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Rehabilitation for Multiple Sclerosis in Adults (I); Impairment and Impact on Functioning and Quality of Life: An Overview

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Abstract: Multiple sclerosis (MS) is a chronic, central nervous system, disabling disease. International Classification of Functioning, and relevant generic and specific outcome measures are reported.

Problems perceived by people with MS (PwMS)affect mobility, sight, continence, feeding or cognitive impairment depending on whether acute, chronic or long-term disability was involved. The most common body function and structure impairments leading to disability and reported by health care professionals are fatigue, weakness, decreased fitness, sensory disorders, pain, upper motor neuron syndromes, ataxia and tremor, balance and postural control, gait pattern disorders, visual, neurogenic lower urinary tract and bowel dysfunction, sexual, autonomic, neuropsychological, neuropsychiatric impairment, dysarthrophonia, dysphagia, respiratory and sleep disorders. The most frequently affected activities and participation include mobility, domestic life, community and social activities, remunerative employment, interpersonal relationships, self-care, learning and applying knowledge, and economic life. Limitation in activities of daily life such as fatigue, pain, visual, continence, sexual and cognitive impairment, depressive disorders, sleep disorders, economic pressure, employment status and lack of information have an impact on Quality of Life (QoL). Increased caregiving tasks, psychological burden, limitation in activities and participation and reduced QoL have a profound influence on caregivers. This paper summarizes the perception of problems and needs, and most of the disease impact on functioning, disability and QoL of PwMS, and the impact on their significant others and caregivers, according to health and social research.

Key words: Multiple Sclerosis, Rehabilitation, Daily life activity, Disability, Quality of life, Caregiver.

Introduction

1.0 Concept MS is considered an immune-mediated, inflammatory, progressive, demyelinating[1,2], axonal loss-producing[3], and disabling disease of the central nervous system (CNS), with lesion dissemination in time and in space[4], which occurs in genetically susceptible individuals[3], is triggered by an exogenous agent[3,5], and displays clinical and pathological heterogeneity inter-individuals and intra-individual pathological homogeneity. This heterogeneity is a consequence of variability in pathological mechanisms, biochemical findings, clinical course, manifestations, and therapeutic response[6]. It is the prototype of idiopathic inflammatory demyelinating disease (IIDD)[7]. IIDD of CNS diseases have included clinical isolated syndromes (CIS); monophasic neuromyelitis optica (NMO); acute disseminated encephalomyelitis (ADEM); unclassified monophasic diseases (until further disease evolution), such as the Marburg variant of MS, and Balo's concentric sclerosis; MS; relapsing NMO; recurrent ADEM, and other unclassified recurrent CNS diseases without dissemination in space[8].

2.0 Epidemiology. **Geographic and Ethnic risk factors**.

The average prevalence of MS in Europe is 50 to 200 cases per 100 000 inhabitants[9,10], the highest ones (188.9/100000) being acknowledged in Sweden as a whole with the highest being recorded at latitude 66º[11]. Thehighest prevalence of the disease is reported in Southwestern Finland, (200-300/100,000)[12].with a geographic area of familial clustering of MS, and with Swedish ancestors[13]; Inthe United States (US), the prevalance ranges from 177 in Olmsted County (Minnesota) to 65 in Weld-Larimer

County (Colorado). In Asia, there are reports which suggest an incidence of 1-2 in China. 8.6-10 in the north of Japan. In Australia the incidence of MS varies from 69 in Otago-Southland to 11 in the north of Queensland[10] . An incidence rate of 72.4, with 73.1, when standardized to European population per 100,000 has been docuemnted in New Zealand [14]. There has been scarce information of MS prevalence in Africa[9,10]. An increasing incidence has been reported in Wales[15], Southwestern[12] and Northern Finland[16], Iran[17] and Canada[18], due to a disproportional increase of incidence among women[12,16] There has been a north-south latitude gradient, in the northern hemisphere, and a south-north latitude gradient, in the southern hemisphere[10]. There have been controversial results regarding age of onset. Some authors estimate this to be 20-40 years of age[2] and others, 35-49, and even 50–64 years, with geographical variations[9]. The female/male ratio ranged from 1.1 to 3.4[9]. In New Zealand, the ratio of females with relapsing remitting (RR) MS / males with primary progressive (PP) MS males has been up to 11[14]. Caucasian populations have been seen to be more frequently affected by MS[10].

3.0 Genetic and Environmental risk factors.

Genetic factors involved in susceptibility to developing MS were reported to be main genetic determinants and lower genetic risk factors or variants[19]. The former were mostly located in the major histocompatibility complex (MHC) region[19]. The latter ones may be either disease- causing or marker variants[19]. MHC class II haplotypes have been related to MS susceptibility, the strongest genetic factor being the HLA-DRB1*15 haplotypes[20]. MHC class II haplotypes have displayed gene products presenting antigens to CD4 +T cells, while MHC class I has presented them to CD8 +T cells[21]. These cells have been reported as the main effectors of the immunological process in

MS[21]. Susceptibility or resistance to MS has been associated with variants in regions of linkage disequilibrium in the genome[19]. Several loci in chromosome 12 have been related to MS susceptibility[22]. Interestingly, the gene encoding the enzyme activating the 25-OHD3 into bioactive 1.25(OH)2D3 (vitamin D3), located in the 12q13-14 region, has been associated with MS[20,22]. Vitamin D3 has displayed a regulatory role in calcium metabolism and a suppressive role in the adaptive immune system. Low levels of vitamin D3 have been related to a greater risk of developing MS[20]. High levels among PwMS have been associated with improved regulatory T-cell function[20]. Environmental factors, such as reduced ultraviolet B exposure, have been reported as a risk factor for HLA alleles population[3,19,23]. Smoking [23] and infectious agents, such as Epstein Barr virus, have also been involved[24]. Acquired defects or epigenetic modifications have become biomarkers of how environmental factors may influence gene expression and may be crucial in linking environment to genetics[19], but the timing and exact role remains unclear.

4.0 Pathophysiology.

MS has displayed both an autoimmune and a neurodegenerative process as mechanisms leading to the disease's development. Within the human adaptive immune system, consisting of a network of regulatory T cells, CD4 +T cells become stimulated, in the periphery[25,26]. Autoreactive CD4 +T cells cross the blood-brain barrier, and migrate into the CNS, there becoming re-activated[26,27]. These T cells' pro-inflammatory products lead to a cascade of complex series of interactions, including infiltration of T-lymphocytes (CD4 +T and CD8 +T), few B lymphocytes and plasma cells, and extensive macrophage/microglial activation[26]. Plasma cells are responsible for production of oligoclonal immunoglobulin within the CNS[28] (See Appendix 1, 2005

Revisions to the "McDonald criteria"). The consequence of this process is the damage of myelin, axons, oligodendrocytes, and the activation of astroglial scarring response[29,30]. As a result of this damage, active/acute pathological lesions in the CNS may occur – acute plaques -, producing demyelination, axonal loss and inflammatory infiltration, to different degrees[29]. Paucity of sodium channels at the Ranvier node has been closely related to the demyelination process, leading to decreased impulse conduction and hyperexcitability [31]. The human adaptive immune system, consisting of a network of regulatory T cells, has been reported as driving these acute inflammatory events, which have been related to relapses[26,32].

The inflammatory process could also lead to reparative processes, by means of neurotrophic factors, whose receptors could be neurons and astrocytes situated in the area of the T-lymphocytes, by remyelination and reorganization of sodium channels along demyelinated axons[32], and by a microenvironment of cells that contribute/inhibit the myelination process[33]. It has been accepted that remyelination requires the proliferation, migration and differentiation of oligodendrocyte precursor cells and the presence of undamaged axons in order to be neuroprotective[29,33]. Remyelination has been referred as a heterogeneous process, since it may occur or not among PwMS[33]. These pathological lesions may be clinically silent.

The innate immune system, consisting of monocytes, dendritic cells, and microglia, has been reported as promoting progressive features of MS, such as axonal loss[26]. The subacute/chronic plaque contains a gliotic core surrounded by inflammatory periphery, including demyelination, not excluding remyelination, axonal pathology and oligodendrocytes loss[26,29]. This chronic plaque has been considered as a neurodegenerative feature, and closely related to the disease's progression. Decreased brain volume or atrophy was considered a marker of tissue loss, although its correlation with disability has not always been strong[34].

During relapses, inflammation in white matter is common. In progressive stages, chronic diffuse neurodegenerative features were common, involving cortex, and *normal-appearing white matter*, with perivascular and parenchymal infiltrates, and especially primary and Wallerian axonal loss being predominant, as well as a decrease in inflammatory lesions[29,32]. These neurodegenerative features were not present during relapses[32].

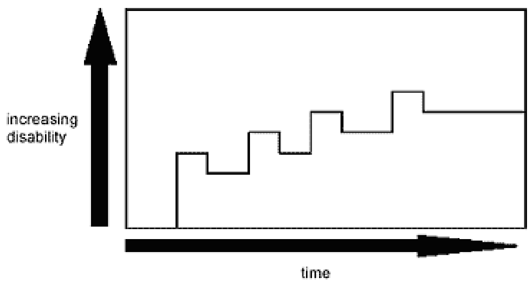
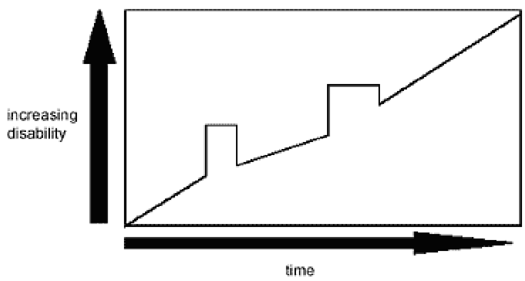
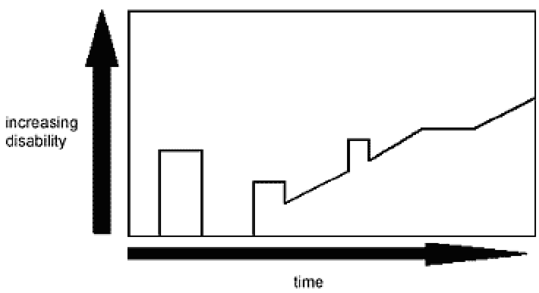
In contrast to patients with secondary progressive (SP) MS, those with PP MS type had fewer perivascular cuffs, decreased parenchymal cellularity, relative reduction in T- and B-cell infiltrates[35,36], and proportionally a higher axonal loss[37], leading to a paucity of active lesions, and to an expansion of chronic lesions[38].

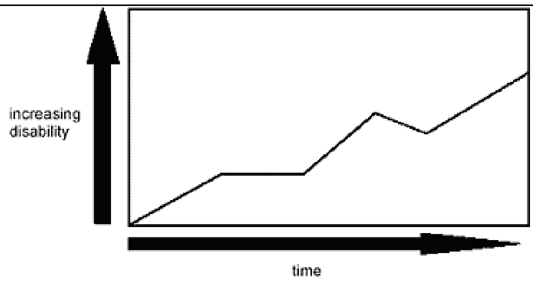
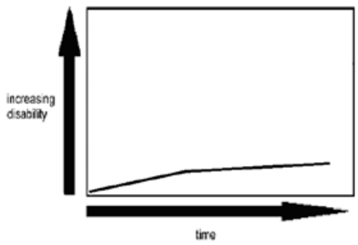
Pathological heterogeneity has an impact on the different response to the pharmacological treatment available among people with MS (PwMS). The underlying mechanisms could be different effector pathways developing the demyelinated plaque among PwMS[32]. It has been suggested that each individual would present a single effector pathway[32]. However, other authors have suggested that these pathways could be the expression of different stages within the same individual[39]. The importance of effector pathways was related to the possibility of stratification of PwMS for therapy tailoring.

