonald criteria permitted an accurate diagnosis of MS before the appearance of a second attack (McDonald 2001). A revision of the McDonald criteria has recently been published (Table 3, Polman 2005).

The diagnosis of MS is still based on clinical parameters focusing on a detailed history of symptoms and signs, and a careful neurological examination. Even the most recent diagnostic criteria cannot be applied without an adequate clinical evaluation (McDonald 2001).

In the present thesis we employed the Washington Conference criteria (Table1) (Poser 1983) in Articles I, II and IV and the McDonald criteria in Article III (Table2) (McDonald 2001).

Table 1. The Washington conference criteria of MS (Poser 1983)

Category	Episodes	Clinical Evidence		Paraclinical Evidence	CSF OCB/IgG-index
A) Clinical definite MS (CDMS)					
A1	2	2			
A2	2	1	and	1[a]	
B) Laboratory supported definite MS (LSDMS)					
B1	2	1	or	1	+
B2	1	2			+
B3	1	1	and	1[a]	+
C) Clinically probable MS (CPMS)					
C1	2	1			
C2	1	2			
C3	1	1	and	1[a]	
D) Laboratory supported probable MS (LSPMS)					
D1	2				+

[a] Evidence for a paraclinical lesion in addition to another separate clinical lesion

Table 2. MRI criteria to demonstrate CNS lesions disseminated in space and time suggestive of MS (McDonald 2001, Polman 2005)

MRI evidence for dissemination in space - three of the following:

≥ 1 gadolinium-enhancing lesion or nine T2 hyperintense lesions if there is no gadolinium enhancing lesion

≥ 1 infratentorial lesion

≥ 1 juxtacortical lesion

≥ 3 periventricular lesions

NOTE: A spinal cord lesion can be considered equivalent to a brain infratentorial lesion, an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions.

MRI evidence for dissemination in time - one of the following:

Detection of gadolinium enhancement at least 3 months after the onset of the initial clinical event, if not at the site corresponding to the initial event

Detection of a *new* T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event

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Table 3. McDonald diagnostic criteria of MS (Polman 2005)

Clinical presentation		Additional data needed for MS diagnosis
Clinical attacks	**Clinical lesions**	
≥ 2	≥ 2	None But paraclinical tests (MRI, CSF) should be done to exclude other diagnoses. If these tests are *negative,* extreme caution needs to be taken before making a diagnosis of MS.
2	1	Dissemination in space, demonstrated by: • MRI *or* • Two or more MRI-detected lesions consistent with MS plus positive CSF* *or* • Await further clinical attack implicating a different site
1	≥ 2	Dissemination in time, demonstrated by: • MRI *or* • Second clinical attack
1 (monosymptomatic presentation; clinically isolated syndrome - CIS)	1	Dissemination in space, demonstrated by: • MRI *or* • Two or more MRI-detected lesions consistent with MS plus positive CSF* *and* Dissemination in time, demonstrated by: • MRI *or* • Second clinical attack
Insidious neurological progression suggestive of MS (PPMS)		One year of disease progression (retrospectively or prospectively determined) *and* two of the following: • Positive brain MRI (nine T2 lesions *or* ≥ four T2 lesions with positive VER**) • Positive spinal cord MRI (two focal T2 lesions) • Positive CSF*

*Positive CSF = oligoclonal IgG bands or an increased IgG index > 0.7; ** Positive VER = abnormal VER of the type seen in MS

1.6. Disease course and prognosis

The disease course is typically described by forms of interplay between relapses and progression. Central features of the clinical experience of MS are relapses with full recovery, relapses with incomplete recovery and chronic progression (Confavreux 2006).

Initially most patients (80-85 %) have a relapsing-remitting course (RRMS) with subacute attacks of neural dysfunction, often with spontaneous and complete remissions (Confavreux 1980, Weinshenker 1989, Myhr 2001). Subsequent relapses will usually occur, often with partial remission and leading to development of nervous system impairment in most patients. Over time, an increasing proportion of the RRMS patients develop a secondary progressive course (SPMS), initially with superimposed relapses, but later a steady progression without relapses and no remission (Myhr 2001, Rovaris 2006). A conversion to SPMS with increasing disability is experienced by 40-50 % of RRMS patients after 15 years and by 80 % after 25 years of disease duration (Noseworthy 2006).

An initial primary progressive course (PPMS) is experienced by 15-20 % of the patients, often presented by slow development of motor dysfunction (Confaveux 1980, Cotrell 1999, Thompson 2000). A progressive course from onset is associated with older age at onset and shorter time to accumulated disability (Myhr 2001).

Minor proportions of the RRMS patients experience a benign course, defined as almost full functional recovery in all neurological systems 15 years after onset (Confavreux 2006), and retain an EDSS score of ≤3.0. Around 20-30 % of patients may experience this favourable form of MS, but unfortunately, it is often temporary and progression to a non-benign course with progressive disability may occur (Hawkins 1999). Furthermore, patients with no or minor physical disability and an appearantly benign disease course, may nevertheless report significantly reduced HRQoL compared with the normal population (Nortvedt 1999, Glad 2006a). Patients with benign MS may also be seriously affected by fatigue, pain and cognitive dysfunction, and a substantial number may have been awarded disability pension due to the disease (Hawkins 1999, Glad 2006b). This illustrates the importance of increased focus on the non-motor, clinically invisible symptoms of MS which limit individual performance.

RRMS often begins clinically with a self-limited attack (relapse or exacerbation) of neurological dysfunction. Often this is a clinically isolated syndrome (CIS) consisting

of a single focal event. The most common presentations are optic neuritis, brain stem syndromes or partial/incomplete spinal cord syndromes (myelopathy/myelitis). Revised MS diagnostic criteria allow earlier diagnosis based upon the development of a new CNS lesion after a single attack even in the absence of a second clinical event as discussed earlier. If there is evidence of clinically silent MRI lesions in CIS patients, there is a risk of more than 40 % to develop new clinical relapses and about 90 % risk of developing new MRI lesions within the next two years (Jacobs 2000, Comi 2001, Kappos 2006). Treatment of CIS (with clinically silent MRI lesions) has shown a reduced risk of new disease activity (Jacobs 2000, Comi 2001, Kappos 2006, Comi 2008). Thus, early diagnosis is important in order to offer optimal treatment for patients.

Median time from disease onset to reach EDSS level of 4.0 (limited walking distance) is 8-10 years, EDSS 6.0 (need of unilateral waling aid to walk 100 m) is about 20 years, EDSS 7.0 (need of wheelchair) is about 30 years and 10 (death due to MS) is about 40 years after onset of the disease (Weinshenker 1989, Midgard 1995, Myhr 2001, Confavreux 2003, Torkildsen Gryttten 2008).

At time of diagnosis most patients with MS request information about the course of the disease and the prognosis, but for the single patient these are highly unpredictable. Changes may occur from one week to another. A number of demographic and clinical factors may have impact on the outcome of the disease. RRMS patients have a more favourable course than PPMS patients. It takes longer time to accumulate irreversible disability for the young onset patients compared to patients with later onset, they, however, become disabled at a younger age than patients with later onset (Vukusic 2007). Male gender, motor and cerebellar symptoms at onset and short inter-relapse interval in the early phase of the disease may predict shorter time to accumulated disability. On the other hand, female gender, optic neuritis and sensory symptoms at onset, longer inter-relapse interval in the early phase of the disease as well as minor sequela from the first relapse have been associated with a more favourable course (Kantarci 1998, Myhr 2001). Recent data, however, have shown that female gender and young onset patients have a higher relative mortality, compared to a matched general population, than male and older age at onset patients (Torkildsen Grytten 2008).

1.7. Treatment

As long as there is no curative treatment for MS, the available therapeutics aiming to reduce and prevent damage to myelin, axons and glia, should be offered to patients suffering from MS at the optimal stage of their disease. Symptoms should be recognized as early as possible and available symptomatic treatment should be tailored to lower the suffering for each individual patient.

Most people with MS suffer from numerous symptoms of which some can be treated relatively effectively, such as pain or paroxysmal symptoms, spasticity, bladder and sexual dysfunction and depression, whereas evidence-based treatments are unavailable for some other disabling symptoms like fatigue, cognitive dysfunction, ataxia, visual loss and oculomotor symptoms, dysarthria, dysphagia and bowel dysfunction.

In the following section the treatment of acute relapses, immunomodulating and immunosuppressive treatment options and symptomatic treatment possibilities are summarized, before treatment alternatives for those symptoms are highlighted which are most important for this thesis.

1.7.1. Treatment of relapses

Even if there is no evidence for long-term effects of relapse treatment, corticosteroids speed up the recovery of both new deficits or worsening of previous ones. The guideline recommendations are oral or intravenous methylprednisolone of 500-1000mg daily for five days (Sellebjerg 2005). To justify the risk of possible short- and long-term side effects of the treatment, the relapse should be severe enough to cause a significant dysfunction. Typical side effects are dyspepsia, disturbance of taste, euphoria, insomnia, and mild weight gain. Depressive symptoms after the end of treatment have been reported, but more seldom are reports of psychosis, pancreatitis and anaphylactic reactions. The long-term risk of osteoporosis might rise, if repeated cures are needed (Dovio 2004). Plasma exchange may be of benefit for severe relapses refractory to treatment with methylprednisolone (Weinshenker 1999).

1.7.2. Disease-modifying treatment

Disease-modifying treatment (DMT) includes immunomodulation and immunosupression, and aim to prevent disease activity, both relapses and progression of disability, but is not curative.

1.7.2.1. Immunomodulation

Five immunomodulatory preparations are available: IFNβ -1b sc., IFNβ-1a sc., IFNβ-1a im., glatiramer acetate sc., and natalizumab intravenously (iv.)

1.7.2.1.1. Interferon-beta (IFNβ)

IFNβ is a naturally produced polypeptide that reduces the risk of new relapses by about 30 % in RRMS. The therapeutic effect on MS is believed to be anti-inflammatory due to a shift from a pro-inflammatory T helper cell 1 (Th1) to anti-inflammatory Th2 type and reducing the migration of inflammatory cells across the blood-brain barrier (Yong 1998). IFNβ-1b is given 250 µg sc. every other day, IFNβ-1a 44/22 µg sc. thrice a week, and IFNβ-1a is given 30 µg im. once a week. Frequent IFNβ side effects are two weeks to three months of flu-like symptoms, headache and myalgia, which mostly appear 2-8 h after injection and resolve within 24 h. Injection-site reactions are frequent and more common in regimens with sc. administration. Bone marrow depression and elevated liver enzymes may occur, and periodic surveillance of blood samples is required.

Neutralizing antibodies (NAB) may be induced by IFNβ treatment, usually within 6-18 months after treatment. The presence of high titers of NAB may reduce the efficacy of treatment. It is therefore recommended to test for the presence of NAB at 12 and 24 months of therapy, and in case of treatment failure (Sørensen 2005).

1.7.2.1.2. Glatiramer acetate (GA)

GA consists of the four amino acids glutamate, lysine, alanine and tyrosine, that similar to IFNβ reduce the risk of new relapses with about 30 % in RRMS (Johnson1995). The therapeutic anti-inflammatory mechanism is probably related to the promotion of TH2 GA-reactive CD4+ Tcells which can accumulate in the CNS, release anti-inflammatory cytokines and thus excert bystander suppression. Although GA is usually well tolerated, injection-site reactions are common and include lipoatrophy. Transient self-limited systemic reactions immediately after

injection consisting of facial flushing, chest tightness, sometimes also palpitation, dyspnoea and anxiety lasting 30 sec to 30 min, are experienced by about 15 % (Johnson 1998).

1.7.2.1.3. Natalizumab

Natalizumab is a monoclonal antibody against 4-integrin and blocks the interaction with its ligand, vascular cell adhesion molecule (VCAM)-1. The mechanism of action is the inhibition of migration of activated leukocytes into the CNS, by preventing the adherence to the endothelium, and thereby hindering activated leukoctes to cross the blood brain barrier.

The pivotal trial (AFFIRM) showed a reduction of the annual relapse rate of 67 % in earlier untreated MS patients when treated with natalizumab as monotherapy. The disability progression was reduced by 42-54 % (after 1-2 years) and the MRI gadolinium enhancing lesions were reduced by 90 %. Natalizumab 300 mg is given as an iv. infusion every fourth week (Polman 2006).

The drug was temporarily suspended due to three cases of progressive multifocal leukoencephalopathy (PML). After a careful examination of 3000 treated patients no additional cases were identified and the drug was approved again, this time as monotherapy for MS. However, after treatment of another 37000 MS patients with natalizumab as monotherapy, four new cases of PML were communicated by the manufacturer. This cohort included about 3700 long-term (24 months) treated patients. Other long-time effects of natalizumab are still unknown, and the risk of PML makes this drug still a second-line choice.

1.7.2.2. Immunosuppression

Mitoxantrone is a synthetic derivate known to interact with nuclear DNA, targeting proliferative immune cells, inhibiting proliferation, inducing apoptosis of T and B lymphocytes, macrophages and other antigen-presenting cells. Mitoxantrone has been used for years in treatment of malignancies such as leukaemia, lymphoma, and breast cancer as well as advanced prostata cancer.

A reduction rate of 60-70 % of relapses, reduced disability progression and MRI disease activity were shown in a randomized, placebo-controlled multi-centre study of 194 MS patients of which 188 could be assessed at 24 months (Hartung 2002).