5.0 Types of clinical course

Types of clinical course are defined as RR MS, SP MS, PP MS and progressive-relapsing (PR MS), and benign MS (B MS). Exclusion of PR MS has been also considered[40]. There is controversy regarding B MS definition. It has been described either an MS type maintaining Expanded Disability Status Scale (EDSS) scores lower than 3.0[41,42] or even lower than 1.5[43], over at least 10 to 15 years[41,42]. In natural history studies, there are 80-87.6%[44]-[45] of patients with RR MS. From the RR MS, 25 % of patients entered SP MS after 5 years [44], and 50-58.2[44-46] %, at 10-20[44-46] years respectively from onset[44], increasing with time[46], while 7 % showed no conversion to SP MS[44]; 12.4-14[44]-[45]% were PP MS[45]. These types have been categorized based on clinical description of relapse presentation and/or progression[47]. Although underlying pathophysiological mechanisms are reported in this categorization[48], this remains uncertain[49]. The PR MS phenotype has been reported as a PP MS which has included relapsing episodes. PP MS has been postulated to be an SP MS with the initial RR phase amputated [50]. Khaleeli[51] (2010) has supported this observation, showing that there was gadolinium-enhancing lesion in a group of patients with early PP MS, and that this lesion decreased throughout the course of the disease. The types of clinical course are described in Table 1.

Table 1. Type of clinical course

TYPE OF CLINICAL COURSE		
TYPE	CLINICAL FEATURES	CLINICAL COURSE
RR MS	Disease with relapses and full recovery, or sequelae upon recovery. Periods between relapses did not show progression. > 55 % of PwMS. Around 50 % of this group developed SP MS. Women/men: 2:1[52]	RELAPSING-REMITTING 
PR MS	Progressive disease from onset, superimposed relapses, with or without full recovery; periods between relapses with continuing progression. 5 % of the PwMS[52]	PROGRESSIVE-RELAPSING 
SP MS	Initial RR course followed by progression with or without occasional relapses, minor remissions and plateaus. 30 % of PwMS[52]	SECONDARY-PROGRESSIVE 
PP MS	Disease with progression from onset with plateaus and temporary	PRIMARY-PROGRESSIVE

	minor improvements. 10 % of PwMS. Progression related to later age of onset ; more sequelae after first relapse; shorter period of time between first and second relapse[52] More frequent in men[53].	
B MS	Fully ambulatory, moderate disability in one body function or body structure, and minimal disability in three to four others[43], less fatigue[42] and cognitive impairment[43], staying in work longer, better physical HRQoL than other PwMS[42,43], but may transit to more severe MS types[42].	BENIGN 

Source: adapted from MS Society of Canada[54]

6.0 Course of the disease

Recent studies on natural history on MS report that from an MS sample, 45 % PwMS had reached EDSS 3; 18 %, EDSS 6; and 3.5 %, EDSS 8[55]. PwMS reached EDSS 6 after an average of 27.9 years from onset[55]. A range between 21 % and 69 % of PwMS required a cane between 15 and 40 years after onset, respectively[55]. There are also reports that a range between 28 to 52 % of PwMS required a cane at a range of 50 to 60 years of age, respectively[55]. These data suggested a slower disability accruement than the data from former longitudinal studies[55].

Several authors agree that RR MS involves two phases in the course of the disease: an early phase from the onset of the disease to the onset of irreversible disability status 3[56] or 4[48] or 6[45]; and a second phase, from the onset of irreversible disability status 3 to irreversible disability status 6[56] or disability status 6[45]. The early phase is coincident with RR phase, while the second phase develops mainly during the progressive phase of the disease[48]. Thereare controversial results regarding the impact of the early phase on disability. Relapses in the first 2[57]-5[45] years after onset of the disease may have no impact on disability progression[48,49] or may influence it[45,56,57], in the short term, but not in the long term[45]. There is general agreement that disease progression and disability progression are correlated[48,49,56].

The pathophysiological mechanisms underlying the relationship between early and second phase are uncertain[49]. Disease course[49] and progression of disability are not different among individuals with RR and PP MS, once those with RR MS reached SP MS, and thus a clinical threshold of irreversible disability [48,56]. Clinical features of progression included sensory-motor symptoms predominantly in the lower limbs[44]

7.0. Factors that influence prognosis

Factors that influence prognosis of the disease and disability progression are shown in Table 2.

Table 2. Factors that influence prognosis of disease and disability progression.

PROGNOSTIC FACTORS			
TYPE OF CLINICAL COURSE			
RR MS		PP MS	
Favorable factors	**Unfavorable factors**	**Favorable factors**	**Unfavorable factors**
Low rate of relapses per year[48,56]	High rate of relapses per year[48,56]	One CNS system involved at onset[50]	More than three CNS systems involved at onset[50]
Complete recovery from the first attack[48,56]	Incomplete recovery from the first attack[48,56]	Longer than 2 years to reach DSS 3[50]	Less than 2 years to reach DSS 3[50]
Greater length of the first inter-relapse interval[57]	Shorter length of the first inter-relapse interval[57]		
Younger age at onset[48,56]	Older age at onset[48,56]		Controversial results in age at onset[50,55]
Females[48,56]	Males[48,56]		Controversial results in gender[50,55]
Later cerebellar involvement[57]	Early cerebellar and brain stem involvement [55,57]		
	Pregnancy related to relapses after delivery[58]		
No comorbidity of musculoskeletal system[59]	Comorbidity of musculoskeletal system[59]	No comorbidity of musculoskeletal system[59]	Comorbidity of musculoskeletal system[59]

	Injurious fall[60]		Injurious falls[60]

8.0 Life expectancy

Life expectancy for MS populations has been reported as ranging from 24.5[50] to 41[61] years from onset. The overall mortality rate is 2.47[62], and was found to rise significantly at 2-9.99 years and over 10 years from onset[63]. Smestad[62] (2009) reported that the significant excess of mortality occurred during the second decade after onset. Median survival time was 45 years among PwMS of a younger age at onset of the disease (21-30 years) versus 23 years among people older at onset (51-60 years)[61]. However, standardized mortality ratesare higher among patients with younger onset of disease than among those with older age of onset, perhaps related to the low risk of dying among young people without MS[61], and reflecting reduction in life expectancy. Regarding gender, the median survival time was longer for women than men[61]. However, women have shown a higher risk of dying than men, in line with their higher standardized mortality rates[61,63], reflecting a greater reduction in life expectancy than the comparative population and than men[62]. The median survival time was 43 years for patients with RR MS[61], and 22[50] to 26[61] years for those with PP MS. The standardized mortality rates were 2.57 for patients with RR MS and 2.99 for those with PP MS[61]. These data were correlated to no significant difference in mean age at death between patients with RR MS and those with PP MS [62]. It is reported that the most frequent immediate cause of death was MS, and infections were the most frequent contributory one. Respiratory infections were the most frequent contributory causes, followed by urinary infections and infections due to decubitus ulcers[62]. Suicide rate was found to be twice that of the corresponding population, and its rate reached its peak shortly after diagnosis[61], being significantly higher among females[62]. No significant differences in cause of death were reported regarding gender and the type of MS[62].

9.0 Diagnosis of Multiple Sclerosis.

Diagnosis followed McDonald's criteria[64] which was modified later[4]. Dissemination in space and time were *sine qua non* criteria for MS diagnosis[4]. Both criteria are included in the Appendix. Consensus-based **differential diagnosis criteria** were recommended by an International Panel of MS Experts[8]. These criteria were based on the recognition of the different diseases included in IIDD, excluding non-demyelinating syndromes, and non-inflammatory demyelinating diseases[65]. The exclusion of these other diseases, through an algorithm, would lead to the MS diagnosis, provided McDonald's criteria were met[65]. Formerly, Poser criteria had been extensively used. These criteria were based on clinical and paraclinical data, including evoked potentials (EP) and cerebrospinal fluid (CSF), excluding Magnetic Resonance Imaging (MRI) data; requiring dissemination in time but not in space to categorize an individual patient as presenting a probable or a definite MS diagnosis[10]. Epidemiological studies have often referred to Poser criteria due to retrospective methods of patients' inclusion[10].

9.1 Conventional MRI based Diagnosis.

Conventional MRI has been a relevant biomarker for individuals suspected of MS[66,67]. Recommendations and guidelines of MRI appliances for definite MS diagnosis were published by the Consortium of MS Centers (CMSC) Consensus Guidelines[68]. These recommendations could be helpful in discriminating MS from other IIDD. Swanton (2006)[69] proposed new conventional MRI-based criteria, in which dissemination in space would require at least one T_2 lesion in at least two of four locations (juxtacortical, periventricular, infratentorial, and spinal cord), and dissemination in time, such as a new T_2 lesion on a follow-up scan. These new criteria proved to be more sensitive and accurate than the conventional MRI McDonald's criteria reviewed [69]. Fluid-attenuated inversion-recovery (FLAIR) sequences improved sensitivity in detecting supratentorial lesions, especially when found in a juxtacortical location[34]. Conventional MRI has proven to be useful in reflecting white matter lesions, while non-conventional MRI perfusion applying arterial spin tagging methods and magnetization transfer ratio could be useful for detecting normal-appearing white matter and gray matter abnormalities[34]. Magnetization transfer ratio could be also useful to reflect spinal cord abnormalities[34].

Conventional MRI gadolinium-enhancement on T_1 and T_2 –weighted sequences was considered a measure of the blood-brain barrier break[34], although limits in specificity and sensitiveness were reported[34,51]. Gadolinium-enhancing lesions were seen mostly among individuals with RR MS, may reflect inflammation and have displayed a poor correlation to irreversible disability[51]. These lesions were also detected in some patients with early PP MS, diminishing over the long-term course of the disease, and absent in most of this latter population[51].

Reversible T_2 lesions might reflect inflammation, edema, demyelination, and axonal loss, in the acute phase, lacking pathological specificity[34,70]. These T_2 lesions could be found in patients with RR MS[34].

Reliable imaging measures distinguishing demyelination from remyelination have not yet been defined, although it has been pointed out that magnetization transfer ratio could be useful to monitor remyelination[34], and that loss of a short T_2 component from a multiecho T_2 decay sequence could express demyelination[34].

T_2 lesions exhibiting T_1 hypointensity were considered as a surrogate of axonal loss[34]. They were frequently detected in supratentorial regions, with reduced correlation to disability, while the ones found in infratentorial areas and spinal cord correlated with disability[34,71]. The last type were reported as being infrequently found, but technological development could improve their detection[71]. Magnetization transfer ratio could be useful to reflect normal-appearing white and gray matter and spinal cord abnormalities[34].

Most of the authors found that conventional MRI correlated poorly with disability progression[6,34,57,72]. T_2 lesion load was however found to correlate to higher overall disease severity[73], and specifically cognitive deterioration[74], and to a moderate degree to disability progression in earlier stages[70] on relapse onset[34]. There were controversial results as regards whether MRI T_2 lesion load displayed a plateauing relationship with disability for EDSS scores above 4.5[75] or not[70].

9,2 Non-conventional MRI based diagnosis .

Non-Conventinal MRI included perfusion MRI and functional MRI. Functional MRI has helped to investigate task-related brain activation and cognitive functioning, being useful to demonstrate treatment –induced neuroplasticity by means of activation of brain areas in cognitive-impaired PwMS[76].

9.3 Evoked Potentials.

Evoked Potentials (EP) are electrical potentials recorded from the nervous system elicited by a specific stimulus. The term EP has been reserved for responses from the CNS. There are broadly two types of EP: sensory and motor-evoked potentials. Sensory evoked potentials are brain or spinal cord responses to sensory stimuli – visual, auditory, somatosensorial stimuli77 that have been useful to detect slow nerve conduction in various sensory axons. Motor EP are produced by stimulating the motor cortex using transcranial electrical stimulation or, more commonly, transcranial magnetic stimulation77. This is a technique that allows assessment of the length and function of the corticospinal tract77. Both sensory and motor EP are multimodal EP78. EP are not specific for MS diagnosis77. Visual EP were included in McDonald's diagnostic criteria, for the PPMS diagnosis, together with MRI data4. Specific somatosensory and motor EP and multimodal EP were reported to be correlated with disability progression and disease severity measured with EDSS on patients with progressive MS type78. It was advocated that EP could be synergistically used with MRI for enhancing the pathological diagnosis and disability progression78.

Aim

The aim of the study was to describe the usefulness of International Classification of Functioning, Disability and Health (ICF) and several outcome measures (OM) to gauge PwMS' health problems and impact on HRQoL and QoL; to detect PwMS' perceived body function, body structure, activities and participation problems, needs arising for PwMS; the main body function and body structure impairment that may occur in PwMS; the impact of body function and body structure impairment on activities, participation and QoL of PwMS; and of being a significant other or a caregiver of a PwMS.

Literature Search

A literature search using multiple literature databases (CINHAL, Cochrane Library, Current Contents, EMBASE, MEDLINE, PEDro, PsycINFO, OT seeker) was conducted. Besides this, a manual search was performed in relevant journals, such as *Multiple Sclerosis*, connected with the main topic and with Rehabilitation (RHB). The search was limited to articles, including items in electronic format, chapters of books, and webpages of MS organizations available in English, from January 1995 to June 2011. The search was undertaken using *MS* as main keywords, and combined with other keywords, such as *RHB, disability, QoL, caregiver,* and different body function and body structure impairment, and related terms. The development of each heading was structured into an introduction, aim and results. A summary of the results was given. In the *Body function and body structure impairment* heading, there was a common introduction and aim, but results and summary were described under each subheading. ICF categories have been added as sideheadings in the *Body function and* *body structure impairment* heading. *Refworks* was used as reference management to index and cite the references in the text.

Results

I. International Classification of Functioning, Disability and Health and outcome measures in MS:

Introduction

ICF is a classification of human functioning and disability[79], a generally accepted framework for describing disability and functioning in RHB[80]. QoL is not covered in this classification[81]. ICF systematically groups health and health-related domains. Within each component, domains are further grouped according to their common characteristics (such as their origin, type, or similarity) and ordered in a meaningful way[79]. OMs were considered instruments for measuring health situations; for setting goals, and measuring the extent to which goals were attained; and for evaluating interventions' effect or the result of the natural history of the disease[82,83]. OMs should meet the classical psychometric requirements of reliability, validity and responsiveness[81]. The demonstration of reliability can be sufficient to ensure the usefulness of an instrument for a discriminative purpose, and validity, for a predictive one, while the responsiveness to changes is required for evaluative purposes[84]. A selected instrument should be appropriate for a specific purpose, sensitive for the target, acceptable for the respondent, feasible for the evaluator, available in the evaluator's milieu, and cross-culture adapted[84]. Generic OMs provide a broad picture of health status across a range of conditions. Specific OMs are more specific for the disorder under consideration and are therefore expected to be more responsive[84].

Goal setting (GS) should be specific, measurable, achievable, realistic and timed (SMART)[83], and within a goal-oriented program[85].

For formal testing of an OM, Rasch analysis – a mathematical measurement model – would be applied[86]. Its usefulness has included reviewing the psychometric properties of existing ordinal scales, and converting ordinal scores to interval level measures. A practical consequence of its appliance would be that in a given OM, whenever harder tasks were affirmed, there would be greater probability that easier tasks would also be affirmed[86].

The following OM were included in this heading: Fatigue Impact Scale (FIS), Modified FIS (MFIS), Fatigue Severity Scale (FSS), modified Aschworth Scale (MAS), timed 10-meter walk test (10-m walk test), 6-minute walk test (6-MWT), Rao's Brief Repeatable Battery (RBRB), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS) , Goal Attainment Scaling (GAS), EDSS, Guy's Neurological Disability Scale (GNDS), MS Impact Profile (MSIP), Extended Barthel Index (E-BI), Functional Independence Measure (FIM), Rivermead Mobility Index (RMI), Functional Status Questionnaire (FSQ), MS Severity Scale (MSSS), MSQoL-54 Instrument (MSQoL-54), MS Impact Scale (MSIS), Short Form-36 (SF-36), and General Health Questionnaire-28.

Aim

The aim was to describe the usefulness of ICF and several scientifically sound and frequently reported goal setting, impairment, disability, activities, and health-related QoL (HRQoL) OM to measure PwMS' health problems and impact on QoL.

Results

Several ICF domains have been considered of special relevance regarding MS, in body function component , such as musculoskeletal functions and movement, urination and sexual functions, sensorial functions and pain, mental function, speech functions by a panel of experts[87]. In body structure component and related to MS, other domains proved to be relevant, such as structure of the nervous system, movement, urinary and reproductive systems[87]. The domains most commonly related to MS, regarding activities and participation, were interpersonal relationships, principal areas of life, community life. The most relevant environmental factor domains in MS were support and relationships, and natural environment[87]. Some empirical studies provided information about functioning, disability and environmental factors in MS, using ICF as a framework[87-90]. Other studies have used different disability OM to measure domains of the different ICF components[91,92].

Specific body function and body structure impairment OMs have been referred to in Table 3.

Table 3.Specific body function and body structure impairment OMs.

NAME	BODY FUNCTION AND BODY STRUCTURE IMPAIRMENT	MAIN FEATURES	CLINICAL USEFULNESS
FIS	Fatigue	Specific OM. Responsive. Recommended by MS Council for Clinical Practice Guidelines (MSCCPG) [93].	To evaluate the perceived impact of fatigue on the lives of PwMS[94].
MFIS	Fatigue	Generic OM. Self-administered questionnaire. 21 items in 3 subscales (physical, cognitive, psychosocial) [95].	Focuses on physical and mental fatigue[96], and psychosocial features.
FSS	Fatigue	Generic OM. Reliable, valid, responsive OM[53,97]..	Has a physical focus[96]. Useful to assess peripheral fatigue[53,97].
MAS	Spasticity	Generic OM. Gold standard for spasticity. To assess the increase in velocity-dependent tonic stretch reflexes[83].	Reasonable measure for the assessment of spasticity[98].
10-m walk test velocities at normal and maximal	Gait velocity	Generic OM. Time needed to walk a 10-m distance, at the individual's own speed, and at maximum individual speed[99,100].	Responsiveness to deterioration of gait from both PwMS and clinicians' perspectives[99].

speeds			
6MWT distance	Distance walked	Generic OM. Distance covered during 6-minute walking[99,100].	Responsiveness to deterioration of gait from both PwMS and clinicians' perspectives[99].
RBRB	Neuropsychological impairment	Generic neuropsychological test battery. Sensitivity is 70 % and reliability, 94 %[95]. To assess verbal and visual memory acquisition and delayed recall, attention, concentration, and speed of information processing[95,101].	Detects real modification in cognitive functioning[101].
BDI	Depressive disorders	Generic OM. 21 item self-assessment OM. Recommended by Goldman Consensus Group (GCG), with a cut off score of 13[102].	To assess depressive disorders in outpatient settings[102].
HADS	Anxiety and depressive disorders	Generic OM. Reliable and valid OM. Self-assessment OM[103,104].	To assess anxiety and depressive disorders in non-psychiatric outpatient settings[104].

GAS, generic and specific impairment, disability, activities, participation, and HRQoL OMs, with information about its psychometric properties and clinical usefulness have been referred to in Table 4.

Table 4. GAS, impairment, disability, activities, disease severity, and HRQoL OM

NAME	MAIN FEATURES	CLINICAL USEFULNESS
GAS	Generic OM. Reliable, valid, responsive [105,106]	To evaluate changes after RHB intervention, in different types of goals [107].
EDSS	Specific, has discriminative validity, lack of homogeneity (impairment and disability OM). Sub-optimal inter-observer reproducibility, and responsiveness [89,108]. Gold standard for MS[103]. Levels: EDSS 0-1.5 (no dis); 2-3.5 (mild dis); 4-6.5 (moderate dis); > 6.5 (severe).	To assess limitations in neurological body function and related disability; and to assess in physical domains of SF-36[103].
GNDS	Specific disability OM. Reliable, valid, responsive[109-112]	To assess activity domain. High correlation with other OM[111].
MSIP	Specific disability OM. Reliable, ICF-based OM[90,113].	To assess body function, activity, participation, environmental factors, components of QoL[90,113].
E-BI	Generic disability OM. 10-item system, to score what the patient can do. Sensitive for PwMS hospitalized for RHB[95]. Ceiling effect for PwMS with moderate disability[97].	To assess functional status in ADL performance.
FIM	Generic disability OM. 18 rating items, each with a 7-point scoring system based on the type and amount of assistance required for basic life activities. Reliable, valid OM in MS studies[114].	To assess functional status in ADL performance[92] and to select treatments and care venues, for payment, for estimating burden of care, and for research[115]
RMI	Generic disability OM. 15 rating items.	To assess personal care activities and

	Reliable, valid, sensitive to changes in a rehabilitation setting over time, rapid and simple to use in the patient's environment[116]	mobility[116].
FSQ	Generic activities OM. Self-administered questionnaire designed to assess physical, psychological, social and role function in ambulatory patients[88,89]	To assess ADL performance, link to ICF's activities and participation domains[88], and responsiveness to deterioration[89].
MSSS	Specific disease severity OM[117,118].	Prediction of disease severity over time, and impact of immunomodulatory drugs[117,118].
MS QoL-54	Specific HRQoL 54-item, adapted from SF-36[119], including 18 items considered as important QoL factors for PwMS. Reliable and valid[95].	To assess physical, emotional health, pain, vitality, health self-perception, social role, cognitive, sexual function[119].
MSIS	Specific HRQoL. Reliable, valid and responsive[112,120].	To assess physical and mental impact of MS[83,121].
SF-36	Generic HRQoL, 36-item survey. Reliable, valid[104].	To assess physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health[97].
GHQ-28	Generic HRQoL OM Responsive to RHB intervention in PwMS [85].	To assess somatic symptoms, anxiety, social dysfunction, and severe depressive disorders [85].