Current dosing regimen is 12mg/m^2 of body surface every third month with reduction during stabilization (Myhr 2008). Due to potential cardiotoxicity, the maximum cumulative dose is 120-140mg/m^2 of body surface. Therapy-related leukaemia has been reported, even years after treatment (Neuhaus 2006). Side effects, well known from cytostatics and lasting up to one week after each treatment, are nausea, fatigue, hair loss and menstrual disturbances, the latter more important for women in the child bearing age.

1.7.2.3. Which long-term disease-modifying treatment for which patient?

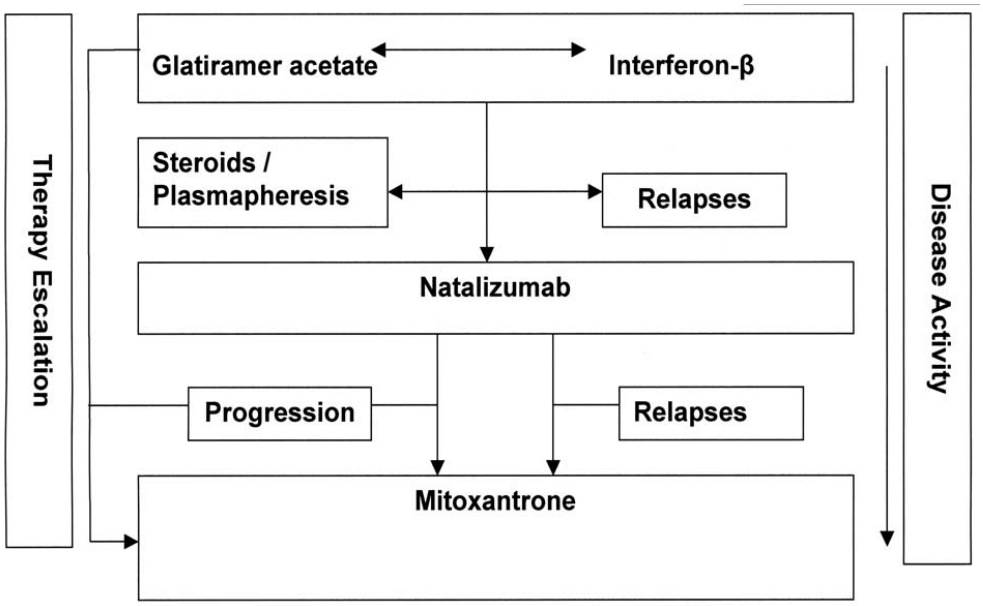
All types of DMTs are aiming to reduce and prevent damage to myelin, axons and glia. Studies have not been able to show a significant effect for patients with MS in the progressive phase of the disease except for the secondary progressive phase with superimposed relapses (Kappos 2004). Treatment trials of all IFNβ preparations and GA have shown a reduction in risk of new disease activity (time to second relapse), reduction in new MRI lesions (Jacobs 2000, Comi 2001, Kappos 2006, Comi 2008) or reduction of disability progression in patients with CIS (Kappos 2007).

For RRMS the first-line DMT is IFNβ or GA. Patients with CIS and severe deficit or multifocal presentation and with multiple clinically silent lesions on MRI should also be offered treatment. Each individual patient who is offered DMT must be evaluated for a treatment regimen which aimes at optimal compliance and takes into consideration the frequency of injections and side effect profiles. High-dose and high-frequency IFNβ treatment has short-term benefits for relapse rate and MRI activity, and the long-term differences in efficacy between high dose/high frequency and low dose/low frequency treatment may be reduced by a significantly lower production of NABs with low-dose and low-frequency IFNβ-1a. Efficacy evaluation should include recording of relapse and disability progression (EDSS), and sometimes an MRI seems necessary. If the compliance is reduced, the efficacy suboptimal (NAB should be measured), or if side effects are intractable, a lowering of the dose (IFNβ-1a, sc.) or switch of therapy has to be considered.

Natalizumab (second-line) therapy is indicated if relapses occur during first-line therapy (Figure 1). If the patient still experiences treatment failure (relapses), mitoxantrone (third-line) therapy should be considered after a three month wash-out period (Figure 1). Thus, patients need a continuous evaluation of treatment effects and side effect to optimize therapy. If the patients experience disease progression

without distinct relapses during first-line (IFNβ or GA) or second-line (natalizumab) treatment, third-line treatment with mitoxantrone should be considered (Figure 1).

Figure 1 Escalation of therapy after treatment failure



1.7.2.4. Pipeline medications

Increasing numbers of therapeutic options are emerging. These include iv.infusion with monoclonal antibodies targeting the haematopoietic antigen CD52 (alemtuzumab), CD25 (daclizumab) and CD20 (rituximab). Several oral preparations have also shown promising results, such as cladribine, firategrast, fingolimide, teriflunomide among others. The future agenda should address the issue of heterogeneity in MS, with a trend towards tailoring individual treatment to disease types and appropriate timing of interventions to match the stage reached in the clinical course (Compston 2006d).

1.7.3. Symptomatic treatment

Although most people with MS suffer from numerous symptoms of which only a few can be treated effectively with pharmaceutical agents, most symptoms can be relieved by a “multi-disciplinary” approach. A wide range of health professionals may

need to be involved including a neurologist, nurse, occupational therapist, physiotherapist, psychologist, ophthalmologist, dietician, speech therapist and social worker. An effective management will require a coordinated input from this multi-disciplinary team able to deal with the multi-faceted nature of the problems. In the following the treatment options for the focal symptoms characteristic for MS are summarized, before a more detailed description of the non-motor symptoms which are the focus of this thesis, are given.

1.7.3.1. Treatment of focal symptoms characteristic for MS

1.7.3.1.1. Motor Symptoms; Spasticity

All triggers of spasticity should be assessed and minimized before anti-spasticity medication is initiated because of possible side effects like increase of weakness, fatigue and urinary incontinence. Treatment of spasticity requires an integrated approach.

First-line medical therapy for spasticity is baclofen, a GABA agonist, more effective on spasticity of spinal cord origin. Tizanidine, an α-2 agonist, not available in Norway, is used for both cerebral and spinal spasticity. It entails less weakness than other anti-spasticity agents. However, hallucination is a well-known side effect of this medication.

Particularly for spasms, benzodiazepines and clonazepam or anti-convulsants like gabapentin or pregabalin are sometimes useful either alone or in combination with baclofen. Severe spasticity inadequately controlled by oral medication might need a programmable intrathecal baclofen pump. For patients with both neuropathic pain and spasticity, intrathecal analgesics can be combined with baclofen.

Botulinum toxin is increasingly utilized in MS patients when spasticity is limited to selected muscles, allowing for preservation of function in other muscles and avoidance of systemic side effects.

Cooling is sometimes used before physiotherapy to prevent spasms. Aids in stretching and strengthing as well as gait assessment are important. Graded exercise training, energy management strategies and physiotherapy are always useful add-on therapy for spasticity and as prophylaxis for contractures or sacral decubiti. The physiotherapist may help the patient with splinting and casting, assistive device for paresis and immobility, orthotics and weight bearing/non weight bearing techniques.

1.7.3.1.2. Brainstem and cerebellum

Several medications (primidone, gabapentine and odansetron) are sometimes helpful for ataxia and tremor, but most patients do not show a significant response (Fox 2001).

Neurosurgical treatment, like deep brain stimulation of the subthalamic nucleus, is in some instances a possible treatment for patients with resting tremor and ataxia.

Speech therapy for patients suffering from dysarthria and dysphagia and an assistive device for restricted communication, may be very helpful for these invalidating symptoms.

1.7.3.1.3. Bladder dysfunction

Detrusor hyperactivity with restricted storage capacity, urgency, increased frequency of micturition and incontinence might be treated with relaxation techniques, later with peroral tolterodin, solifenacin or darifenacin daily. A moderate effect of desmopressin on nocturia was reported in a meta-analysis. Desmopressin may, however, cause hyponatriaemia which must be controlled for (Bosma 2005).

Detrusor sphincter dyssynergia with emptying dysfunction is better treated with self-administered intermittent catheterisation. Surgical options may be necessary, like a suprapubic catheter, which avoids the risk of urethral erosion (women), or traumatic hypospadias (men). A suprapubic catheter allows for sexual intercourse. Other surgical options are cystoplasty or ileovesicostomy.

1.7.3.1.4. Bowel dysfunction

As bowel constipation may be worsend by reduced fluid intake, physical inactivity and a fiber-deficient diet, these risk factors have to be ruled out or corrected if possible, before other therapeutic options are assessed like bulking-per-diem, metamucil, mild osmotics, lactulose or suppositories (glycerin, dulcolax). Sometimes enemas or even manual stimulation may be nessecary. Rarely, in the case of faecal incontinence, an ileostomy may be the solution.

1.7.3.1.5. Sexual dysfunction

Sexual dysfunction can be multifactorial. Control of spasticity and energy-conserving positions may be important as well as identifications of drugs, pain and fatigue which all can worsen the sexual function.

Sildenafil, tadalfil and vardenafil have shown to be effective and well tolerated in achieving and maintaining sufficient erection (Fowler 2005). Older drugs like yohimbin or injection of the prostaglandin aloprostadil into the cavernous body of the penis are second-line therapeutics (Henze 2007). Lubricants can be helpful for both genders if decreased lubrication develops.

Vacuum pump and penile implants are less used after the new oral medications entered the market. Vibrator stimulation and eroscillator may be helpful. Information about selected serious websites should also be offered.

Psychotherapy and information about how to live with a sexual dysfunction are important as disabled MS patients have sexual needs and many have to learn that sex must not necessarily involve intercourse and culminate in orgasm.

1.7.3.2. Symptomatic treatment of non-motor symptoms

1.7.3.2.1. Pain

Treatment strategy for pain depends upon the differentiation of the various types of pain related to MS. Few studies have focused on the treatment of pain in MS patients. Therefore, studies dealing with pain treatment in other conditions have to be considered, e.g. neuropathic pain of other aetiology. It has to be underlined that a new pain in an MS patient should not be accepted to be MS-related without a diagnostic clarification. Many patients with MS experience more than one pain syndrome; combinations of dysesthesia, headaches and/or back or muscle and joint pain are frequent. A careful analysis of each pain syndrome will allow the design of the appropriate treatment plan using various medical and non-medical options (Pollmann 2008).

Neuropathic central pain, like “burning” paresthesia, is treated with tricyclic anti-depressives (TCA), for example amitiptyline, or anti-epileptics such as gabapentine, pregabalin, lamotrigin, etc. Painful paroxysmal symptoms such as trigeminal neuralgia or PTS are treated with anti-epileptics as first choice, e.g. carbamazepine, oxcarbacepine, lamotrigine, gabapentine, pregabaline etc. Combinations of drugs with different modes of action can be particularly useful for reducing adverse events. Duloksetin is an anti-depressive, serotonin and noradrenalin re-uptake inhibitor, useful for treatment of peripheral neuropathic pain, and has also been reported effective in treating pain of central neuropathic origin.

Non-steroidal anti-inflammatory drugs (NSAID) are second-line drugs in the treatment of neuropathic pain. As third-line therapy, opioids may be required. Neurosurgical treatment, e.g. trigeminal decompression as well as glycerol injections, well known for treatment of trigeminal neuralgia in non-MS patients, may sometimes be offered MS patients suffering from trigeminal neuralgia (Athanasiou 2005). Gamma-knife is the least invasive and safest neurosurgical treatment, however, microvascular decompression provides the longest-lasting pain relief even if thus procedure involves some risk of neurological complication according to recent guidelines on TN management (Cruccu 2008).

Corticosteroids are the drug of choice in treating painful optic neuritis, while NSAIDs are effective for muscle and joint pain. Headache and migraine are treated after the same options as for patients without MS.

Drug treatment of pain related to spasticity includes anti-spastic agents such as baclofen (GABA analogue) or tizanidine (α2 agonist), and in patients with phasic spasticity, gabapentin or levetiracetam may be helpful. However, pain related to spasticity, pressure lesions or malposition-induced joint or muscle pain often improve with adequate physiotherapy and optimally adjusted aids and may require additional treatment with paracetamol or NSAIDs.

Treatment-related pain due to sc. injections of IFNβ or GA may be reduced by optimizing the injection technique and by local cooling. Myalgia can be reduced by administering paracetamol, ibuprofen or naproxen. The potential increase of pre-existing headaches after starting treatment with IFN may require optimization of headache therapy or even prophylactic treatment.

Transcutanous electric nerve stimulation (TENS) may be useful for some patients suffering from chronic dysesthetic extremity and back pain.

Coping strategies or cognitive behavioural therapy (CBT) as well as relaxing manouvers should always be recommended for patients suffering from chronic pain syndomes.

1.7.3.2.2. Depression

The first step in treatment of psychiatric distress is to rule out and treat conditions that may actually be responsible, at least in part, for the symptoms, such as fatigue, sleep problems, pain and side effects of medications.

To my knowledge, only two pharmacological treatment studies of depression were performed as small randomised placebo controlled trials (RCT) in patients with MS (Schiffer 1990, Ehde 2008). The efficacy of a five-week course of desipramine for the treatment of major depression was assessed in 28 patients in the former. The patients on desipramine improved significantly compared to the placebo group. Side effects limited the desipramine dose in approximately half of the patients. The latter study included 42 patients randomised to 12 weeks of treatment with paroxetine or placebo. This study reached no significant results.

It is, however, recommended that MS patients suffering from depression should be offered anti-depressive treatment independent of the MS disease. Clinical experience suggests that currently available medication against depression is as effective for people with MS as it is for those without (Silver 1990). First-line options are SSRIs due to the much better side effect profile, fewer contraindications, and a significantly lower chance of negative drug interactions. Due to the sedative effect and/or their ability to reduce pain, tricyclics, like nortriptyline or aminotriptyline, may be the treatment of choice for patients with chronic pain or sleep disturbance along with depression (Siegert 2005).