Other specific and generic OMs have not been included, in view of the vast number of these[83,100], and the aim of this paper.

Summary

ICF is a promising framework for the assessment, rehabilitative and evaluation outcomes of PwMS. GAS has been seen to be effective at monitoring goal achievement. The following impairment, disability, activities, participation, and HRQoL OMs have proven to be useful assessment tools: EDSS is the goal standard for impairment and disability assessment in MS, and has been referred to in clinical trials, despite its poor responsiveness to interventions; GNDS for body function domains has been seen to have a high correlation with other OM; MSIP for body function, activity, participation, environmental factors, and components of QoL; E-BI for functional status in ADL performance; FIM for functional status in ADL performance, and selecting treatments and care venues, for payment, for estimating burden of care, and for research; RMI for personal care activities and mobility; FSQ for ADL performance and linking to ICF's activities and participation domains, and responsive to deterioration; MSSS for prediction of disease severity over time, and impact of immunomodulatory drugs; MSQoL-54 for physical, emotional health, pain, vitality, health self-perception, social role, cognitive and sexual component of HRQoL; MSIS for physical and mental impact of MS; SF-36 for physical and mental health and social functioning; GHQ-28 for anxiety, insomnia, social dysfunction, and depressive disorders. The following OM to assess body function and structure domains have proven to be useful assessment tools: FIS for impact on activities of daily living (ADL) and QoL, recommended by the MSCCPG; MFIS for physical, mental, and psychosocial features; FSS for physical fatigue; MAS is considered the gold standard for spasticity, but with sub- optimal responsiveness; 10-m walk test and 6MWT distance have been useful for assessing deterioration of gait from both the patient and the examiner; RBRB for cognitive functioning; BDI for depressive disorders at outpatient settings, recommended by the

GCG, and HADS for depressive disorders and anxiety at non-psychiatric outpatient settings.

II. Patients' perceptions about their problems and needs

Introduction

There has been no full agreement on GS between PwMS and the interdisciplinary RHB team[122], reflecting some discrepancy of perceptions of problems and needs. It therefore seemed of interest to seek the patients' perceptions of problems and needs. PwMS' perceived needs may lead to prioritize interventions' goals, in order to recover function. Different levels of disability have displayed different prioritization of goals, expressing response shift[123,124]. PwMS establishing goals' hierarchy may be the step prior to GS.

Aim detect PwMS' perceived body function, body structure, activities and participation problems, needs arising for PwMS, and their view of recovery.

Results

PwMS found different problems and needs, depending on their disability level. Heesen[125] (2008) reported that PwMS, stratified according to the United Kingdom (UK) Disability Scale, found that walking, visual function and speech had the highest scores in early stages, while long-term disease sufferers referred to visual function, walking and cognition as of higher relevance. PwMS with more functional limitations had a higher perception of risk of wheelchair-dependency, but a lower perception of seriousness, regarding lifetime risks[126]. Stineman[123] (2008) reported that PwMS referred to independence in bowel, bladder and eating functions as being more relevant while being hospitalized and acutely disabled, in a PwMS sample stratified according to FIM. People with long-term disabilities scored higher for cognition and communication[123].

PwMS perceived receiving medical treatment as being important to meet their needs especially in the minimal disease impact group; among the moderate-severe disease impact group, obtaining socio-environmental support; enhanced care was similarly relevant for all the groups; information provision was identified as a strong need in the minimal and mild disease impact groups (See *Comprehensive information for PwMS, significant others and caregivers*); paramedical RHB packages of comprehensive care components, especially physiotherapy (Ph), and non-professional care were closely correlated with the moderate and severe disease impact group[127]. The sample was stratified according to MSIS 29[127].

In a research study with a Swedish cohort, Ytterberg[128] (2008) reported results that were in concordance with those of Forbes'[127] (2007). Most of the patients preferred an earlier medical diagnosis, and were less satisfied with psychologists, especially with regard to information, accessibility and availability[128]. They were also not satisfied with accessibility to physicians, and to information on social insurance/vocational rehabilitation (VR). PwMS as a whole reported the need and were satisfied with the accessibility to nurses and occupational therapists. There were controversial results regarding accessibility to physiotherapists. While there was agreement about the need of these professionals[127,128], especially among moderate and severe disease impact groups[127], there were controversial results regarding the accessibility to them. Forbes[127] (2007) reported unmet needs, while Ytterberg[128] (2008) found that most of PwMS were satisfied with the availability and accessibility to physiotherapists. Information needs were reported in an early post diagnosis PwMS sample, regarding optic neuritis, education sessions and sources of reliable information among general practitioners, ophthalmologists and neurologists[129].

Summary

Walking and visual limitations were frequent problems in the early stage and long term, while cognition became a problem in the long term. PwMS in earlier stages have reported physical disability, disease-related distress and anxiety as more relevant, while those at later stages have highlighted cognitive and communication problems. Problems of continence and eating were relevant during acute disability. Accessibility to medical assistance was not at the perceived best level, and neither was the information on social insurance/VR. Psychologists were claimed to offer less information, and be less available and accessible. The perception about the need for nurses and occupational therapists was good. The perception of availability and accessibility to physiotherapists was controversial, which could be due to different accessibility among different geographical areas. Further information on visual impairment, need for education sessions and information from physicians was perceived.

III. Body function and body structure impairment

Introduction

MS lesion can be present in multiple sites throughout the CNS, affecting different body functions and body structures, depending on the size, intensity and location of neurological lesions. Some conceptual definitions in the literature concerning the impairment are provided.

Fatigue is referred to as a subjective lack of physical and/or mental energy that was perceived by the individual as interfering with their usual or desired activities[130]. There is a lack of universal definition of fatigue.

Muscle weakness has been referred to as a lack of muscle strength[131]. Muscle strength has also been referred to as a component of physical fitness.

Decreased tolerance to exercise and cardiovascular (CV) and respiratory (Resp) dysfunction are constructs connected with body function and structures' adaptation to exercise. CV endurance, body composition, muscular strength, muscular endurance, and flexibility have been included as physical fitness components[132]. CV endurance is the ability of the circulatory and Resp system to supply oxygen during sustained physical activity[132] and has been expressed as maximal aerobic capacity[133]. **Assessment**. Tolerance to exercise has been reflected in heart rate and Borg rating of perceived exertion[134,135]. Maximal aerobic capacity's metrics were maximal oxygen consumption (VO_2 max). Muscular strength's relevant parameters were isokinetic and isometric strength.[136]

Sensory disorders assessment referred to quantitative sensory examination which

included tactile, cold and heat detection, and vibration perception threshold[136].

Pain syndromes (PS) in MS could be distributed as acute and chronic ones[137]. Chronic PS in MS could be classified into three broad categories, as in other chronic pain conditions: neuropathic pain (NP); nociceptive or non-neuropathic pain (NNP); and mixed pain (coexistence of both types of pain)[138]. NP has been defined as a direct consequence of a lesion or disease affecting the somatosensory system[139]. NP could be of central or peripheral origin[140]. PS were described as 1. Trigeminal neuralgia (TN) and other paroxysmal pain, such as Lhermitte´s sign (LS) (acute NP)[137]; 2. Dysaesthesic limb pain or burning pain, as NP; 3. Optic neuritis (acute NP[137]); 4. Peripheral pain, that could be directly related to MS or from another origin, as NP; 5. Painful tonic spasms and painful spasms due to spasticity, as NNP; 6. Myalgias and flu-like syndrome related to Immunomodulatory agents, as NNP; 7. Back pain with or without sciatica, due to immobilization or to disk degeneration pathology, as NNP, mixed pain; 8. Other musculoskeletal pain, such as arthralgias, neck and shoulder pain, as NNP; 9. Osteoporosis, as NNP; 10. Pain due to pressure lesions; 11. Headache, as NNP[141,142]. The clinical characteristics of some of these syndromes were as follows: Lhermitte´s sign was described 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[143]; dysaesthesic limb pain or burning pain, as a continuous burning pain, affecting both legs and feet, usually worse at night and that can be exacerbated by physical activity[143]; painful tonic spasms, as spasms that occur several times per day, last less than 2 minutes each, can be preceded by somesthesic aura and triggered by touch, movement, hyperventilation, or emotions; headaches were migraine type.

Spasticity is one symptom and positive sign of upper motor neuron syndrome (**UMNS)**[144], characterized by increased resistance of muscle to external stretch, depending on the velocity of muscle stretch[145]. This has been clinically manifested by increased tonic muscle activity, exaggerated deep tendon reflexes, spread of activity to distant segments, and clonus with sustained stretch[145]. Other positive signs of UMNS have been reported such as co-contraction, associated reactions, spastic dystonia, and increased muscle stiffness[144]. As negative UMNS signs, weakness, loss of dexterity, mainly in fingers, and loss of selective control of limb movement have been described[144].

The concept of **ataxia** has included various abnormalities in balance and in postural control (PC) and in the execution of movement, leading to incoordination, dysmetria, dysdiadochokinesis and tremor[146]. Tremor has been defined as rhythmic, involuntary oscillatory movement of a body part[147], this being an action type among PwMS[148]. Assessment has used OM, such as the Fahn-Tolosa-Marin rating scale, and motion transducers, and more recently mathematical methods to combine both tools[149].

Postural control disorders (PCD) and compensating strategies could be evaluated by means of postural OM, instrumental assessment, such as steady standing[150] and sitting[151]; changing posture[151]; and compensating strategies under self-generated and external perturbations[150]. Reported assessment tools were posturography or stabilometry[152], somatosensory EP[153], and functional tests[150]. Vestibular and somatosensory afferent impairment could be analyzed by means of posturography. For this purpose, the individual was assessed in upright/sitting position, with eyes open/closed, in different timing, base of support and stance positions[150,154]. Balance and postural strategies using self-generated perturbations tests included (Functional Reach Test, Arm Raise test, and Step Test)[150]. Balance and postural strategies using external perturbations could be assessed provoking an external tug to PwMS (Shoulder tug test)[150].Assessment could allow the most affected afferent/ efferent system and the expected compensating available strategies to be detected.

Qualitative gait assessment included **walking tests**, such as the 25-Foot Walk Test[155], 2- and 6-MWT[156], 10-m walk test[157]; **self-report indices**, such as Activities and Participation Questionnaire Agreement[158] and MS Walking Scale[156]. **Quantitative**

assessment included **accelerometer**-based technology (ABT)[158], **motion analysis** (MA) and **dynamic electromyography** (DEMG). Gait parameters obtained with ABT were reported as number of strides over continuous time-intervals[158]. MA allowed kinetic and kinematic parameters to be obtained. **Kinetics** included joint moment and ground reaction forces; **kinematics** included **time-distance parameters**, such as gait speed, stride length, cadence, double support time[159]; and the study of **range of motion** of hip, knee and ankle[160]. DEMG assessed electrical muscle activity[161,162]. ABT was useful for gait assessment at the individual habitual setting, and allowed habitual walking performance to be assessed[156,158]. MA and DEMG required a controlled setting with dynamometric platforms[161], for kinetics, a video-based three-dimensional motion measurement system with a bony landmark system, for kinematics[163], and a dynamic polyelectromyographic system for DEMG. ABT may contribute to real-life walking impairment assessment[156], while MA and DEMG were useful to evaluate gait disorders (GD), even in PwMS with EDSS lower than 2.5[157], progression of disability, compensating mechanisms, and modifications after therapeutic interventions[161,162,164]

Visual field assessment has included standard automated perimetry to monitor recurrence and progression of the visual impairment[165] and visual function tests, such as high contrast visual acuity measured by Snellen charts and low contrast letter acuity[166].

Pelvic floor muscle (PFM) dysfunction has included bladder, bowel, and sexual dysfunction due to muscle dysfunction. The function of the PFM may be impaired in PwMS[167], and this impairment has been a factor related to urinary and fecal continence problems and sexual dysfunction[167], among both genders of PwMS, especially in women. Clinical assessment of PFM has included visual inspection, digital palpation, specific maneuvers, electromyography (EMG), pressure measurements and imaging[168].

EMG biofeedback measures muscle contraction and provides information on relaxation and contraction phases[169].

Neurogenic lower urinary tract dysfunction (NLUTD) could be manifested as irritative, obstructive and mixed symptoms. Irritative symptoms or overactive bladder syndromes (OAB) included urgency, increased urinary frequency (including nocturia) and/or urge incontinence[170], expressing problems of storage[171]. Obstructive syndromes (OS) could be hesitancy of micturition (more common in male), increased micturition frequency and overflow incontinence, expressing problems of voiding[172]. Mixed syndromes included urgency, hesitancy, interrupted or poor stream, and double voiding, increased micturition frequency and overflow incontinence[170,171], expressing storing and voiding problems[171]. Urodynamic tests and studies (URO) were considered important to document NLUTD's cystomanometric patterns[172], postvoidal residual urine and vesicourethral reflux[173]. The European Association of Urology adopted the Madersbacher classification system to categorize NLUTD's cystomanometric patterns[172]. Different levels of detrusor hyperrreflexia combined with different levels of dyssinergic urethral sphincter closure and activity led to NLUTD categorization. This one included OAB, underactive bladder and different bladder/sphincter dyssinergia leading to different levels of OS [170]. Assessment of urinary incontinence (UI) included the 24-hour pad test, which provides information on urine leakage, and a day-to-day bladder diary to record urine leakage[174,175].

Neurogenic bowel dysfunction (NBD) assessment included digital rectal palpation and echography for evaluating rectal pathology; anorectal manometry for sensory perception threshold and internal and external anal sphincter contraction[176].

Sexual dysfunction included organic and psychogenic causes of desire, arousal, and orgasm in both gender, sexual pain disorders in women[177], and erectile dysfunction in men.

Sexual dysfunction could be classified as primary, secondary and tertiary[178]. Primary sexual dysfunction was referred to CNS disorders due to the disease; secondary sexual dysfunction was related to interfering MS symptoms or impairment; tertiary sexual dysfunction, to non-organic interfering factors[178].

The main **autonomic dysfunction (**AD**)** features in MS have been related to CV system and body temperature. The most frequent impairment was cardiac arrhythmia, orthostatic intolerance, and intolerance to heat[179,180]. A slow rise in heart rate at the start of a dynamic exercise protocol (or attenuated heart answer) in PwMS has been reported as a consequence of CV AD[181]. The **diagnostic procedures** for CV AD were made up of several tests that included the heart rate response and blood pressure modifications to deep breathing, Valsalva maneuver, passive tilt-up test, and sustained hand-grip[180].

Neuropsychological (NeuroPsy) or cognitive impairment included at least one of these areas: memory, attention, processing speed, visuospatial abilities and executive functions[82,141]. The most frequent NeuroPsy battery used in PwMS has been reported to be the RBRB, which has shown to be a reliable, practical tool that has detected variability from real modification in cognitive functioning[101]. N**europsychiatric impairment** included psychological (Psy) disorders such as mood or affective disorders, and behavioral changes. **Mood or affective disorders** included anxiety and depressive disorders. **Anxiety disorders** included Anxiety Disorder due to a General Medical Condition[182]. **Depressive disorders** included major depression, dysthymic disorder; bipolar disorders; and mood episodes, such as manic or hypomanic episodes[182,183]. Depressive disorders may be clinically reflected as irritability, anger, and somatic disturbances[183]. **Behavioral changes** included emotionalism, confabulations, paranoid ideas, irritability, and alcohol and substance abuse[148183]. Emotionalism was referred to a state where emotions and their expression could no longer be self-controlled. Emotionalism included symptoms such as pathological laughing and crying, emotional incontinence and involuntary emotional expression disorder, which conformed pseudobulbar affect syndrome[183].

Dysarthria (articulation dysfunction) and dysphonia (phonation dysfunction) may be present in the same individual, as dysarthrophonia **(DysA)**[141]. There are different patterns of DysA: spastic, ataxic, and mixed patterns[184,185].

Dysphagia (Dysph) is defined as a disturbance of the complex sensorimotor functions of swallowing[186]. Two assessment tools have been considered as the gold standard for diagnosing and monitoring Dysph in individuals with Dysph of neurologic etiology[187]: trans-nasal fiber-optic endoscopic evaluation of swallowing (FEES) and video-fluoroscopic swallowing study (VFSS)[186,188].

Resp dysfunction included ineffective cough, atelectasis, aspiration, pneumonia and acute Resp failure[189,190]. **Functional assessment** included muscle strength and endurance**.** Inspiratory and expiratory muscle strength could be assessed by means of maximal mouth pressure, including maximal inspiratory and expiratory pressures (PI_{max} and PE_{max}). Muscle endurance could be assessed by means of maximal voluntary ventilation (MVV). Reduced cough efficacy was assessed by means of Pulmonary Index (PI)[189,191]. High scores of PI were a predictor of expiratory muscle weakness[189].

Sleep disorders. The different sleep disorders that have been reported are insomnia, sleep apnea, restless syndrome, narcolepsy and rapid-eye movement, sleep behavior disorder[52] and circadian rhythm disorders[192]. The restless syndrome included urge in the legs to move, which improved with movement of the legs, worsening at rest, especially in the evening[193]. Narcolepsy included sleep attacks, hypnagogic/hypnopompic hallucinations, cataplexy, sleep paralysis, and disrupted nocturnal sleep[192]. Sleep behavior disorder included lack of muscle atonia during REM sleep, and acting out dreams, with kicking, punching, and getting out of bed[192]. Polysomnography is a tool to assess biophysiological changes during sleep.

Aim

The aim was to describe the main body function and body structure impairment that may occur in PwMS and lead to disability, limit activities and restrict participation, throughout the course of the disease, including epidemiological, clinical features, and pathophysiology.

1.Fatigue and b4552Fatigability.

Results

Epidemiological features. The prevalence of fatigue in PwMS was 50-90 %[94], rather higher when compared with the general population, where the estimation is 10-60 %[94]. Fatigue was considered to be the severest impairment, with the highest prevalence in all disease course subgroups[194]. **Clinical features.** Chronic fatigue criteria were related to duration over time (longer than 6 months) and were described elsewhere[94]. It was suggested that there was no relationship between fatigue and effort sense during physical activity[135]. There was however no general agreement[181,195]. There *was* general agreement as to fatigue being correlated with cognitive dysfunction[94,196], including reduced alertness[197] and impaired processing speed[198]. Bol[199] (2010) reported that mental fatigue, but not physical fatigue, accounted for a substantial part of cognitive complaints. Controversial results about the relationship between fatigue and depressive disorders have been provided[94,96,183,196]. Several authors reported that PwMS with fatigue gave significant higher depression scores [96,196]. Other authors affirmed that this relationship was not yet entirely clarified[183,200] or even that fatigue and depressive disorders were independent symptoms[94]. Significant correlation between fatigue and disrupted sleep was reported [93], with diurnal sleep[200], and with daily sleepiness[192]. A correlation between fatigue and AD was reported, including attenuated heart response to change of position and hand grip, and thermo-sensitivity[201-203]. It has been reported that patients with PP[120,200,202] and SP MS[204] displayed fatigue more frequently than those with RR MS. There were controversial results regarding impact of fatigue on physical performance. Wynia[194] (2008) reported that fatigue was a significant predictor of physical functioning, while Smedal[205] (2010) found no association between fatigue and physical performance. Clusters of three symptoms consisting of fatigue, depressive disorders and pain were reported as an independent correlate of physical activity in individuals with RR MS[206]. PwMS with this symptom cluster were less engaged in exercise behavior[206]. No relationship has been shown regarding fatigue and age, gender, clinical activity, and duration of the disease[200,202]. There were controversial results regarding the relationship between fatigue and disability and ambulation. Haussleiter (2009) found no relationship[183], while Mills (2010) reported a strong relationship between fatigue and MS impact, with a clear increase in fatigue once walking ability was affected[200].

The **pathophysiology** of fatigue was described as being multi-factorial and could be of central origin, as in other chronic conditions[94,207]; and peripheral[93]. The description of the underlying mechanisms of central and peripheral fatigue has been controversial. Central fatigue could be explained as a consequence of an impaired central motor activation, with a morphological and functional basis[198,208,209], and disturbances in the sympathetic vasomotor system[202]. Peripheral fatigue was associated with other interfering symptoms, such as a poor sleep pattern, resulting from pain, nocturia, infection, spasticity, depressive disorders, immunomodulatory agents and sedating medication[82]. Peripheral fatigue could be due to neuromuscular disorders, leading to disuse atrophy and overall deconditioning[93]. Andreasen[208] (2009) suggested that impaired cortical motor activation would be a neurobiological substrate underlying fatigue, regardless of whether fatigue is categorized as primary (central) or secondary (peripheral). This affirmation would imply changes in trends of treatment strategy of fatigue[208].

Summary

Fatigue is one of the most common symptoms in MS. It interferes with activities, it is correlated to cognitive dysfunction and frequently associated with depressive disorders, sleep and AD. Pathophysiology has produced controversial results regarding its central and peripheral origin.

2. b730Muscle power functions. Muscle weakness.

Results

Epidemiological features. The prevalence of weakness in PwMS may be found in up to 90 % of these people[52]. **Clinical features.** Slowly progressive weakness of the lower extremities was frequently seen in MS[52] leading to walking disability[131] and decreased PC. Features of weakness include muscle weakness, impaired velocity-dependent and strength motor function, and muscle fiber atrophy to a lesser extent[131]. Spasticity has been correlated with weakness[52], but not fatigue[131]. Weakness consecutive to neurological impairment, and weakness associated with deconditioning (See *Decreased tolerance to exercise and cardiovascular and respiratory dysfunction*) could lead to abnormal gait or immobility[210]. In such conditions, weakness contributed to muscle contractures and increased muscle atrophy[211]. A **differential diagnosis** with other diseases should be investigated whenever slowly progressive weakness in lower limbs, within progressive myelopathy, is detected[52].