Cognitive behavioural approaches in the treatment of depression which aim to help people adjusting to and coping with suffering from MS, have been reported to show some beneficial effect (Walker 2007). Psychotherapy with the development of active coping skills, such as CBT, is preferable (Feinstein 2004). Treatment should be individualized, combining psychotherapy and medication in an integrated biopsychological treatment plan (Goldman Consensus Group 2005). Counselling and social support have also been helpful in the treatment of chronic depression (Bisschop 2004).

A theoretical model of depression in MS was recently suggested, where four variables may moderate the relationship between common MS sequele and depression (Arnett 2008). The proposed variables are social support, coping, conceptions of the self and illness, and stress. The mentioned MS sequele are fatigue, physical disability, cognitive functioning and pain. According to this model, the risk for depression starts with the onset of MS. The authors underlined that depression in MS is treatable and unlikely to remit without treatment because of the stability of depression in MS. Untreated depression may have a “devasting consequence for the patients day-to-day functioning” (Arnett 2008).

1.7.3.2.3. Anxiety

The treatment of anxiety in MS patients is based on studies conducted on the general population of psychiatric patients, as no study of anxiety in MS patients is available. There is, however, no reason to believe that the findings would not extend to MS (Feinstein 2004).

Recent research has shown that SSRIs (eg. paroxetin, sertraline, escitalopram) are effective in treating generalized anxiety disorders (Stocchi 2003, Ball 2005, Davidson 2004). Even if the treatment of anxiety with SSRI is becoming more common, benzodiazepines are still the cornerstone of treatment of anxiety disorders due to their rapid onset of action and reliable efficacy (Kaplan 2005). The risk of developing tolerance and dependence exists, and attention and memory deficits, sedation and associated worsening of fatigue are especially problematic for patients with MS as well as an increased incidence of falls and fractures (Kaplan 2005). In combination with SSRI, the plasma benzodiazepine concentration may increase.

Psychotherapy and behaviour modification in combination with pharmacotherapy are often found to be more clinically effective than medications without concurrent counselling in the treatment of anxiety (Wilken 2007).

1.7.3.2.4. Fatigue

Understanding and treating fatigue is a great challenge for clinicians, researchers as well as for the patients themselves. It is important to identify and, if possible, treat contributors to fatigue including pain, sleep disturbances, nocturnal spasm, nocturi, psychological stress, depression, and deconditioning, as well as being aware of medications which worsen fatigue such as anti-spasticity agents, anti-epileptics, sedatives etc. Treatments currently available for fatigue include both pharmacological and non-pharmacological approaches.

Several pharmacological treatments of fatigue have been tried, but only four drugs have shown some effects in RCT studies. Authors of a Cochrane review concluded that the five RCT studies published had limitations (due to size, shortness of treatment period, design and use of different measurement tools), and that the modest effect shown was questionable (Pucci Cochrane 2003, Branas 2000). Amantadine (monoaminergic, cholinergic, glutaminergic CNS effects) is the most widely used drug. Modafinil (α 1-adrenergic, a wake-promoting psychostimulant) was shown effective in one study (Rammohan 2002), but the study design was not

optimal, and a second better designed study showed no improvement of the treated patients (Stankoff 2005). Pemoline (dopaminergic CNS stimulant) showed a positive trend (Weinshenker 1992), but as pemoline may induce severe liver toxicity it is not recommended as treatment for fatigue in MS (Berkovitch 1995). Fampridine (4-Aminopyridine, potassium-channel blocker) is reported to be useful for MS-related fatigue. However, a sustained-release formulation did not support this benefit in preliminary studies (Goodman 2007).

A fifth drug, Aspirin (Acetyl Salicyl Acid, ASA) was tested in a daily dosage of 1300 mg in a small crossover study (not RCT). Aspirin was preferred by 39 % of the patients. Due to the adverse effects of prolonged high dose ASA, such as gastrointestinal bleeding, it can not be recommended (Wingerchuck 2005).

A recent review of treatment of fatigue concluded that regardless the quality level of the studies reviewed, the effectiveness of both pharmacological and psychosocial/psychological interventions was at best modest and often absent (Lee 2008).

Immunomodulatory therapy does not influence fatigue. A recent study reported no difference in fatigue among treated and untreated patients (Putzki 2008). All used DMTs are able to reduce inflammation and disease activity. The results of this study are therefore surprising. In a postal survey of 9205 MS patients, respondents who had changed DMT from IFNβ to GA, had lower fatigue levels than the respondents who had changed the opposite way in the prior six months (Hadjimichael 2008). As IFNβ is known to produce flu-like symptoms this may cause secondary fatigue initially.

Non-pharmacological treatment of fatigue include energy management strategies, cooling therapies, graded exercise training, physiotherapy and inpatient rehabilitation (Navipour 2006, Grahn 2008, Schwid 2003, Mostert 2002, Storr 2006).

1.7.3.2.5. Cognitive symptoms

Treating associated symptoms like pain, sleep impairment, depression and fatigue intuitively seems to help in enhancing cognitive function. These measures are commonly addressed in clinical practice despite lack of published reports to support that notion (Pierson 2006).

Commonly used medications in MS can, however, also negatively affect cognitive performance like medications against spasticity and anti-convulsants.

Anti-cholinesterases, especially donepezil, have indicated improvement of deficits in memory and verbal learning in MS patients (Krupp 2004, Christodoulou 2006). Optimizing of immunomodulatory treatment (GA and IFNβ) also seems important for limiting the progression of cognitive dysfunction (Amato 2006).

The goal of non-pharmacologic treatment of cognitive impairment in MS is a prevention of progression, by promoting a therapeutic "milieu" in which optimal cognitive functioning can occur, and specific interventions which are known to be effective in remediating cognitive disorders of any aetiology. Emotional well-being and stabilization of affective disorders positively affects cognitive performance.

Cognitive rehabilitation (CR) is a treatment that has been incorporated into several clinical fields, such as occupational therapy, neuropsychology and nursing. Ideally, CR programs should be individualized to meet patients' specific needs and goals. Unfortunately the few studies that have addressed CR in MS did not find evidence of significant improvement in cognitive function following treatment (Jonsson 1993, Foley 1994, Lincoln 2002, Solari 2004). Multidisciplinary rehabilitation directed at cognitive and physical dysfunction has, however, been reported effective in relation to disability, QoL and emotional well-being in MS (Freeman 1999).

1.7.3.2.6. Rehabilitation

Passivity and inactivity due to motor and non-motor symptoms of MS gradually increase the weakness and worsen the physical dependence, and "rehabilitation is still the only way to improve this disability in MS" (Kraft 1999).

The main goal of rehabilitation medicine is to prevent or minimize disabilities, and to optimize function in order to normalize social integration as much as possible. A rehabilitation program must therefore be initiated and evaluated at an appropriate level of ability and participation.

A number of clinical trials have demonstrated the effectiveness of multidisciplinary care both within an inpatient (Freeman 1997, 1999) and outpatient setting (Di Fabio 1998). Some studies have demonstrated the effectiveness of physiotherapy in improving mobility and function (Petajan 1996, Lord 1998, Solari 1999), while others failed (Fuller 1996). One multidisciplinary rehabilitation study of patients with MS was unable to find evidence supporting the effectiveness in all assessed parameters (Storr 2006). Although physiotherapy, exercise and "rehabilitation" have been offered

this patient group for years, the knowledge is scanty according to which therapy is best for each patient.

1.8. Health-related quality of life

Altough the term “quality of life” (QoL) has been incorporated into everyday vocabulary during the last decades, there is no consensus on a definition of “QoL” or what components comprise an individual’s subjective health status. The concept of QoL has gradually come to mean a combination of subjectively assessed dimensions or areas of life, including physical and social functions, emotional or mental state, tiredness, pain and sense of well-being.

The term health-related quality of life (HRQoL) describes distress and functional impairment that may be influenced by the disease. HRQoL emphasizes the nervous system, mental and social complications as well as the traditional impairment and disability domains, accounting for the total burden of the patients experience (Benito-Leon 2003).

In developed countries there has been a shift of interest during the last decades from acute life-threatening infections, where evaluation of medical care could be measured in mortality, to chronic diseases with varying degrees of distress. Especially when evaluating new drugs, the examination of the costs to the society compared to the benefits of the new drugs is necessary. In RCT it is common to include standardised health assessment profiles as an outcome measure (Article IV). This makes it possible to identify any adverse implications for the QoL of patients that may be uncovered by traditional clinical, radiological or laboratory measures. Treatment of patients suffering from MS is often aimed at lessening the distress and to maintain an as high as possible level of independent functioning. HRQoL is therefore often especially valuable in the evaluation of different management approaches for MS.

Reduced overall HRQoL in MS patients has been reported (Pfennings 1999, Shawaryn 2002, Zivadinov 2003, Benedict 2005). HRQoL is lower in MS evev when compared to other chronic disorders (Rudick 1992). Perhaps not surprisingly, MS patients with pain symptoms have a poorer overall QoL than those without pain (Svendsen 2005), and greater pain severity is associated with poorer QoL (Kalia 2005, Forbes 2006). Excessive fatigue, increasing age and duration of disease have also been associated with reduced HRQoL (Merkelbach 2002, Janardhan 2002,

Loge 1998, Sullivan 1998, Pfennings 1999). Patti and colleagues suggested the importance of sustaining employment after the diagnosis of MS in a study of 648 patients. Education also had a great influence on HRQoL. The authors suggested that a higher level of education resulted in “a better ability to cope with the challenges of a chronic disease such as MS” (Patti 2007).

2. AIMS OF THE STUDY

The aims of this study were:

I. To evaluate the frequency, intensity, location, characteristics, and consequence of sensory and pain symptoms among MS patients and to record the use of medications.

II. To examine the prevalence of depression and anxiety symptoms amongst MS patients, and to compare the prevalence with the Norwegian general population. In addition, evaluate demographic and clinical predictors of symptoms of depression and anxiety, as well as currently treatment of these symptoms, amongst the MS patients.

III. To evaluate how fatigue was associated with demographic, clinical, HRQoL and physical performance variables and to investigate whether change in fatigue was associated with change in HRQoL and physical performance after inpatient physiotherapy.

IV. To compare health-related quality of life (HRQoL) among patients with secondary progressive MS with a population control group, and correlate longitudinal (HRQoL) data of these patients to clinical and demographic variables.

3. MATERIAL AND METHODS

Three different study populations were used to address the research questions in this thesis. Articles I (n=142) and II (n=140) included MS patients living in Asker, Bærum, Skedsmo and Lørenskog, Article III included 60 MS patients treated at Haukeland and Akershus University Hospitals, Norway, and Article IV included 345 MS patients included in a nordic multi-centre study in Denmark, Sweden, Finland and Norway.

3.1. Material

3.1.1. Articles I and II

3.1.1.1. Study population

In Articles I and II all MS patients from four municipalities (Asker, Bærum, Skedsmo and Lørenskog) in the County of Akershus, Eastern Norway were defined as the target population (218.984 inhibitants). The patients were recruited from the Departments of Neurology at Akershus University Hospital, Lørenskog, Rikshospitalet University Hospital, Oslo, and the local MS societies. Patients with clinical definite MS without severe cognitive impairment (Mini Mental State Examination $\geq$ 24), psychiatric impairment (psychosis) or other serious concurrent disabling disease that precluded participation, were enrolled.

Initially, 280 patients were identified, but 50 of these were excluded due to relocalisation to other parts of Norway (n= 29), severe cognitive impairment (n =14), severe psychiatric or medical impairment (n= 3), revised diagnosis (n= 1) or death (n= 3). Of the remaining 230 eligible patients, 64 (44 females and 20 males) refused to participate or did not respond to a written invitation of participation. Twenty-four patients underwent only neuropsychiatric assessment and two were only clinically examined. Thus, 140 patients who underwent both clinical and neuropsychiatric examinations were included in Article II. Neuropsychiatric assessment was not included in Article I, and therefore two only clinically examined patients could be enrolled, making 142 patients available for analyses in this article.

3.1.1.2. Data collection

The patients were MS diagnosed according to the criteria of Poser (Poser 1983) and classified according to initial course as relapsing-remitting MS (RRMS) or primary

progressive MS (PPMS) (Lublin 1996). Onset of disease was defined as the year of the first symptom. A complete neurological examination was performed including EDSS scoring. The patients were all examined at the out-patient department of the hospital after a rest and in a standardized setting.

Depression and anxiety were evaluated by the Hopkins Symptom Checklist-25 (HSCL-25). Additional variables included cognitive function, evaluated by the Paced Auditory Serial Addition Task (PASAT) (Gronwall 1977, Huijbregts 2004). The patients were categorised as having fatigue according to a yes/no-question, defining patients as having fatigue if they had had such symptoms more than 50 % of the day for more than 6 weeks and if this influenced daily functioning or quality of life.
Pain was registered as chronic pain if it lasted more than 1 month (Moulin1988). Episodic pain was defined as a transient symptom of shorter duration, lasting < 1 month, but longer than paroxysmal symptoms that lasted for only seconds or a few minutes (such as Lhermitte's symptom, pain or burning sensations or trigeminal neuralgia).

The current use of all prescribed medications as well as employment was registered during the interview. The patients were further asked if they had obtained treatment by a psychiatrist or psychologist, or if they felt an unmet need.

3.1.1.3. Reference population

A population-based study, the OsLof study, consisting of individuals interviewed in 2001, formed the basis of the reference population in paper II. The OsLof study was designed to examine general health and mental health within two geographically diverse areas, one urban and one rural. The participants were interviewed with a fully structured interview which assessed a broad range of topics related to mental and physical health including HSCL-25 with a similar procedure as for the MS patients. A total of 1691 individuals participated in the interview (response rate 74 %) in 2001 (Sandanger 2007).

3.1.2. Article III

3.1.2.1. Study population

A total of 60 MS patients (McDonald 2001) were recruited from the Departments of Neurology at Akershus and Haukeland University Hospitals. Only patients independent of assistance, Expanded Disability Status Scale (EDSS) 4.0-6.5

(Kurzke 1983) were included. Patients were excluded if they were known to have heat intolerance, had had a relapse interfering with their function the month prior to screening, cognitive dysfunction, or other co-morbidity that possibly could preclude intervention or performance at evaluation tests. None of the patients received medication against fatigue.

After nine months 56 patients were available for analysis. One dropped out because of a relapse during treatment, one because of pregnancy and one due to college studies after treatment. A fourth patient dropped out at month three of follow-up due to serious erysipelas.

The mean age at onset of disease was 31.8 (+-SD 8.9) years, and mean age at study baseline was 49.2 (+-SD 8.0) years (range 26.61 years). The initial disease course was PPMS in three patients and RRMS in 53 patients, of whom 18 had developed SPMS.

The patients were randomly allocated to inpatient physiotherapy at the rehabilitation centre Hakadal (n=30) or in Tenerife (n=30) in a cross-over trial investigation of the climate influence on the effect of physiotherapy. In the present study we used data from repeated measurements over nine months (before cross-over); at screening, baseline, after four weeks of treatment, and follow-up three and six months after treatment. In the present study we ignored the division into two treatment sites and considered the total sample as a cohort.

3.1.2.2. Data collection

The patients fulfilled the diagnostic criteria of McDonald (McDonald 2001) and were classified as RRMS, PPMS or SPMS (Lublin 1996). The patients were all examined at the out-patient department for screening and follow-up after tree and six months (Haukeland or Akershus). At baseline and after intervention they were all examined at the intervention site (Hakadal or Tenerife). The examination by the neurologist (AGB at Akershus and the interventions sites, SBG at Haukeland) included the EDSS and a somatic examination. Six minutes walking test (6MWT) was performed by a trained nurse (Andersson 2006). Berg Balance Scale (BBS) and Timed “Up and Go” (TUG) were performed by the physiotherapists (Berg 1989, Podsiadlo 1991). The self-report scales, Fatigue Severity Scale (FSS) and the Multiple Sclerosis Impact Scale (MSIS-29) were collected at screening, baseline, after intervention and after three and six months of follow-up.

3.1.2.3. Intervention

All six physiotherapists at each site completed a four-day training course before the start of the study. The patients were offered an individualized 60 minute long physiotherapy for four weeks, every working day. The intervention was based on the Bobath concept (Gjelsvik 2008) to improve physical function through motor learning, emphasizing the individual's own movement control. Physiotherapy was individually tailored after analysis of movement in functional activities. In this way the cause of the limited activity was sorted out and the right component of dysfunction treated.

3.1.3. Article IV

3.1.3.1. Study population

In this multi-centre study we analysed 345 SPMS patients, 142 men and 203 women, from Norway, Sweden, Denmark and Finland that had been included in a previous RCT of IFNβ-1a treatment (Andersen 2004). The results of the trial did not reveal any beneficial effect of the treatment on any outcome measure. The mean age at inclusion was 44.3 (±SD 8.3) years, disease duration from onset was 13.0 (±7.4) years and the mean duration of SPMS was 5.0 (±4.1) years. The mean EDSS score was 4.8 (±1.4).

Patients were diagnosed as having clinically definite RRMS according to the criteria of Poser (Poser 1983). All patients had converted to SPMS, defined as a progressive deterioration of disability for at least 6 months, with an increase of the EDSS (Kurtzke 1983) of at least one point during the last 4 years, with or without attacks. EDSS at baseline was ≤6.5.

Progression of the disease was defined as an increase in EDSS of one point or more (or 0.5 points for the patients with a baseline EDSS of 5.5–6.5). This was confirmed at two consecutive visits with an interval of 6 months.

At month 30, HRQoL scores were available from 318 patients.

3.1.3.2. Data collection

Disability was assessed at baseline and every 6 months using EDSS (Kurtzke 1983), Arm Index (Barnes 1997) and Ambulation Index (Weiner 1993). Fatigue was scored by visual analogue scale (VAS) (Weinshenker 1992, Grant 1999), and HRQoL by the Nothingham Health Profile Part I (NHP-I) (Hunt 1981, Jenkinsson 1988). Relapses were recorded throughout the study.

3.1.3.3. Control group

The population-based control group included 217 healthy Norwegians (101 women, 116 men) with a mean age of 47.6(±7.2) years (Naess 2007). All lived at home.

3.2. Methods of measurements

3.2.1. Disability assessment; Expanded Disability Status Scale (EDSS)

The Expanded Disability Status Scale (EDSS) is a neurologist-rated scale rating disability caused by MS on a continuum of 0 (normal neurological examination) to 10 (death due to MS) in 20 steps (Appendix: 9.1). The instrument addresses impairment (symptoms and signs) at the early level (0-3.5), mobility in the middle range (4-7.5), and upper limb (8-8.5) and inability to communicate effectively or eat or swallow (9-9.5) in the late stage (Kurtzke 1983). Patients intermittently or constantly needing a cane or crutch to walk a distance of 100 metres score 6, and a score of 4 means that the patient can walk about 500 metres without aid or rest.

For more than two decades, outcome measurement in MS has relied heavily on EDSS. It is the most common measure of impairment/disability for MS patients and of outcome in clinical trials making comparisons between trials and populations possible. For a trained neurologist it is easy to use and the intra-rater reproducibility is adequate (Hobart 2000). This was the main reason for choosing EDSS as a disability measure in our studies (Articles I-II-III –IV).

3.2.2. Pain assessment; Short Form Health Survey 36 (SF-36)

The SF-36 is a concise, generic, 36 item questionnaire, which measures eight multi-item dimensions encompassing functional status, well-being and overall evaluation of health (McHorney 1993). Bodily pain, general health perceptions, mental health, physical functioning, role functioning including both emotional and physical, social functioning and vitality are the eight dimensions included in the questionnaire. Item scores within each of the eight dimensions are coded, added and changed to a scale form where 0 represents the worst and 100 represents the best possible health state measured by the questionnaire.

We used the two items of bodily pain in SF-36, as a supplement to the semi-structured interview about pain in MS (Article I). One question is related to the intensity of pain and the second one is related to the pain influence on daily

activities. We used them separately. In Article II the influence of pain on anxiety and depression was assessed.

In Article IV pain was analysed as a subdimension of HRQoL using the NHP-I. The NHP-I is explained separately below.

3.2.3. Depression and anxiety assessment: Hopkins Symptom Check List (HSCL-25)

HSCL-25 is a self-report screening measure for symptoms of anxiety (questions 1-10) and depression (questions 11-25). HSCL-25 is short and simple to carry out, and has shown a high agreement with physicians' ratings of emotional distress (Winokur 1982). It is a pure one week prevalence measure of symptoms, and psychometrically intelligible in that all items are rated in the same way with no reference to change (better or worse than "usual" or "before").

The HSCL-25 requests that the respondents tick off on a scale from (1), not at all to (4), very much, as to which degree they had been bothered by the symptoms during the past week. The higher the score, the higher the number or severity of the symptoms (minimum score 1, maximum score 4). A psychiatric diagnosis (depression or anxiety) was defined if a person scored 1.75 or above (Winokur 1984). This scale was used in Article II.

3.2.4. Fatigue assessment

3.2.4.1. MS-Specific Fatigue Scale (MS-FS)

MS-FS is a self-reporting scale consisting of six items (Schwartz 1993). The patients rate the extent to which each item is applicable to them on a scale from 1 (disagree) to 7 (fully agree). The average of the six items is the final multiple sclerosis-specific fatigue scale score. The scale is relatively specific to MS fatigue and assesses exogenous and endogenous effects on fatigue (heat, inactivity, stress, depression, cool, positive experiences) (Article I and II).

3.2.4.2. Fatigue Severity Scale (FSS)

The Fatigue Severity Scale is a nine-item scale which assesses the effect of fatigue on activities of daily living. Each statement (eg, "I am easily fatigued", "Fatigue interferes with my work, family or social life") is rated on a scale of 1 (strong disagreement) to 7 (strong agreement). The individual's score is the mean of the

numerical responses to the nine statements. A cut off of 4 is used to select fatigued from non-fatigued (Krupp 1989), (Article III).

3.2.4.3. Visual Analog Scale (VAS)

Patients rated fatigue by placing a mark on a 10-cm visual analog scale every 6 months. Minimum score 0 = no pain, maximum score = 10, worst pain thinkable, (Article IV).

3.2.5. Health related quality of life (HRQoL) assessment

3.2.5.1. The Multiple Sclerosis Impact Scale (MSIS-29)

The MSIS-29 is a scale which measures the physical and psychological impact of MS from the patient's perspective (Hobart 2001). The scale was developed from in-depth interviews of people with MS. The instrument contains 20 items measuring the physical and 9 items measuring the psychological impact.

MSIS-29 high scores= greater impact (minimum score 0, maximum score 100), (Article III).

3.2.5.2. Nottingham Health Profile Part I (NHP-I)

The Nottingham Health Profile (NHP) is a generic HRQoL questionnaire (Hunt 1980, 1985, Jenkinson 1988). It is divided into two sections. We only used the first, containing 38 questions, proposed to measure perceptions of subjective health, within six dimensions, which could be adversely affected by ill health: emotional reaction, energy, physical mobility, pain, sleep and social isolation. The questions are answered using "yes" or "no" and are weighted so that a score of 0 indicated no problems, while a score of 100 indicates all possible problems within an area. The NHP-I was used in Article IV.

3.2.6. Assessment of cognition; Paced Auditory Serial Addition Task (PASAT).

PASAT evaluates cognitive functioning (Gronwall 1977). The test consists of sixty tape-recorded numbers that are presented in 3-second intervals. The patient has to add the two last heard numbers and give the answer orally. The score represents the proportion of correct answers. Minimum score 0, maximum score 60. Mean value for healthy persons is about 50 (Huijbregts 2006). PASAT was used in Article II.

3.3. Statistical methods

For statistical analysis we used the Statistical Package for the Social Sciences (SPSS, Chicago IL) for Windows version 11.01 (Article IV), 13.0 (Article II and III) and 14.0 (Article III).

3.3.1. Article I

Chi-square tests were employed for categorical variables (gender, initial course etc) Analysis of variance (ANOVA) was used to test for a possible influence of EDSS, disease duration, age at onset, at examination on the frequency of pain symptoms. Statisitical significance was defined as $p< 0.05$.

3.3.2. Article II

Mean scores of depression and anxiety in MS patients were compared with Mann-Whitney U-test, as well as 95 % CI. Comparisons between the general and MS populations were corrected for age, by weighting these to represent the distribution of the Norwegian population.

To investigate the relationship between possible risk factors and depression or anxiety, respectively, a logistic regression model was used. First univariate analyses were performed for each possible clinical and demographic risk factor, including gender, age at onset, initial course of the disease, disability (EDSS), cognition (PASAT), fatigue and pain. Variables that showed some association to the studied dependent variable ($p<0.25$), 95 % CI not including zero, were selected as candidates for the multivariate model.

3.3.3. Article III

Bivariate correlation analysis (Pearson) was performed at baseline between fatigue (the dependent variable) versus demographic, clinical, HRQoL and physical performance measures (independent variables). The proportion of explained variance of fatigue was analysed in a multiple regression model (blocked four-level). Changes in FSS, MSIS-29, 6MWT, TUG, BBS and EDSS over different time periods were analysed by general linear model (GLM) for repeated measures with time as within subject factor. If the time factor was significant ($p \leq 0.05$), Bonferroni-adjusted paired t-tests were used for pairwise comparisons between baseline and the different time periods. In case of missing values, the mean change of the total group was

added to the previous test values. To examine whether change in fatigue was associated with change in HRQoL and physical performance measures, bivariate correlation of change scores were examined from baseline to after treatment and from after treatment to six months after treatment.

3.3.4. Article IV

Differences in NHP-I sum scores between patients and controls were analysed using the Wilcoxon rank-sum test. The distribution of subscores were heavily skewed (median = 0 among the controls), and NHP-I subscores were therefore categorised into the presence of problems (score >0) or not (score = 0), and analysed using logistic regression analysis.

Changes within the patient group in both NHP-I sum scores and subscores from baseline to month 30 and differences in sum scores related to treatment (IFNβ or placebo), gender and clinical disease activity (progression or not and relapses or not), were analysed using the Wilcoxon rank-sum test, or Wilcoxon signed ranks test when dependent variables were present.

The associations between demographic and clinical variables and the NHP- I sum score were analysed using multiple linear regression analysis and the subscores by multiple logistic regression analysis. In these analyses, EDSS was categorised into two groups defined as EDSS score ≤3.0 and >3.0. Arm Index scores were categorised into 0, 1, 2 and >2 (Barnes 1997). Other variables included were gender, age, disease duration and fatigue scores.

4. SUMMARY OF RESULTS

The objective was to study presence and influence of non-motor symptoms in patients with MS. Furthermore, the aim was to assess if treatment was given and to focus on treatment possibilities. The results are given separately for each article.