The **pathophysiology** of muscle weakness was mostly related to damaged central motor drive, which affected velocity-dependent and strength motor function[131]. Muscle weakness has also been associated with decreased physical activity[195], leading to reduced aerobic capacity[212], atrophy and loss of muscle strength[133]. Atrophy was a result of impaired peripheral muscle function related to fat-free cross-sectional muscle area. These peripheral changes may be a consequence of a damaged central motor drive and of less physical activity[131]. Weakness may be a consequence of progressive myelopathy as a result of central conduction problems, explaining the presence of spasticity related to weakness[52]. However, acute transverse myelitis and radiculopathy were seldom described as causing weakness in MS[52]. Thermo-sensitivity was associated with the increase in weakness[52,203].

Summary

Weakness is a most common impairment in MS, affecting mobility, mainly walking. It is frequently related to spasticity, but not to fatigue. Weakness is a consequence of a disrupted central motor drive, and of peripheral muscle function. Weakness may be a result of myelopathy, especially in the presence of spasticity.

3. b455. Functions related to tolerance to exercise. b 460. Associated sensations to cardiovascular and respiratory function. Decreased tolerance to exercise and cardiovascular and respiratory dysfunction

Results

Epidemiological features. According to a survey, it was reported that 71.4 % of PwMS endorsed no exercise, which was higher than in the sedentary control group and three times more than in the general population[213]. Patients with PP MS were seen to be significantly less active than those with RR MS[214]. **Clinical features**. Tolerance to exercise has been observed to be either similar to matched normal controls, regarding rate of perceived exertion, among mild disabled PwMS[135] or to present a lower tolerance than for the non-MS population[179,195]. This discrepancy was due to different disease severity[215]. PwMS may have both a normal CV response to exercise[212] and a decreased one, if the autonomic system was affected[195]. VO_2 max was lower among PwMS[133,212]. Muscular strength and endurance may be also reduced. The consequence of a poor health-related physical fitness or deconditioning helped to decrease muscle function (See *Muscle Weakness*). **Pathophysiology.** Low tolerance to exercise has been related to autonomic dysfunction and to reduced CV endurance[216], especially in PwMS with moderate disability (EDSS > 6)[195]. Reduced CV endurance was due to a decrease in the capacity of oxygen transportation[179], and may be also a consequence of decreased function of Resp muscles [195,217] (See *Respiratory impairment*). Impairment and disability level have been reported as not influencing CV endurance[218]. Decreased muscle strength was related to muscle atrophy, with a lower number of type I fibers, shifting towards a greater proportion of type IIa and IIax fibers or an increase in the proportion of hybrid fibers[219]; and reduced size of all types of fiber, which could be due to disuse, not excluding the possibility of neural lesion as the background[217,219]. Neural mechanisms could lead to a reduced ability to activate motor units, and to lower motor unit firing rates[133]. Decreased muscle endurance has been closely and positively related to a diminished VO_2 max [133].

Summary

PwMS displayed a lack of exercise practice, with lower levels than the general population. PwMS may have normal or disturbed tolerance to exercise and/or CV endurance. The effects of CV dysfunction include a decreased VO_2 max. The effects of lower muscle strength and endurance are muscle weakness. The consequence of poor health-related physical fitness or deconditioning made a contribution to diminished muscle function.

4. b260 Propioceptive functions. Sensory disorders.

Results

Epidemiological features. The prevalence of sensory disorders was up to 90 % among PwMS[52]. **Clinical features**. The most frequent initial symptom of MS was acute or subacute onset of numbness or tingling in one or more distal parts of the limbs, which travels proximally, increasing in intensity[52], especially in RR MS type. Sensitivity to temperature symptoms, mainly in feet; tactile sensitivity symptoms (numbness, hypoesthesia and hyperesthesia); vibration sensitivity, kinaesthesia and dermolexia symptoms, were common among PwMS[140]. The **relationship** found between sensory symptoms and central pain[136,140] was of interest (See *Pain syndromes*). Loss of propioception has led to disability in gait and dexterity[52]. Sensory symptoms may disappear after a few days or weeks of the disease[220]. **Pathophysiology** of sensory disorders was related to myelopathy at the dorsal column and medial lemniscus pathways in cervical or brainstem areas[52,136].

Summary

Sensory disorders have been seen to be relevant for the relationship with central pain, especially, sensitivity to temperature. Tactile vibration sensibility and kinesthesia may interfere with gait and dexterity.

5. b280-289 Pain syndromes

Results

Epidemiological features. The prevalence of PS was as much as 86 % among the MS population[141,143,221]. Chronic[137,222] PS were the most frequent ones. There were controversial results regarding the most prevalent type of pain. Some authors reported that central pain was the most frequent type of pain[136,143,222], and within this, dysaesthesic limb pain or burning pain (17 %). Kalia[104] (2005) found that non-neurogenic pain was more common than the neurogenic type, in a sample of mild to moderate MS sufferers. **Clinical features**. Neurogenic pain was described as more severe than non-neurogenic pain[121]. Relationships between PS and other impairment required further research, such as depressive disorders and fatigue in PwMS[136]. It was not yet clearly defined whether depressive disorders and fatigue were risk factors for pain or if they were a consequence of pain[136]. Newland[223] (2005) found that depressive disorders and cognitive impairment were not significantly more prevalent among PwMS with pain versus those without pain. Pain and sleep disorders were strictly associated[224].

There was general agreement that pain displayed a positive correlation to **factors,** such as age, duration of disease, severity of impairment, PP MS, and psychosocial factors, such as catastrophizing[143,225,226]. As regards gender, the risk of pain was comparable, but the severity of pain was greater in women[143] (103). Headaches affected women more often than men. These were mostly related to relapses [136].

The different PS had different **pathophysiological** mechanisms and treatment approaches. TN and other paroxysmal pain, dysaesthesic limb pain or burning pain; and optic neuritis has been considered as neuropathic pain of central origin[142,143]. The underlying central pain mechanisms have been described as impairment at the CNS, affecting the spinothalamo-cortical pathway, causing hyperexcitability, with ephaptic spread to normally conducting neurons[143] and sensory disturbances, mainly in sensitivity to temperature and pain[136,140]. Painful tonic spasms had demyelination as background and other spasms were a consequence of spasticity, but the direct relationship with pain was a mechanical muscle contraction[143]. Back and other musculoskeletal pain, and osteoporosis were considered as having a musculoskeletal origin[142]; myalgias and "flu-like" syndrome were a result of interpheron b therapy side effect[136]; pain could also be a consequence of malposition and mechanical sores[142]. Brainstem lesions could be the generator of migraine-type headaches[142].

Summary

Depressive disorders can be either risk factors for developing pain, or a consequence of pain. Being older, having longer disease duration, a more severe impairment, a progressive MS type, and psychosocial factors have been considered risk factors for developing pain, whilst women are at risk of more severe pain.

6. b735 Muscle tonus functions. Spasticity and other signs of upper motor syndrome.

Results

Epidemiological features. The prevalence of spasticity and other signs of UMNS was as much as 90 % among PwMS[52]. **Clinical features**. The clinical consequence of UMNS has included loss of musculotendinous extensibility, which has led to a smaller range of joint motion, and thus to pressure sores, with risk of sepsis and eventually death[145]. Abductor contractures may lead to reduced perineal hygiene and sexual dysfunction[145,227]. It may include painful spasms, which interfere with sleep, and may induce fatigue[52]. Spasticity has been associated with poor PC[228] and with GD. Spasticity levels were found to increase with disease progression[162]. On the other hand, spasticity was described as an impairment compensating for weakness regarding walking, standing and transferring[52]. Spasticity itself can be increased as a consequence of precipitating factors, such as urinary tract infection (UTI), or pressure sores, increased body core temperature, fracture, psychological stress, disease progression, among other factors[145].

Pathophysiology of UMNS in MS could be explained as a result of demyelinating lesions in the upper motor pathways. These lesions have affected the balance of inputs from the descending supraspinal pathways to the motor and interneuronal circuits of the spinal cord and have altered spinal cord activity[144], leading to various types of muscle overactivity of the UMN[144]. There have been reports of a lack of reciprocal inhibition of the antagonist muscles via the 1a fibre monosynaptic connection with a spinal interneuron, which is responsible for pathological co-contraction[144,145]. Lesions in the brain lead to spasticity associated with anti-gravity muscle groups, and in the spinal cord, to both flexors and extensor muscles[145]. In PwMS both types of muscle response may be present. Spasticity has also displayed an impact on the rheological properties of muscles and soft tissues leading to atrophy and contractures[144].

Summary

There is a general consensus that spasticity and other signs of UMNS may lead to PCD and GD. It may lead to pain, contractures, and may interfere with sleep, and lead to increased fatigue. Spasticity may compensate for weakness regarding walking, standing and transferring, under certain circumstances. Spasticity may be heightened by precipitating factors.

7. b765 Involuntary movements functions. Ataxia

Results

Epidemiological features. The prevalence of ataxia was as much as 80 % of PwMS[229]. **Clinical features.** Truncal ataxia interfered with sitting and standing balance, which was highly incapacitating for walking. Ataxia could be associated with dysarthria and dysphagia[230]. Cerebellar origin ataxia led to diminished motor learning, impaired ability to perform complex visuomotor skills automatically, and to adapt locomotor trajectory to novel visual input, and lower capacity to retain an attained level of adaptation[231]. Different types of tremor have been reported in PwMS' upper limbs, such as distal postural (fine) tremor, with a small or no kinetic component; distal postural/ kinetic tremor; proximal postural/ kinetic tremor; proximal and distal postural/kinetic tremor; isolated intention tremor[148]. Proximal, and proximal and distal postural/kinetic tremor have been associated with marked dysmetria and with the most disabling type of tremor[148].The association of upper limb distal intention tremor with trunk ataxia was very disabling[141]. Tremor was closely associated with higher scores of EDSS[52].

Physiopathology. One most frequently affected anatomical site was the cerebellum and its connections[146,211], resulting in limb ataxia characterized by a lack of co-coordination and control of limb movements leading to poor balance and PCD, transfer disorders and GD[231].

Summary

Ataxia affects functions related to balance, PC and gait. It is frequently associated with DysA and Dysph. PwMS show different types of combined postural and action tremor. Upper limb tremor associated with truncal ataxia was related to higher levels of disability.

8. b755 Involuntary movements functions. Balance (BD) and postural control disorders.

Results

Epidemiological features. PwMS often had BD and PCD, even with mild disability and minimal spasticity and ataxia [154]. Limited balance and PC were one of the most frequent causes leading to falls[60]. **Clinical features**. PwMS displayed awkward standing and sitting balance[150,151], and PCD[156,227]. PwMS developed compensating strategies to maintain the upright posture, which varied according to the disability's anatomical origin[153], compensating for sensory function[154] and different levels of disability measured with EDSS[153]. These strategies nevertheless displayed only relative efficacy, thus explaining a more frequent rate of falls among PwMS than among the general population[153]. Fatigue was not seen to be an interfering symptom for BD and PCD[150]. Cognitive dysfunction could interfere in balance and PC[153]. Most of PwMS with BD and PCD had greater length and velocity of center of pressure excursion in anterior-posterior and medial-lateral axes, as an expression of limited PC[154]. PwMS with vestibular afferents disorder gave a poor performance with eyes closed or in surrounding visual sway and subject's body sway, with foam pads under the subject's feet by means of posturography. PwMS with somatosensory afferents disorder showed impaired performance with eyes closed or in a surrounding visual sway and subject's body sway, with or without foam pads under the subject's feet[154]. As compensating strategies, delayed postural responses were common in PwMS with cerebellar and propioceptive BD and PCD, longer in the cerebellar cases[153]. PwMS with propioceptive BD and PCD required more visual compensating strategies. PwMS with propioceptive imbalance displayed an increased use of prediction to scale their responses to the amplitude of an upcoming external perturbation, as a means of compensating for delayed postural responses[153]. This type of compensating strategy was missing in PwMS with cerebellar BD and PCD[153]. Tests of external perturbations were the most commonly affected ones[150]. PwMS with cerebellar BD and PCD and those with higher EDSS scores showed less ability to learn visuopostural co-ordination-based strategies and perform these automatically[231].