4.1. Article I: Pain and sensory complaints in multiple sclerosis

A total of 74 % of the MS patients reported sensory and/or pain symptoms. Pain only was reported by 66 % and was most frequently located in the limbs and lumbar region. The presence and intensity of pain was independent of gender, age at onset and examination, disability level, disease course and duration. Paresthesia, neuralgic and muscular pains were the most frequently reported characteristics of the symptoms. About 40 % of the patients reported that the complaints had important influence on daily activities.

Only one third of the patients were treated for their pain, but most patients (62 %) among those that reported strong or very strong pain symptoms received therapy.

Fatigue was reported by 66 % of the patients, and higher intensity of pain symptoms was associated with the presence of fatigue ($p= 0.043$).

4.2. Article II: Depression and anxiety amongst multiple sclerosis patients

Almost one third (31 %) of 140 investigated MS patients reported symptoms of depression, while 19 % reported anxiety, both significantly higher compared to the general population ($p<0.001$).

Fatigue and younger age at onset were significantly associated with symptoms of depression, while fatigue and pain, lower EDSS score and younger age at onset were associated with symptoms of anxiety.

Only 16 % of the depressed patients received treatment (anti-depressive drugs, psychological or psychiatric treatment), and only 11 % of those with anxiety were treated for their symptoms (psychological or psychiatric treatment only). Of the untreated study population with symptoms, 18 % expressed their need of treatment by a psychiatrist or psychologist.

4.3. Article III: Fatigue in multiple sclerosis is associated with self-perceived health, but less with physical performance

Four weeks of daily individualized physiotherapy significantly improved fatigue ($p< 0.001$), disability ($p=0.001$) and HRQoL ($p<0.001$), independently of gender, MS course, disease duration and baseline disability score (EDSS) in 56 MS patients with stable disease.

Physical performance was assessed by 6MWT, BBS, TUG and EDSS, fatigue by FSS and HRQoL by physical and psychological MSIS-29 scores. The improvements were lost after three months, except for 6MWT, BBS and TUG which were still significant both after three ($p<0.001$) and six ($p=0.003$) months. In a correlation and four block regression analysis the lack of association between fatigue and physical performance was demonstrated. HRQoL accounted for the largest proportion (26 %) of explained variance of fatigue, while physical performance measures accounted for only 4 %.

This might indicate that changes in fatigue are explained by other factors than improvement in physical performance supported by the finding that fatigue returned to baseline after three months despite sustained improvement in 6MWT, BBS and TUG.

4.4. Article IV: Health-related quality of life in secondary progressive multiple sclerosis

A total of 345 patients with SPMS reported significantly lower HRQoL according to NHP-I sum and subscores adjusted for gender and age, than controls from the general population ($p<0.001$).

At baseline, increased fatigue ($p<0.001$), EDSS ($p<0.001$) and Arm Index scores ($p=0.008$) were independently associated with reduced HRQoL according to the NHP-I sum scores.

After 30 months HRQoL scores were available for 318 patients. The NHP-I sum scores did not differ by gender ($p=0.13$) or treatment (IFNβ-1a vs. placebo at month 30; $p=0.48$). The NHP-I subscore of pain ($p=0.02$) and physical mobility ($p<0.001$) worsened throughout the study period. Relapses did not influence the sum scores ($p=0.74$), but disease progression worsened HRQoL ($p<0.002$).
Increased fatigue ($p=0.001$), higher age ($p<0.001$) and EDSS > 3 ($p=0.02$) were associated with worsening of pain subscores. Fatigue ($p=0.003$) and EDSS >3.0

(p=0.02) were associated with worse sleep scores. Finally, increased fatigue (p<0.001), EDSS >3.0 (p=0.001) and younger age (p=0.03) were associated with social isolation.

5. GENERAL DISCUSSION

5.1. Discussion of results

In these articles addressing non-motor symptoms in MS patients, it was striking how common these symptoms were, and how few patients received treatment.

5.1.1. Prevalence of non-motor symptoms

5.1.1.1. Pain

Our findings that 66 % of the patients experienced pain symptoms during the four weeks prior to examination (Article I), were in the range reported by a cohort from Denmark (79 %) and Canada (53 %) and a recent systematic review (75 %), (Svendsen 2003, Archibald 1994, O'Connor 2007).

A recent European survey of chronic pain in the general population including 2018 Norwegians from the general population, was recently undertaken (Brevik 2006). The mean age of this population was comparable (50 years) to our study of pain, but the proportion of women (57 %) was somewhat lower (our 67 %). Different instruments and definitions for assessing pain were used. Pain intensities 1-4 on a VAS scale (1-10) were excluded. The mean prevalence for the Norwegian population was 30 %, while for all included patients (46.394) from fifteen European countries and Israel, the prevalence was only 19 % (Brevik 2006).

If we excluded the weak and very weak pain in our study, the numbers of patients suffering from pain would have been reduced from 93 to 67 (47 %). Furthermore, the prevalence of *severe* pain among the pain-sufferes in the general Norwegian population was 24 % (Brevik 2006), in contrast to 39 % of our MS patients.

Even with some limitations concerning the comparison of the two studies, it seems clear that MS patients suffer more often and more intensively from pain than the Norwegian general population.

5.1.1.2. Depression and anxiety

The prevalence of symptoms of both depression and anxiety among MS patients in our study (Article II) confirmed earlier reports (Chwastiak 2005, Janssens 2003). The prevalence of depression and anxiety was significantly higher in patients with MS compared to the Norwegian population. In the Norwegian general population symptoms of depression are significantly higher among females. Like others we did

not find gender difference among MS patients (Chwastiak 2002, Figved 2005, Kessing 2008). Okiishi therefore hypothesized that MS may contribute to a core patho-physiology of depression (Okiishi 2001).

5.1.1.3. Fatigue

The prevalence of fatigue in our population (Article I and II) was similar to the range reported previously by others (Freal 1984, Vercoulen 1996, Krupp 1989, Mostert 2002). Fatigue was more common than in the Norwegian general population, even if comparisons are difficult due to the use of different scales (Loge 1998). The prevalence of fatigue in our heat tolerant patients (Article III) was in the same range.

5.1.2. Association of non-motor symptoms to other factors

5.1.2.1. Pain

Previous reports have shown increasing frequency of chronic pain correlated to increasing age (Ehde 2003, Svendsen 2003, Solaro 2004, Hadjimichael 2007) and duration of disease (Archibald 1994, Solaro 2004). This was not confirmed in Article I, as we found the presence and intensity of the pain symptoms to be independent of age at onset and age at examination (Article I). Article IV, however, showed that increasing age was associated with worse NHP-I pain subscore. In this study however, only SPMS patients with a limited range of disability and a higher EDSS and fatigue score were included (Article IV).

We also found that pain was independent of disease course, duration, and disability (Article I). This was confirmed by a recent study of 128 Italian MS patients (Grasso 2008). Others have reported greater likelihood of pain in patients with greater disease severity (Ehde 2003, Solaro 2004), which is in agreement with our results in Article IV stating that higher EDSS was associated with worse NHP-I pain subscore. The differences might again be explained by the difference of the populations due to age, disease duration, EDSS and the number of patients included.

Previous studies have shown that men and women seem to have a comparable risk for pain (Stenager 1991, Archibald 1994, Indaco 1994, Ehde 2003, 2006, Solaro 2004), but that females reported more severe pain (Warnell 1991, Hadjimichael 2007). We also found pain symptoms independent of gender with a trend towards more severe pain among females (data not shown). This was in contrast to the

Norwegian general population, where women suffer more frequently from pain than men (Breivik 2006).

Similar to others (Warnell 1991), we found an increasing intensity of pain to be associated with the presence of fatigue. Fatigue symptoms may of course have been worsened by the side effects of pain medication among the treated patients (Article I).

5.1.2.2. Depression/Anxiety

Patients with early onset of the disease had more often symptoms of both anxiety and depression, while no association between duration of disease and depression was detected (Article II). The mean duration of disease was 19 years, and patients with the longest disease duration may have adapted coping strategies, which could have modified the prevalence of major depression (Lazarus 1984).

One previous population-based study supported our finding of a lack of association between disability levels (EDSS) and depression (Gottberg 2006), while others have reported a positive association (Chwastiak 2002, Fruehwald 2001, Figved 2005). In a study of patients with newly diagnosed MS, an association between symptoms of anxiety and low disability level was identified. A change in disability status over two years was not accompanied by changes in anxiety and distress (Janssens 2006).

Koch and colleagues investigated 228 patients with MS for fatigue and depression. Disease progression was regularly assessed. After 10 years, 96 patients of the original cohort could be re-evaluated. Fatigue and depression tended to persist at the same levels over time as well, and symptoms were unrelated to disease progression (Koch 2008). The study was limited by the large number of patients lost by the time of follow-up. These results were in contrast to our study. We observed that patients with lower disability had higher risk of anxiety compared with high disability, but the risk was *reduced* over time. This might again possibly be explained by our longer follow-up period (19 years) (Article II).

Depression was not predicted by the presence of pain in our study (Article II), consistent with a previous report (Stenager 1995), but somewhat different from another which found depression to be associated with pain in women only (Kalia 2005). A relationship between pain, fatigue, and depression in MS patients has been

suggested (Forbes 2006), and recent data have provided support for a biopsychosocial understanding of chronic pain in MS (Osborn 2007).

Anxiety symptoms were 4.5 times more frequent among patients reporting pain, and over 5 times more frequent among patients with fatigue (Article II). The risk of symptoms of anxiety was higher among those with younger age at onset. Data on anxiety amongst patients with MS are, however, largely sampled from patients attending MS clinics, which make comparisons to previous reports more difficult (Korostil 2007, Janssens 2003).

5.1.2.3. Fatigue

In Article I increasing intensity of pain was found to be associated with fatigue, as reported by Warnell (Warnell 1991). Fatigue was associated with depression with a more than three times higher odds ratio, and anxiety more than five times, compared to patients without fatigue (Article II). Chwastiak and colleagues also reported disabling fatigue to be strongly associated with clinically significant depressive symptoms in a community sample of 739 MS patients. They therefore recommended screening for depression in MS patients reporting disabling fatigue (Chwastiack 2005). This association of increased fatigue and depression has been shown in both previous and later studies as well (Krupp 1989, Vercoulen 1996, Bakshi 2000, Penner 2007, Romberg 2007).

Among our 56 heat tolerant patients, fatigue improved significantly immediately after four weeks of inpatient physiotherapy (Article III). However, even though the physical performance was sustained at three and six months after physiotherapy, fatigue returned to baseline indicating that fatigue is explained by other factors. In contrast to our results two other studies showed improvements of fatigue to last for six weeks (Patti 2002) and three months (McCullagh 2008) after out-patient treatment. An explanation of the difference might be that the improvement of fatigue could be related to changes in the environment. Out-patients might be able, during the treatment, to change their habits and environment, and to go on with these changes after ended treatment. In contrast, in-patients may lose the social aspects among the participants and the relaxed atmosphere at the rehabilitation site, when coming home to their everyday duties. This might be one of the reasons for the fatigue to return to baseline at least after three months. Schwartz and colleagues

found 139 MS patients to report less fatigue if they found the environments suitable for their psychological or physical condition (Schwartz 1996).

We found no association between fatigue and physical function. This was supported by other studies (Bakhsi 2000, Newman 2007, Van den Berg 2006). This finding might explain that improvement of physical function does not necessarily improve fatigue, and in planning intervention aimed to reduce fatigue, broader aspects of coping strategies should be considered for inclusion.

Fatigue was only correlated to HRQoL at baseline, and HRQoL also explained the highest variance of fatigue (Article III). This correlation was also compatible with earlier reports (Merkelbach 2002, Fisk 1994), as well as our own results finding fatigue to have a major impact on HRQoL among SPMS patients (Article IV).

Among our 56 patients (Article III), we found none of the demographic (age, sex, work status, location of treatment) or clinical variables (course and duration of the disease, DMT, EDSS) to be correlated to fatigue at baseline. Flachenecker and colleagues also demonstrated the lack of correlation between fatigue and age, disease duration and immunomodulating therapies (Flachenecker 2002).

5.1.2.5. HRQoL

Like McCabe and colleagues we found HRQoL to be reduced in MS patients compared to the general population (McCabe 2002), and like others, we found the reduced HRQoL score to be strongly associated with increased disability as measured by the EDSS and the Arm Index (Article IV). This probably reflects a general reduction in perceived HRQoL along with progression and increased severity of disease (Benedict 2005, Pfennings 1999, Shawaryn 2002, Zivadinov 2003). We found disease duration and age not associated with reduced HRQoL (Article IV). This is in contrast to previous studies (Merkelbach 2002, Loge 1998, Sullivan 1998). These variables were however, strongly associated with disability (EDSS).

Fatigue and unfavourable Arm Index scores were independently associated with the energy level sub-score. As the mean EDSS score was 4.8 in this cohort (Article IV), this may be related to the importance of optimal arm function in patients with decreasing walking ability.

Among our SPMS patients increasing age was associated with lower (worse) NHP-I pain sub-score as found by others (Moulin 1988, Stenager 1991). In contrast, our previous report (Article I) showed that pain was independent of most clinical and

demographic variables, including age. This difference may, however, at least partly be explained by differences in study populations.

Shorter disease duration was moderately associated with reduced emotional reaction score (Article IV). Others have found less depression among older patients with longer disease duration (Murray 1995, Ford 2001, Pittock 2004). We could not further explore this issue, since specific depression scores were unfortunately not included in this study.

We found a moderate association between younger patients and higher social isolation scores, in addition to increased EDSS score and fatigue (Article IV). This may relate to the same mechanisms as for emotional reaction. It is reasonable to believe that the lower level of acceptance among younger patients will lead to social isolation.

Increased EDSS scores were associated with unfavourable NHP-I sleep scores in addition to fatigue (Article IV). This may be explained by increased spasticity and reduced mobility and may lead to awakening at night. Pain and bladder dysfunction may be the cause of delayed sleep and awakening at night (Tachibana 1994, Fleming 2005), and may influence daytime fatigue (Potolicchio 1991).

The NHP-I sum score at follow-up (30 months) showed no significant change. In contrast, subscores of physical mobility, consistent with progression (EDSS), and pain worsened throughout the observation period (Article IV). Similar results have also been reported by others (Canadian Burden of Illness Study Group 1998, Pfennings 1999, Zivadinov 2003). However, no significant overall change could be found.

The improvement in subscores of sleep and emotional reactions was not significant, but might be the explanation of the non-significant sum score change. The reason for the improvements of sleep and emotional reactions during the study period is unclear, but might be due to the positive experience of regular follow-up and the sleep problems might have been treated. However, the results were not significant (Article IV).

Relapses did not influence HRQoL, which is compatible with another study (Merkelbach 2002), but permanent disability worsened the HRQoL and seemed more important for patients with MS than relapses (Article IV).

Physiotherapy intervention of four weeks, analysed in Article III, was followed by improved fatigue and HRQoL. After three months the improvements were lost, even

if the physical performance was sustained, indicating fatigue and HRQoL might be explained by other factors than improvement in physical performance alone.

5.1.3. Treatment

5.1.3.1. Pain

One third of the patients reporting strong and very strong pain received no treatment for their pain, and only one third of all the pain patients received medication for their symptoms. Unfortunately we had no information about earlier pain relieving modalities in the untreated patients. This would have been of great interest, since pain is difficult to treat, and patients might discontinue the treatment due to adverse effects and/or ineffectiveness.

5.1.3.2. Depression and anxiety

The proportion reporting treatment of depression (anti-depressive drugs or psychological support) was also surprisingly low, although symptoms of depression indicated by HSCL screening may only be one third of those with a depression according to a diagnostic interview. This probably means that our patients with symptoms of depression were not all in need of treatment. Even with this limitation the treated number was too low.

Undertreatment of depression and anxiety, as well as pain, could be due to a limited focus on these problems, or to the idea of the treating physicians that it is normal to be depressed or suffer from anxiety and pain for patients with MS. A similar low treatment rate was also reported in another Norwegian study, where only 6 % of the depressed MS patients received anti-depressants (Figved 2005). Others have reported treatment frequencies ranging from 11- 48 % (Gottberg 2006, Korostil 2007). In one study 29 of 45 (64 %) pain patients (Archibald 1994) were treated during the month prior to interview, and in another only 31 % (Stenager 1991) were treated. In the Danish study, patients with minor pain syndromes and headaches relieved by unprescribed analgesics were excluded. This may explain both the lower numbers of patients with pain (45 %), and the low number of treated patients in this Danish study.

The importance of identification and treatment of depression in MS has been illustrated by reports indicating that psychiatric disorders seem to be the major risk

factor for the increased frequency of suicide among MS patients (Stenager 1992, Stenager 1996). It has been shown that the single most useful intervention to prevent suicide is improved identification and treatment of depressive disorders (Goldman Consensus Group 2005). Depression seems also to predict progression of disability in MS (Nortvedt 2000, Vissendijk 2004). Another study indicated that treatment for depression was associated with reduction of pro-inflammatory cytokines (Mohr 2001), and one demonstrated a reduction of gadolinium-enhanced lesion load on MRI (Puri 2001). Treatment of depression in MS patients may, in addition, also improve adherence to immunomodulatory therapy (Mohr 1997) and reduce fatigue (Mohr 2003).

5.1.3.3. Fatigue

As fatigue is a highly subjective symptom, a potential placebo effect must be kept in mind, irrespective of the treatment offered. The benefits gained related to fatigue and psychological well being might be a result of physiotherapy, as well as the social and emotional support from the group and the atmosphere at the rehabilitation sites (Article III).

The reduction in fatigue might also be related to a greater sense of environmental coping as this is indicated to be the best psychosocial predictor of both global fatigue and fatigue-related distress for MS patients (Schwartz 1996). The positive effect on fatigue diminished after the environment had changed back to “normal”, as did the improvements of both the psychological and physical scores of MSIS-29.

5.1.3.4. HRQoL.

IFNβ treatment did not influence HRQoL in our SPMS population (Article IV), or in the previous study of the same population (Andersen 2004). In another study of SPMS patients no treatment effect on relapses and disability progression was achieved (Zivadinov 2003). Importantly, adverse events did not influence the patients’ HRQoL (Zivadinov 2003). Others have, however, reported some beneficial effects from IFNβ in SPMS, including improvement in several HRQoL dimensions (Freeman 2001, Cohen 2002).

A recent study by Rudick and colleagues concluded that HRQoL of patients with RRMS (2113 patients included) was significantly lower than the general US population as measured by SF-36. HRQoL was found to be correlated to the severity

of the disease, and HRQoL improved significantly with natalizumab treatment (Rudick 2007).

Individualized physiotherapy as a method to improve functional activity was thought to also increase HRQoL (Article III). Surprisingly, this study showed, that even if the improvements in physical performance lasted up to six months, HRQoL dropped to baseline after three months of follow-up. As HRQoL is shown to be influenced not only by progression and disability, but also by fatigue, sleep, pain and social isolation, patient care should still be regarded as a cornerstone in the treatment of patients suffering from MS.

5.2. Material considerations

5.2.1. Article I and II

The study population included in Article I and II was heterogeneous with MS patients with a wide range of disease duration and disability levels. As shown in previous population-based studies (Weinshenker 1989, Myhr 2001), disability, as measured by EDSS, showed a bi-modal distribution. This, together with the distribution of other characteristics, such as gender, and age at onset, indicated inclusion of a representative MS population. However, the proportion of PPMS (26 %) was somewhat higher than reported in previous natural history studies (15-20 %) (Confavreux 1980, Weinshenker 1989).

An explanation for this could be the diagnosing procedure. The information given in the records of patients was assessed in order to find patients who met the Poser criteria for definite, or laboratory supported definite MS. At the clinical visit (EDP and AGB) the patients were categorized as PPMS, RRMS or SPMS according to the anamnestic information given by the patients, whithout the use of the records. The mean disease duration in this population was 20 years. Some patients may have forgotten earlier exacerbations and were therefore categorised as PPMS instead of SPMS explaining the high number of included PPMS patients.

Our initial population of 280 patients probably included close to all cases in the area, according to the supposed prevalence of 125-150 per 100.000 inhabitants (suggesting 270-330 patients in the area). However, it is possible that non-members of the MS society with a benign MS disease, without a need for a neurological consultation over the last ten years were missed, as well as severely disabled

patients living in institutions without visiting the hospital for the last 10 years. It seems reasonable to assume that this does not account for many individuals.

We were only able to include 51 % of the eligible population (142 of 280). Compared to gender and age no bias was obvious between included and not included patients. This low inclusion is a limitation of the study as we have no knowledge about pain, fatigue, depression and anxiety among the patients not included. The response rate is, however, compatible with both previous and later studies (Stenager 1991, Rae-Grant 1999, Hadjimichael 2007, 2008, Ehde 2003). In one study of pain the patients were paid 25 dollars for completing the survey which may be the reason for a response rate as high as 68 % (Ehde 2006).

HRQoL, depression, anxiety, pain and fatigue may be influenced by several co-existing diseases or disorders found in the general population. Therefore it is important in epidemiological research, important to have control groups consisting of individuals which are comparable to the study population with regard to age and sex.. The lack of a control group was a limitation in Article I.

In Article II the same population was studied as in Article I. A comparison to the general population was possible according to anxiety and pain as we used the same instruments and method of interview as in the OsLof study (Sandanger 2007).

5.2.2. Article III

The study population in Article III was limited to those with moderate disability (EDSS 4.0-6.5), and probably consisted of highly motivated patients. On the other hand, severely disabled patients could not have participated in such an intensive program. The exclusion of heat intolerant patients may have biased the study population, as heat is known to worsen fatigue. However, the prevalence of fatigue at baseline was comparable to previously reported populations (Freal 1984, Krupp 1989, Mostert 2002, Beiske 2004). Thus, our findings may apply also to the heat intolerant MS population with moderate disability.

The most important limitation of this study was the lack of a control group. However, the inpatient status is artificial and can not be compared to living at home. We therefore found it inappropriate to use patients on a waiting list as a control group. Due to economic limitations and the capacity at the rehabilitation centres, it was not possible to randomize half of the patients to a none-therapy group. A recent

meta-analysis of effect of exercise training on QoL in MS reported a prosperous effect on QoL in studies both with and without control groups (Motl 2008).

5.2.3. Article IV

In Article IV 92 % of the patients with SPMS completed 30 months in the study (318 of 345 patients). The control group included 217 healthy Norwegians of similar age. All patients and controls lived at home. We had no data related to socioeconomic status, and this may be a limitation.

5.3. Methodological considerations

In a disorder like MS, in which no diagnostic test is available and the diagnosis is based on anamnestic evaluation, clinical examination and supportive paraclinical evaluations, it is important to use standardised and well-defined diagnostic criteria for the disease. All patients included in this thesis, fulfilled the conventional criteria for diagnosis. The populations studied were clearly defined and the chosen scales have been well validated, making comparisons between studies possible.

An ideal method for measuring symptoms of depression, anxiety, fatigue, pain, disability and QoL does not exist. It is important to choose a method suitable for the population involved. Knowledge of both advantages and limitations of the instruments is necessary. The chosen scales must be valid, reliable, responsive, feasible and acceptable. A generic scale is essential when making a comparison to the general population, or people with other health problems. The disadvantage of generic scales is the lack of specific relevance, making them less sensitive to disease specific symptoms. Sometimes a combination of generic and disease specific measuring scales may be appropriate.

5.3.1. Disability

We used EDSS as a measure of disability. For more than two decades, the outcome measurement in MS has relied heavily on EDSS, making comparisons between trials and populations possible. For a trained neurologist it is easy to use. The inter-rater reproducibility is adequate for group comparison studies. However, the intra-rater reproducibility is variable and the EDSS has also been criticised for non-linearity and poor responsiveness (Hobart 2000, Benito-Leon 2003).

The patients included in Article I and II were only examined once (by either EDP or AGB). The inter-rater reliability was therefore an important issue. This was to some degree controlled for by pre-study EDSS training focusing on inter-rater differences.

In an intervention study it is important to use the same examiner throughout the study (Article III). However, half of the patients (Haukeland) were examined by another neurologist at screening and follow-up at three and six months. The EDSS of the examined population was 4-6.5. The patients were also examined by the 6MWT. The combinations of the EDSS at this level of disability and the 6MWT "objectivated" the EDSS, and made the inter-rater reliability less conspicuous.

In the multi-centre study (Article IV), the patients were followed every sixth months for 30 months by the same neurologist at each centre. The EDSS scored by the neurologist was also strongly associated with the patients' self-reported subscore for physical mobility. This confirms the validity of the scoring, and this strong association was also probably the reason why no other variables were independently associated with this subscore.

The EDSS has also been criticised for overemphasising mobility and not capturing all the elements involved in the global impact of MS (Hobart 2000, Benito-Leon 2003). This limitation is corrected for by adding other measurements of both disability and HRQoL in Article III and IV. In Article III disability level was assessed by EDSS and physical performance by 6MWT, BBS and TUG. HRQoL was assessed by MSIS-29 including both a physical and psychological component. In Article IV disability was assessed by EDSS, Arm Index and Ambulation index. HRQoL was assessed using the NHP-I which in addition to a dimension of physical mobility also includes five other dimensions (pain, sleep, energy, emotional reactions and social isolation).

5.3.2. Pain

In addition to a semi-structured interview and clinical examination as a measure of pain, we used two questions about intensity of pain and the influence of pain on daily activities from the SF-36 (Article I). The SF-36 is widely used and has undergone extensive testing of validity and reliability in several countries including Norway (Loge 1998). It has been found to be more sensitive to lower levels of disability. It was designed with the intension of supplementing disease specific measures.

However, the retrospective reporting of pain symptoms (last four weeks) is of course a methodological limitation.

The International Association for the Study of Pain (IASP) has redefined neuropathic pain and introduced a grading system of definite, probable and possible neuropathic pain for clinical and research purposes. IASP defines “neuropathic pain as a pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (Treede 2008). This revision serves to distinguish neurologic pain from, e.g., musculoskeletal pain that arises indirectly from disorders of the motor system (nociceptive pain).

In Article I we diagnosed pain according to location, duration, characteristics, intensity and influence of pain on function. The focus of the article to describe pain and no intervention was initiated. By using the IASP grading system it is possible to test groups of patients with different pain types, and to test the underlying pathophysiology or response to treatment, making the use of this system preferable in future studies.

5.3.3. Depression and anxiety

For the diagnosis of symptoms of depression and anxiety we employed the HSCL-25, which is primarily a screening assessment tool (Article II). Therefore, all patients with symptoms of depression in the screening did not necessarily fulfill a formal diagnosis of depression and were not in need of treatment. A previous Norwegian population-based survey reported a prevalence of psychological distress (anxiety and depression) (HSCL-25 score ≥1.75) of 16 %, while according to the gold standard, the Composite International Diagnostic Interview (CIDI), the same sample had a population prevalence of about 5 % for anxiety and depression (Sandanger 1998). Nevertheless, the Hopkins Symptom Check List-25 (HSCL-25) has been validated to be a good predictor of depression (Sandanger 1998).

The HSCL has been tested in both population studies and patient populations (Hesbacher 1980, Sørensen 1987).