Pathophysiology. UMNS and ataxia have been involved as major motor efferent impairment for BD and PCD[228,232]. Ataxia may be of two different origins: cerebellar ataxia, and propioceptive or somatosensory ataxia. BD was greater in PwMS with propioceptive ataxia whenever visual compensation was ruled out, whilst BD was no greater in those of cerebellar origin under the same environment features[233]. BD and PCD required the integration of multiple sensorimotor afferents, such as visual, vestibular and propioceptive functions, in order to keep the body center of mass steady over the support base[153,228]. Cognitive dysfunction may interfere in balance and PC[153].

BD and PCD led to an increase in energy expenditure and have been considered a main factor in gait disturbances[150,228].

Summary

BD and PCD are common among PwMS, and may potentially lead to falls. BD and PCD are a consequence of motor efferent impairment, such as UMNS and cerebellar ataxia; and of sensory afferent impairment, such as somatosensorial impairment, leading to propioceptive ataxia; and of visual and vestibular impairment. Different OM and instrumental measures can be used to assess features of BD and PCD. PwMS develop different compensating strategies according to the efferent and afferent CNS impairment of BD and PCD. Learning visuopostural co-ordination-based strategies and performing these automatically is diminished in PwMS with cerebellar BD and PCD, and in those with higher EDSS scores.

9. b770 Gait functions. Gait disorders.

Results

Epidemiological features. It was reported that up to 85 % of PwMS[162], and among these, 78.8 % of those with progressive MS and 20.1 % with RR MS, displayed some degree of GD[234]. **Clinical features.** PwMS with EDDS scores of 3.5-5.5 could walk with difficulty but independently, and those with 6-6.5 required aids for walking. PwMS with EDSS scores of 7-7.5 were wheelchair-bound most of the time. Different **patterns of gait** were reported among PwMS, such as **spastic**[162,164], **cerebellar ataxic**[164], **propioceptive ataxic**[235], and with **mixed patterns**, such as ataxic (cerebellar or propioceptive)-spastic[164,236]. **Gait apraxia** or gait initiation failure was reported as a limitation for PwMS and as being underrecognized[237]. Gait kinematics may not be uniform among PwMS within the same GD; and among those with different severity[162] and duration of the disease[164], according to disease heterogeneity and progression. PwMS had higher variability inter individuals of kinematic data compared with healthy controls[160]. No significant variability of kinematic data was found either within the day or related to fatigue[238]. Muscle weakness at knee extensors and hip flexors was correlated with reduced speed, and considered a predictor of ambulatory dysfunction[159]. Reduced speed and prolonged double limb support were described as markers of instability[157]. PwMS with GD developed **compensating mechanisms** for lack of balance, in order to avoid falls[162]. Decreased speed and stride were present in overall PwMS with spastic GD[161,162,164]. The most extensively documented GD was the **spastic** type[157,162,164]. Martin[157] (2006) reported a spastic GD whose main feature was a slow stiff ankle GD, in a PwMS sample with EDSS scores 0-2.5. Givon[164] (2009) described a slow stiff knee GD, in a PwMS sample with EDSS scores equal to or lower than 5.5. **Cerebellar ataxic** gait was characterized by a shorter swing time and widening of the base support[164]. **Pathophysiology.** GD may be the consequence of impairment at different areas of the CNS leading to different body dysfunctions, such as muscle weakness, spasticity, ataxia, sensory, visual and vestibular symptoms, fatigue[164] and AD[162], compromising balance and gait progression. Stabilizing strategies were the consequence of mechanical responses of musculoskeletal structures related to movement, and of somatosensorial, visual and vestibular function compensating mechanisms[153,156].

Summary

Gait is the most frequent body function impairment among PwMS. PwMS with GD scored between 3.5 and 6.5 in EDSS. Different gait pattern disorders have been reported, according to neurological impairment, spastic and ataxic GD being the most frequent ones. PwMS develop automatic compensating mechanisms for lack of balance to avoid falls, in accordance with the underlying neurological mechanism of GD. Decreased speed in overall GD, ankle or ankle-knee-hip mechanisms, in spastic GD and widening of the base support in cerebellar ataxic GD have been reported as a result of interacting impairment mechanisms and stabilizing strategies.

10. b210-229 Sight and related functions. Visual impairment

Results

Epidemiological features. The prevalence of optic neuritis (ON) during the course of the disease was reported to be 20 % (101)-65 %[52]. ON has been reported as one of the most frequent disorders among patients with RR MS, mainly at the first relapse and among females[52,220]. At the first relapse, about 13 % of the impairment may be oculomotor disorders, including internuclear ophthalmoplegia (INO), which is the most common ocular motor disorder (OMD), with a prevalence of 30 %[52,141]. Uveitis in MS was 2.4-3.5 %, commonly found among young females[220]. Clinical features. Loss of vision in PwMS has been described as a consequence of ON, and of uveitis[220]. In ON, the deficit was mainly in the central visual field[220]. Blurred vision has been associated with ON and ocular motor disorders (OMD). OMD included INO and nystagmus[220]. INO consists of ipsilateral adduction, eye deficit, with abducting nystagmus in the contralateral eye[52]. Nystagmus may increase during eye fixation[141]. Diplopia has been related to OMD[220]. Pain has been associated with ON and uveitis[220]. Pain has been reported to be most frequently periorbital and to increase with eye movement, and it may precede, be concomitant with, or follow the loss of vision[52]. Visual impairment negatively correlated with mobility[239]. Disturbances in visual acuity were reported to have an impact on performing NeuroPsy visual-based tests[240]. Reductions in low contrast acuity scores interfered in visual tasks, such as driving, reading speed, and facial recognition[166]. ON may require differential diagnosis with other diseases, such as Lyme disease, sarcoidosis, and Leber's optic neuropathy[52]. ON's **pathophysiology** has been reported as an inflammation of the optic nerve, INO's pathophysiology, to a demyelinating lesion in the medial longitudinal fasciculus[52].

Summary

The most frequent visual disorders are ON and INO. ON may lead to impaired visual acuity and pain; INO, to blurred vision and nystagmus. Not all individuals with ON will develop MS and ON can be also included as a different type of IIDD – neuromyelitis optica or Devic's disease (see *Introduction*) and other conditions. ON requires the exclusion of other diseases. This visual impairment may limit neuropsychological tests' performance. Reduction in visual acuity interfered in instrumental ADL.

11. S620 Pelvic floor muscles structure. Pelvic floor muscles dysfunction.

Results

Clinical features. Reduced PFM contraction was detected and reflected in maximal voluntary muscle contraction and endurance, especially in women[174,175]. This reduced function of PFM correlated with urgency and frequency, but not always with UI[241]. Men showed similar levels of urgency and frequency to women, but more feeling of incomplete emptying, while women had more episodes of UI[175]. PFM dysfunction's role in UI was reported in PwMS with mild-moderate EDSS scores[174]. PFM dysfunction could lead to urinary or to fecal problems or to both[241], and to sexual dysfunction.

Pathophysiology. PFM dysfunction may be due to lower motoneuron disease, affecting the pudendal nerve and thus the puborectalis muscle and the external urethral sphincter;

and to the pelvic nerve, affecting levator ani[241]. PFM dysfunction may be the consequence of mechanical damage to the pelvic floor structures, especially in women[241]. Upper motoneuron pathway disorders can also affect PFM, as happens in individuals with spasticity[214241]. Coordinated micturition and defecation require intact pontine-sacral connections, although dissociation of the reflex activity in both sphincters has been described[241]. PFM and the urethral sphincter may have an inhibitory effect on detrusor activity, which would decrease in cases of PFM dysfunction[175] .

Summary

PFM dysfunction, such as reduced muscle strength and endurance, has been seen to play a role in urgency and frequency, in UI, and in feeling of incomplete emptying in PwMS.

12. **b610-639 Urinary functions. s610-639 Structure of urinary system. Neurogenic lower urinary tract dysfunction.**

Results

Epidemiological features. The prevalence of NLUTD was reported as being up to 99 % among PwMS[112,170]. The prevalence of OAB or irritative syndromes was 37-99 %, and of OS, 34-79 %[112]. Irritative and obstructive symptoms may coexist and affect up to 59 % of men and 51 % of women[112]. The prevalence of UI was reported in 31 % of PwMS, which was higher than among the general population[112]. Detrusor hyperreflexia had a prevalence range of 34-99 %, detrusor arreflexia, 0-40 %, detrusor-sphincter dyssynergia (DSD), 5-83 %[112,170]. Detrusor hyperreflexia and DSD were combined in 43-80 % of MS cases[170]. Lower UTI has been reported to be 13-80 %[170]. **Clinical features.** PwMS with OAB and thus, irritative symptoms, more frequently involved UI, and severe pyramidal damage[170]. PwMS presenting OS and mixed syndromes commonly displayed urinary retention leading to UTI[173]. Those with DSD showed also frequent voiding problems and thus, UTI[173]. Hence fever and pain, whenever present, warranted further examination. UTI could eventually lead to hydronephrosis.

Although NLUTD, and DSD within its different syndromes, could be present even in early stages of the disease[171], most of the authors agreed that its severity correlated with the duration of the disease[112,170,242] and severity of the impairment[112]. There were no significant NLUTD differences between individuals with SP and PP[242]. Clinical features may not be fully correlated to the underlying NLUTD pattern[171]. NLUTD, sexual and bowel dysfunction were seen to be correlated, NLUTD usually occurring first[52,112]. NLUTD may interfere with other impairment, such as poor sleep due to nocturia; abdominal pain; increased spasticity[112]. **Risk factors** for urinary tract complications in PwMS have been reported by a Francophone expert panel[170]. There was strong evidence that duration of MS, especially after 15 years from the onset of the disease, indwelling catheter use, high maximum amplitude of the uninhibited contractions of the detrusor, permanent high detrusor pressures during filling (threshold > 40 cm H2O), and postvoid residual volume in excess of 300 ml were risk factors for urinary complications, especially UTI[170], as in other neurogenic populations. Other factors were considered such as DSD, age over 50 years; and male sex[170]. Although NLUTD may lead to upper UTI[170,173], no increased risk of renal failure was reported [170]. Mortality due to NLUTD was observed[112], but this data continued to be underestimated[170].