5.3.4. Fatigue

Fatigue is essentially a subjective problem, and many instruments have been developed to assess fatigue and to measure its severity for both clinical and research purposes. The patients’ own perception of the symptom is most important,

and it is therefore appropriate to choose a self-report measure, as there is no gold standard for fatigue assessment. Gulick and colleagues concluded that self-monitoring of symptoms can be done accurately by patients with diseases of the nervous system (Gulick 1993).

In Article I and II the patients who answered yes to be fatigued after a definition of fatigue had been given, were also tested with the MS-FS. The fatigue screening question (fatigued yes/no, after defining fatigue as an unexplained tiredness which limits daily activities or QoL) separated the patients well, showing a mean score of 2.54 (SD 0.57) among those reporting absence of fatigue, compared to fatigued patients 5.37 (SD 1.31) ($p< 0.001$, Mann-Witney U) when they were tested due to the MS-FS. The scale is relatively specific to MS fatigue and assesses exogenous and endogenous effects on fatigue (heat, inactivity, stress, depression, cool, positive experiences).

Even though we used multiple logistic regression analysis to show that MS patients who reported fatigue had more than three times higher risk of symptoms of depression compared to patients without fatigue, there are some limitations (Article II). Due to the nature of the symptoms of depression and fatigue, fatigue may be a part of depression and, furthermore, there may be common underlying mechanisms in MS contributing to both depression and fatigue (Wichers 2002).

In Article III fatigue was scored according to FSS. The FSS has been found to successfully identify features of fatigue specific to the medical ill. It is useful in classification of patients and has been shown to be sensitive to clinically significant changes. The use of FSS was, however, a limitation, because a unidimensional scale cannot distinguish between different aspects of MS-related fatigue, and their particular relation to depression and disability progression.

In Article IV we evaluated fatigue solely using a visual analogue scale. In an assessment of fatigue evaluated by VAS, the FFS and the Fatigue Impact Scale (the most used fatigue scales), La Chapelle and colleagues found these scales to be strongly correlated, indicating an appropriate scoring in our study (LaChapelle 1998).

5.3.5. Health related quality of life (HRQoL)

QoL assessment represents a relatively new field in MS research. Since the first study was published in 1992 on this topic, several measures of HRQoL have been used for MS patients (Gruenewald 2004).

In Article III it was important to choose a HRQoL measure sensitive to change after four weeks of intervention. MSIS-29 had been examined in a separate postal survey of 1250 MS Society members. The results of five psychometric properties (data quality, scaling assumptions, acceptability, reliability and validity) indicated the MSIS-29 to be clinically useful and scientifically sound, and supported its use as an outcome measure in different clinical settings. A recent evaluation of MS-specific HRQoL instruments summarized MSIS-29 as having good internal consistency, direction, magnitude and pattern of correlations consistent with prediction (Riazi 2006).

In Article IV we used NHP-I, a non-disease-specific generic instrument to compare patients and controls. Self-report measures were chosen, as patients and doctors do not necessarily agree about assessment of disability (Rothwell 1997), and cognitive dysfunction in MS does not have a major impact on the reliability and validity of self-reported health measures (Gold 2003, Marrie 2003).

The NHP is a questionnaire, extensively tested for validity and reliability, used to measure perceived ill health in chronically sick patients (Dornan 1992, Grimby 1995), as well as for assessing the efficacy of medical interventions on subjective health (Essink-Bot 1995). Limitations of the NHP include its inability to suitably register patients or patient groups with only minor afflications, and its difficulty in observing small improvements in subjective health. This is largely due to the fact that the NHP was created to measure effects on quality of life in severely ill patients. We found the instrument suitable for our SPMS patients with a relatively advanced disease (mean EDSS of 4.8), and a mean disease duration of 13 years.

The high proportion of zero score among population controls was a limitation related to the NHP analyses. Therefore, we categorised the scores into the presence of problems (score>0) or not (score = 0) and made the comparisons by logistic regression analysis. This also illustrated the variation of problems related to the different NHP subscores among the controls, ranging from 12 % related to social isolation to 44 % related to sleep. The comparisons of NHP scores among patients and controls were adjusted for age and gender.

6. CONCLUSIONS

6.1 Practical consequences

Pain is a frequent and disabling symptom which may be independent of demographic and clinical variables in MS patients. The high frequency of the symptoms and the low frequency of treatment call for increased attention and improved treatment strategies to this problem.

Symptoms of depression and anxiety are 2-3 times higher than in the general population, but few patients received treatment for their symptoms. Depression and anxiety both independently and in interaction with other MS symptoms have major impact on patients' functioning. Currently available symptomatic treatment seems to be effective for MS patients, and may also reduce associated symptoms such as fatigue. Thus, increased focus on depression and anxiety among MS patients is needed to establish the appropriate treatment.

Fatigue improved after four weeks with inpatient physiotherapy, but the patients' perception of fatigue was not correlated with improvement of physical performance, as fatigue scores worsened after three months while 6MWT, BBS, TUG were still improved. Improvement of fatigue after inpatient physiotherapy may therefore be explained by other factors than physiotherapeutic treatment alone. Thus, a broad strategy accounting for both physical and psychological aspects seems to be needed in intervention programs aiming at improving fatigue also in a long-term perspective.

HRQoL is strongly influenced by physical disability (EDSS) and progression of the disease. However, non-ambulatory symptoms such as fatigue and pain and dimensions related to sleep, emotional reactions and social isolation also have major impact on the patients' QoL. Increased focus on optimising symptomatic treatment and psychosocial patient care could probably improve the patients' HRQoL. Thus, even though these patients usually do not benefit from immunomodulatory therapies, which imply regular follow-ups, it is still important also to offer patients in this stage of the disease a regular ambulatory care program.

6.2 Directions for further research

Pain, depression and anxiety, as well as fatigue, are common complaints in patients with MS. The reasons for under-diagnosing and low frequency of treatment for these symptoms are unknown. A study evaluating this is warranted as well as the use of a control group to analyse the differences to the general population.

In this context, it would also be of interest to compare the treatment offered to patients followed by regular visitis at the out-clinic, to those with more sporadic visits. However, treatment for anxiety and depression as well as pain in MS patients is not widely studied. Further studies are therefore highly needed also including intervention studies (RCT) testing physiotherapeutic and or pharmacological treatments.

A randomized controlled study (RCT) of fatigue and depression in inpatients with MS allocated to an intervention group (physiotherapy or coping strategies) or a non-intervention group is warranted to test both environmental and treatment effects on different fatigue scales.

A study of how to motivate patients to continue with physical activity in order to maintain the improvement after intensive inpatient physiotherapy is important. Little is known about the optimal dose and frequency of both physiotherapy and exercise.

7. ERRATA

Article I

In ”Assessment of sensory and pain complaints”, paragraph three (page 480), it is stated that fatigue was assessed by the Chalder Fatigue Questionnaire (FQ). We actually used this method, but the published data on fatigue in the patient population of Article I and II were collected and analysed according to the method described in Article II.

Article II

Page 241, last paragraph, line 9: Incorrect: fatigue had *3.9 times higher odds (1.48-10.27)* Correct: fatigue had ***3.2 times higher odds (1.14- 8.71)***

Page 242, paragraph 2 and line 8: Incorrect: odds of *depression*. Correct: odds of ***anxiety***

Page 243, first paragraph and line 6: Incorrect: Patients included *60.9 %,* Correct: Patients included: ***50 %*** (140/280).

Page 243, paragraph 7 and line 3: Incorrect: *Two* previous population-based studies support our findings of no associations [7,8]; Correct; ***One*** previous population-based study support our finding [7].

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9. APPENDICES

9.1. Expanded Disability Status Scale (EDSS), (English version)

9.2. Fatigue Scale Score (FSS), (Norwegian version)

9.3. Multiple Sclerosis Fatigue Scale (MS-FS), (Norwegian version)

9.4. Multiple Sclerosis Impact Scale (MSIS-29), (Norwegian version)

9.5. Nothingham Health Profile-I (NHP-I), (Norwegian version)

9.6. Short Form-36 (SF-36), (Norwegian version)

9.7. Hopkins Symptom Check List (HSCL-25), (Norwegian version)

Neurological Assessment. Kurtzke Functional Systems (FS)

Pyramidal Functions

0 Normal
1 Abnormal signs without disability
2 Minimal disability
3 Mild to moderate paraparesis, or hemiparesis; severe monoparesis
4 Marked paraparesis or hemiparesis, or moderate quadriparesis; or monoplegia
5 Paraplegia, hemiplegia, or marked quadriparesis
6 Quadriplegia

Cerebellar Functions

0 Normal
1 Abnormal signs without disability
2 Mild ataxia
3 Moderate truncal or limb ataxia
4 Severe ataxia in all limbs
5 Unable to perform coordinated movements due to ataxia

Brainstem Functions

0 Normal
1 Signs only
2 Moderate nystagmus or other mild disability
3 Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
4 Marked dysarthria or other marked disability
5 Inability to swallow or speak

Sensory Functions

0 Normal
1 Vibration or figure-writing decreased only in one or two limbs
2 Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory decrease alone in three or four limbs
3 Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs
4 Marked decrease in touch or pain or proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs
5 Loss of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
6 Sensation essentially lost below the head

Bowel and Bladder Functions (Rate on the basis of the worse function, either bowel or bladder)

0 Normal
1 Mild urinary hesitancy, urgency, or retention
2 Moderate hesitancy, urgency, or retention of bowel or bladder, or rare urinary incontinence
3 Frequent urinary incontinence
4 In need of almost constant catheterization
5 Loss of bladder control
6 Loss of bowel and bladder control

Visual (or Optic) Functions (Record the presence of temporal pallor)

0 Normal
1 Scotoma with visual acuity (corrected) better than 6/9
2 Worse eye with scotoma with maximal visual acuity (corrected) of 6/9 to 6/18
3 Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 6/18 to 6/30
4 Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 6/30 to 6/60; grade 3 plus maximal acuity of better eye of 6/18 or less
5 Worse eye with maximal visual acuity (corrected) less than 6/60; grade 4 plus maximal acuity of better eye of 6/18 or less
6 Grade 5 plus maximal visual acuity of better eye of 6/18 or less

Cerebral (or Mental) Functions

0 Normal
1 Mood alteration only (does not affect EDSS score)
2 Mild decrease in mentation
3 Moderate decrease in mentation
4 Marked decrease in mentation
5 Dementia or chronic brain syndrome - severe or incompetent

Other Functions (Any other neurological findings attributable to MS)

A. Spasticity

0 None
1 Mild - detectable only
2 Moderate - minor interference with function
3 Severe - major interference with function

B. Others

0 None
1 Any other neurological findings attributed to MS:
Specify

Neurological Assessment. Kurtzke Expanded Disability Status Scale (EDSS)

0 Normal neurological exam (all grade 0 in FS*)

1,0 No disability; minimal signs in one FS* (i.e., grade 1)

1,5 No disability, minimal signs in more than one FS* (more than one FS grade 1)

2,0 Minimal disability in one FS (one FS grade 2, others 0 or 1)

2,5 Minimal disability in two FS (two FS grade 2, others 0 or 1)

3,0 Moderate disability in one FS (one FS grade 3; others 0 or 1)
or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory

3,5 Fully ambulatory but with moderate disability in one FS (one grade 3)
and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)

4,0 Fully ambulatory without aid, self-sufficient, up and about 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters

4,5 Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters

5,0 Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g. to work a full day without special provisions); (Usual FS equivalents are one FS grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)

5,5 Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0)

6,0 Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than one FS grade 3+)

6,5 Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+)

7,0 Unable to walk beyond approx. five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone)

7,5 Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+)

8,0 Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems)

8,5 Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations generally 4+ in several systems)

9,0 Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+)

9,5 Totally helpless bed patient; unable to communicate effectively or eat/ swallow; (Usual FS equivalents are combinations, almost all grade 4+)

10 Death due to MS

Note 1: EDSS steps 1,0 to 4,5 refer to patients who are fully ambulatory, and the precise step number is defined by the Functional System score(s). EDSS steps 5,0 to 9,5 are defined by the impairment to ambulation, and usual equivalents in Functional System scores are provided

Note 2: EDSS should not change by 1,0 step unless there is a change in the same direction of at least one step in at least one FS

* Excludes mental function grade 1

Det nasjonale kompetansesenter for multippel sklerose
Nevrologisk avdeling, Haukeland Sykehus

Med støtte fra Astra Norge AS

Baseline 1a; Norge **Pas. nr.** ☐ ☐ **Initialer** ☐ ☐ ☐

Dato: _____

CIOPIMS –

(Fylles ut av pasient)

FATIGUE SEVERITY SCALE (FSS)

Hvor enig/uenig er du i hvert av de følgende 9 påstander?
Sett en ring rundt det tallet som passer best, hvor 1 betyr at du er "sterkt uenig" og 7 betyr at du er "helt enig" i påstanden.

1. **Mitt pågangsmot blir/er dårligere når jeg er utmattet**

   1 2 3 4 5 6 7

   Sterkt uenig *Helt enig*

2. **Jeg blir utmattet ved anstrengelser**

   1 2 3 4 5 6 7

   Sterkt uenig *Helt enig*

3. **Jeg har lett for å bli utmattet**

   1 2 3 4 5 6 7

   Sterkt uenig *Helt enig*

4. **Utmattelse nedsetter min fysiske funksjonsevne**

   1 2 3 4 5 6 7

   Sterkt uenig *Helt enig*

5. **Utmattelse skaper ofte problemer for meg**

   1 2 3 4 5 6 7

   Sterkt uenig *Helt enig*

6. **Utmattelse fører til at jeg har dårlig fysisk utholdenhet over lengre tid**

   1 2 3 4 5 6 7

   Sterkt uenig *Helt enig*

7. **Utmattelse virker negativt inn på mine gjøremål og forpliktelser**

   1 2 3 4 5 6 7

   Sterkt uenig *Helt enig*

8. **Utmattelse er ett av mine tre mest plagsomme symptomer**

   1 2 3 4 5 6 7

   Sterkt uenig *Helt enig*

9. **Utmattelse virker negativt inn på mitt arbeid, familie og øvrige sosiale liv**

   1 2 3 4 5 6 7

   Sterkt uenig *Helt enig*

MS-spesifikk fatigue-skala

Instruksjon:
Be pasienten om å rangere på en skala fra 1 til 7 om de er uenig eller helt enig i utsagnene nedenfor.
Beregn ***MS spesifikk Fatigue-skala score*** ved å dele total scoren for alle spørsmålene på 6.

1. Varme fører til fatigue

1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐
Helt uenig						Helt enig

2. Lange perioder med inaktivitet fører til fatigue

1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐
Helt uenig						Helt enig

3. Stress fører til fatigue

1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐
Helt uenig						Helt enig

4. Depresjon fører til fatigue

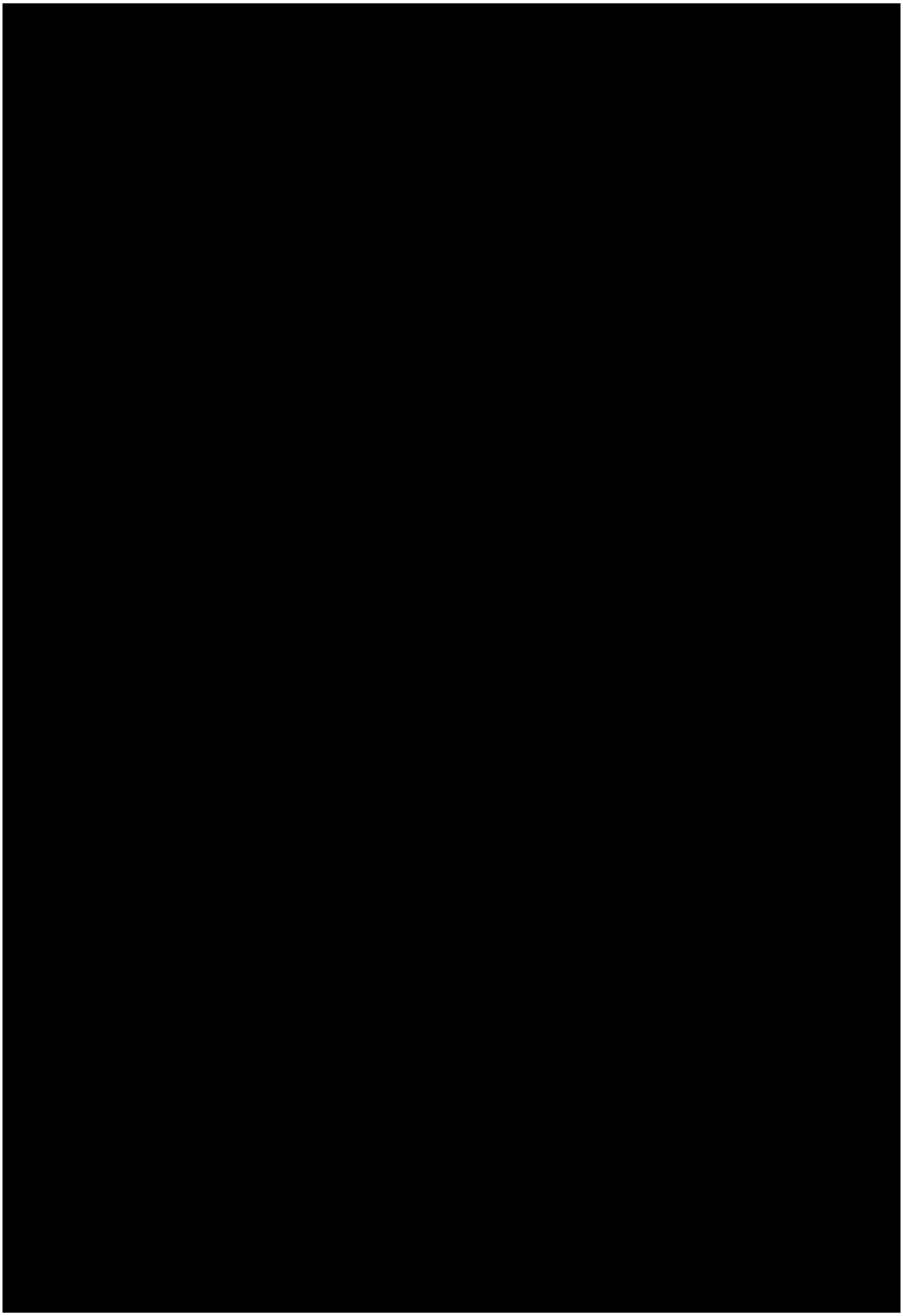
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐
Helt uenig						Helt enig

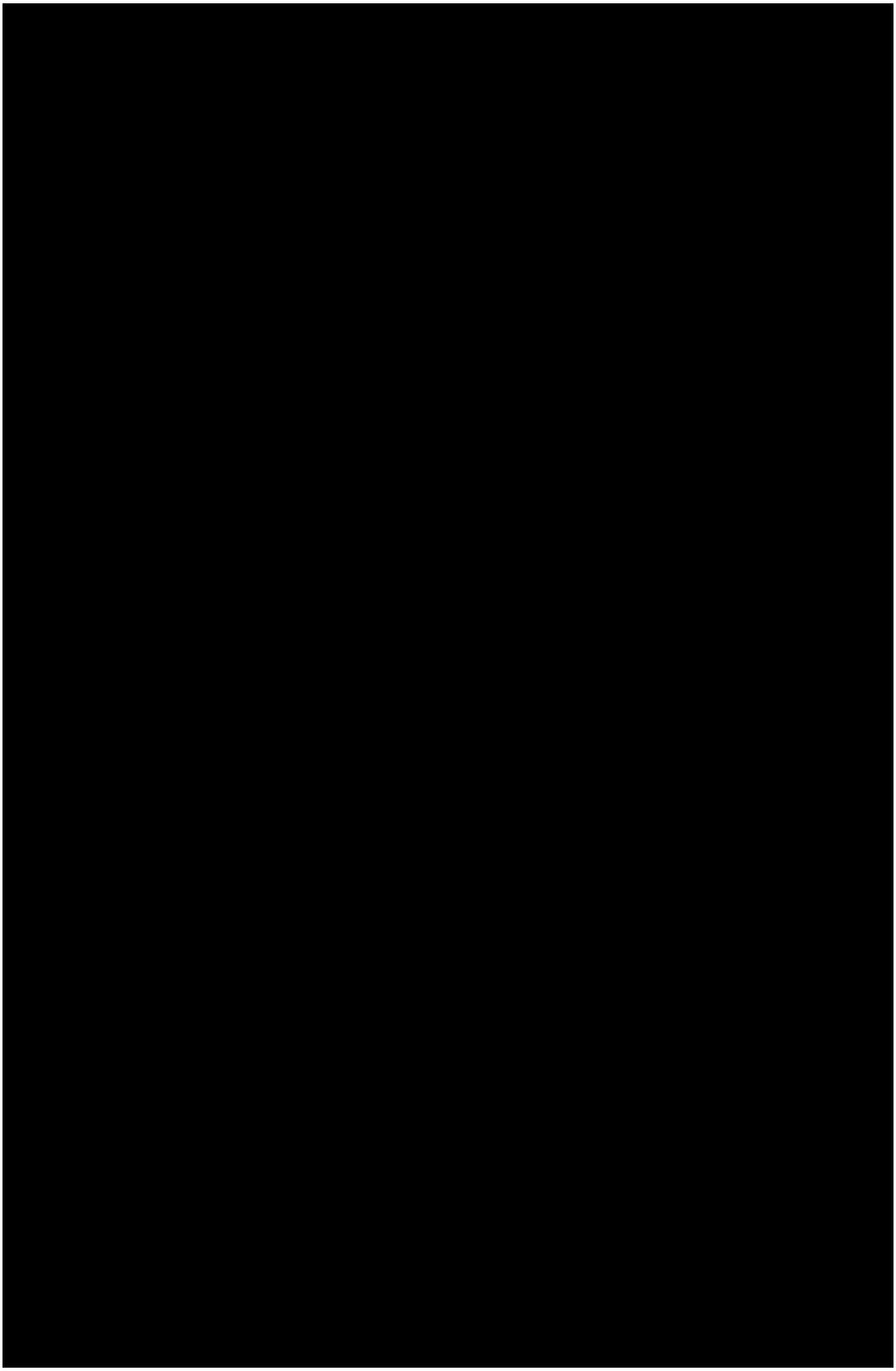
5. Kjølige tempraturer reduserer fatigue

1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐
Helt uenig						Helt enig

6. Positive opplevelser (lystbetonte aktiviteter) reduserer fatigue

1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐
Helt uenig						Helt enig





NHP-Helseprofil

OBS!
Les igjennom spørsmålene grundig før du fyller inn i rubrikkene

Nedenfor finner du en oppstilling over en del problemer du kan stå ovenfor i hverdagen.

Sett et kryss for JA for de problemene du har akkurat nå.

Sett et kryss for NEI for de problemer du ikke har.

Selv om du er usikker, skal du sette et kryss i den ruten som likevel passer best akkurat nå.

Obs! Det er ønskelig at du svarer på alle spørsmål, men det er ikke et absolutt krav.

	JA	NEI
1. Jeg kjenner meg alltid trøtt		
2. Jeg har det vondt om natten		
3. Jeg føler meg nedfor		
4. Jeg har uutholdelige smerter		
5. Jeg må ta tabletter for å sove		
6. Jeg husker ikke hvordan det er å ha det morsomt		
7. Jeg føler meg anspent		
8. Det gjør vondt når jeg forandrer kroppsstilling		
9. Jeg føler meg ensom		
10. Jeg kan bare bevege meg innendørs		
11. Jeg har vansker med å bøye meg		
12. Alt føles som en anstrengelse		
13. Jeg bruker å våkne svært tidlig om morgenen		
14. Jeg klarer ikke å gå		
15. Jeg har problemer med å få kontakt med andre		
16. Dagene føles lange		
17. Jeg har problemer med å gå i trapper		

JA NEI

18. Jeg har vanskeligheter med å strekke meg etter noe_____

Obs! Husk at selv om du er usikker, ber vi deg likevel krysse av for det som passer best med din situasjon akkurat nå.

JA NEI

19. Det gjør vondt når jeg går_____
20. Jeg blir lettere irritert nå enn før_____
21. Jeg føler det som om ingen står meg nær_____
22. Jeg ligger våken det meste av natten_____
23. Jeg har følelsen av å miste kontakten over meg selv_____
24. Det gjør vondt når jeg står_____
25. Jeg har problemer med å kle på meg_____
26. Jeg orker svært lite_____
27. Jeg har vanskeligheter med å stå lenge (for eksempel ved oppvaskbenken eller på bussholdeplassen)_____
28. Jeg har stadige smerter_____
29. Det tar lang tid før jeg sovner_____
30. Jeg føler jeg er til byrde for andre_____
31. Mine bekymringer holder meg våken om natten_____
32. Jeg føler som om livet ikke er verdt å leve_____
33. Jeg sover dårlig om natten_____
34. Jeg har problemer med å komme overens med andre_____
35. Jeg må ha hjelp for å gå utendørs_____ (for eksempel noe eller noen å støtte meg på)_____
36. Det gjør vondt når jeg går i trapper_____
37. Jeg føler meg nedstemt når jeg våkner_____
38. Det gjør vondt når jeg sitter_____

28. SMERTER

SF36 BP

Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 ukene?
Sett kryss ved ett tall

Ingen	Meget svake	Svake	Moderate	Sterke	Meget sterke	
☐	☐	☐	☐	☐	☐	230/

I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid?
(gjelder bådehusarbeid og arbeid utenfor hjemmet).

Ikke i det hele tatt	Litt	En del	Mye	Svært mye	
☐	☐	☐	☐	☐	231/

HSCL-25

Nedenfor er den en liste over symptomer eller problemer som folk av og til har.
Vær vennlig å les hvert enkelt punkt grundig,og vurder hvor mye hvert symptom var til plage eller ulempe for deg siste uke (til og med idag)
Sett kryss i den raden som passer best

		1 ikke i det hele tatt	2 litt	3 en god del	4 Svært mye
a	Plutselig skremt uten grunn				
b	Føler du deg engstelig				
c	Føler du deg svimmel eller kraftløs				
d	Nervøs eller urolig				
e	Hjertebank				
f	Skjelving				
g	Føler du deg anspent eller opphisset				
h	Hodepine				
i	Anfall av redsel eller panikk				
j	Rastløshet, kan ikke sitte rolig				
k	Føler deg slapp og uten energi				
l	Anklager deg selv for ting				
m	Har lett for å gråte				
n	Tap av seksuell interesse eller nytelse				
o	Dårlig apetitt				
p	Vanskelig for å få sove				
q	Følelse av håpløshet med tanke på fremtiden				
r	Føler deg nedfor				
s	Føler deg ensom				
t	Har tanker om å ta ditt eget liv				
u	Følelse av å være fanget				
v	Bekymrer deg for mye				
w	Føler ikke interesse for noe				
x	Føler at alt krever stor anstrengelse				
y	Føler at du ikke er noe verdt				

10. ARTICLES