Level of disability, including mobility, dexterity and self-care, over time, influenced NLUTD management[171,242]. Practical guides on how to diagnose, follow-up and manage NLUTD in PwMS were described elsewhere[170,171]. Some controversy has been found regarding URO indications. The UK panel of experts advocated URO for PwMS with

NLUTD under specific conditions[171]. A Francophone expert panel recommended it for every PwMS with NLUTD[170]

Regarding **pathophysiology,** there was strong evidence that NLUTD was mainly the result of spinal cord disease. The several types of NLUTD's cystomanometric patterns were the result of disconnection between centers in the brainstem, critical to neurological control, and the sacral part of the spinal cord[171]. Disease progression led to unmasking of the vestigial sacral reflex arc, resulting in a loss of volitional and synergistic control of the micturition reflex. The unmasking of the sacral micturition reflex center and/or removal of cerebral inhibitory pathways by suprapontine neural plaques would decrease sympathetic inhibitory activity, leading to detrusor hyperrreflexia[242]. A sacral plaque may be the cause of detrusor arreflexia[242].

Summary

The most prevalent NLUTD have been OAB, leading to irritative symptoms and incontinence. OB and DSD were frequently associated with voiding difficulties, and thus with UTI. Clinical features may not be fully correlated to the underlying NLUTD pattern. NLUTI were more prevalent among older PwMS and those with long-term, progressive and more severe disease. There were no significant differences between SP and PP PwMS. NLUTD, sexual and bowel dysfunction proved to be correlated, NLUTD usually occurring first. Risk factors include duration of the disease and indwelling catheter use. Level of disability influenced NLUTD management. Guidelines for NLUTD management have been developed and recommended.

13. b525 Defecation functions. s540 Structure of intestine. Neurogenic bowel dysfunction.

Results

Epidemiological features. The prevalence of NBD was up to 70 % in PwMS with a long duration of the disease and an EDSS score > 5[141,242]. Forty-five percent of this dysfunction may also occur early in the course of the disease[242]. **Clinical features**. NBD led to constipation, diarrhea, and/or fecal incontinence[141,176,242]. The **relationship** of NBD with **other impairment** showed that NBD correlated with NLUTD[112], but they were not correlated with any pattern of urinary dysfunction[243]. It increased with duration of the disease and age at onset, and was not correlated with gender[243]. The **pathophysiology** of NBD was underlying a lack of CNS modulation of the intrinsic nervous system, from the sympathetic and parasympathetic systems, resulting in longer colonic transit time and constipation[244] and increased threshold of the anorectal inhibitory reflex, thus not warning the patient to seek the toilet in time[176,243]. Other factors that may influence bowel function in MS could be loss of mobility, suppressing the urge to defecate, and the use of drugs whose actions may adversely affect bowel function[244].

Summary

NBD mostly involves constipation, diarrhea and fecal incontinence, and is frequently associated with NLUTD.

14. b640-679.Genital and reproductive functions. s698 Structure of genital and reproductive systems (SGRS), other specified, 699 SRGS, unspecified. Sexual dysfunction.

Results

Epidemiological features. The prevalence of sexual dysfunction was as much as 80 % in PwMS[141]. **Clinical features**. Women showed difficulties in reaching orgasm, with sexual performance, frequency of intercourse, dwindling libido, arousal, vaginal lubrication and weak vaginal muscles, while men reported difficulties with frequency of intercourse, sexual performance, masturbation erection and orgasms, intercourse erections and orgasms, and retarded ejaculation[178,245,246]. PwMS with spasticity could exhibit adductor spasms which interfered in sexual relationships[247]. Patients with any progressive MS type reported sexual dysfunction more frequently than those with RR MS type. Sexual dysfunction was usually associated with age, duration of disease[178], neurological impairment measured with EDSS[245], and level of education[178]. Sexual dysfunction may also be present even in the absence of severe disability[178]. NLUTD/NBD had a positive correlation with sexual dysfunction[245]. **Pathophysiology.** Primary dysfunction was directly caused by demyelination in spinal cord and AD[248]. Secondary dysfunction could be a consequence of other existing impairment, such as fatigue, weakness, spasticity, mobility restriction or NLUTD and neurogenic bowel dysfunction, and cognitive impairment. Tertiary dysfunction was due to psychological, emotional, social and cultural influences that could interfere in sexual functioning[178].

Summary

Sexual dysfunction is reported as altered genital sensation, decreased libido, problems with arousal and orgasm, lower vaginal lubrication, and difficulties with getting or keeping an erection; and are associated with age, duration of disease, neurological impairment, NLUTD and NBD, and a low level of education.

15. s140. Structure of sympathetic system, s150 Structure of parasympathetic system. Autonomic dysfunction.

Results

Epidemiological features. The prevalence of AD has been controversial, taking into account the conflicting data about frequency and distribution of these abnormalities[180]. Approximately 80 % of PwMS had AD, leading to urinary, defecation, and genital function disorders[217]. Merkelbach[249] (2006) reported CV AD prevalence between 10 and 50 %, and orthostatic intolerance, as much as 50 %. **Clinical features.** Flachenecker[180] (2001) reported an association between parasympathetic dysfunction, such as delayed heart rate, and severity of disease, measured with EDSS; and between sympathetic dysfunction, such as orthostatic intolerance, and long-term clinical activity. As regards thermo-sensitivity, some PwMS have been reported to display a uniform change in rectal temperature from beginning to end of exercise, regardless of initial temperature (in healthy individuals, this increase is steeper from start to finish), expressing a different heat reaction during exercise[203]. The consequence may be premature fatigue[203] and low tolerance to exercise[181,195], even with a small increase in internal temperature, such as 0.5ºC [250]. Further autonomic laboratory testing was recommended in thermo-sensitive PwMS, whenever prescribing therapeutic exercise (TE) or if exposed to high temperature[181,195]. The **pathophysiology** of cardiac dysfunction was described as heterogeneous, predominantly involving the parasympathetic system, and to a lesser extent, the sympathetic one[249]. Orthostatic intolerance has been reported as a result of an impaired sympathetic vasoconstriction[249]. Parasympathetic dysfunction has been closely related to the progression of disability in PwMS; and sympathetic dysfunction, to the clinical activity of MS[180]. AD was included as one of the underlying pathophysiological mechanisms of urinary, defecation, and genital function disorders (See *Neurogenic lower urinary tract dysfunction. Neurogenic bowel dysfunction. Sexual dysfunction*). Merkelbach[249] (2006) and O'Connell[94] (2007) pointed out that AD could be one of the pathophysiological mechanisms leading to fatigue in PwMS.

Summary

AD is considered a part of pathophysiological mechanisms of different MS symptoms, and it is a symptom itself in its CV expression and thermo-sensitiveness. CV AD impairment and heat sensitivity were relevant regarding exercise, monitoring abnormal responses thus being recommended, with a view to decision-making. This AD impairment involved a delayed heart rate response at the start of dynamic exercise, orthostatic intolerance, and premature fatigue and intolerance to exercise, when exposed to heat or during exercise.

16. b140-189. Specific mental functions. Neuropsychological and neuropsychiatric impairment.

Results

Epidemiological features. The prevalence of **NeuroPsy or cognitive impairment** was 30-70 % among PwMS[251]. Up to 80 % of them had a mild cognitive impairment. **Memory** was preserved in approximately 40 % of PwMS, 30 % had moderate dysfunction and 30 % suffered severe impairment[251]. **Dementia** may occur in 10-25 % of PwMS[183]. The lifetime prevalence of **depressive disorders** was 50-79 %, which was higher than among other neurological and chronic diseases or among the general population[183,252,253]. A 12-month prevalence rate for **major depressive disorders** was reported as 6.3 %[254]. Effects included bipolar affective disorder, euphoria and pseudobulbar affect[183]. **Bipolar disorders** were double the rate of the general population's[183]. Euphoria prevalence was 13-25 %[183]. Psychosis prevalence was 2 %, irritability, 35%, pathological laughing and crying, 10%, with varying degrees of severity[183,253]. **Suicide attempts** occurred in 15-30% of PwMS[102,253]. The prevalence of **anxiety disorders** rated from 19 % to 37 %[183,253].

Clinical features. Regarding **cognitive impairment,** there was a relative decline in tasks that required recent memory, attention, processing speed, visuospatial abilities and executive functions, during the lifetime of the disease. As a consequence, forgetfulness, lack of verbal fluency, impaired attention, slowness of thought processes and impaired ability to manipulate information were common disorders [183]. There was considerable variability in the pattern of cognitive impairment among PwMS[255,256]. Memory was the most widely researched aspect of cognitive dysfunction[257]. Severity varied widely among individuals. There was general agreement that PwMS had difficulty with delayed recall or delayed evocation of information, and recognition was often less affected than the memory requiring effort[258]. The outcome of this was an impaired ability to access long-term memory, while acquisition and storage would be preserved. Attention was compromised, as shown by decreased alertness[82]. Slowness of thought processing was frequent among PwMS[183]. Visuospatial abilities were affected in the domains of spatial recognition[259], and recognition of objects and colours[260]. PwMS with deficits in executive functions showed difficulty in self-regulating their behavior and establishing new behavioral repertoires[261]. PwMS showed problems taking decisions and anticipating their consequences, difficulties with concept formation, abstract reasoning, initiation and inhibition of responses, planning and sequencing actions[183,261]. Cognitive impairment has been reported to be more frequent and severe in progressive types, especially in the SP MS variety[183]. The disease course showed that mild cognitive symptoms were frequent, already during the early phase of the disease[52]. In this stage, cognitive impairment could be misleading as depressive disorder or other forms of psychiatric dysfunction[253]. Cognitive impairment was associated with severe depressive disorder, sexual dysfunction, a worse disability status, poor social and work outcomes, and interfered in treatment adhesion, in early stages[252,253]. Although libido usually dwindled in PwMS, those with behavioral changes could exhibit a pathological increase in this. **NeuroPsy assessment** should include Neuropsy tests that would not require visual acuity, motor speed or coordination for adequate performance[251]. Neuropsy assessment results may contribute to a better understanding of the cognitive profile of PwMS, GS, disability evaluation, vocational and occupational orientation, follow-up, and legal competence assessment[262]. Regarding Psy disorders, **anxiety** was present shortly after the diagnosis and remained unchanged throughout a two-year follow-up, as reported by Janssens[263] (2006). The author considered that early anxiety was a predictor of long-term anxiety. It was not defined whether these patients had already displayed anxiety prior to the MS diagnosis[263]. **Depressive disorders** were more frequent than apathy and withdrawal[183]. Depressive disorders could shape some features of fatigue, sleep disorders and lack of attention leading to differential diagnosis with other MS impairment[253]. The relationship between depressive disorders and fatigue must still be clarified (See *Body function and body structure impairment. Fatigue.*). It was reported that severe depressive disorders could interfere with cognitive function in the areas of rapid information processing, working memory and executive function in PwMS[252,264], but there was no general consensus[102]. Depressive disorders were associated with a diminished sense of coherence (capacities that facilitate coping with stressors)[265]. There were controversial results regarding the association of depressive disorders and socio-demographic subgroups, disease duration, and severity[265,266]. Depressive disorders may interfere in treatment adhesion[102]. The most frequent risk factor for suicidal ideation was the presence and severity of depressive disorders[102]. Anxiety and social isolation were added risk factors[253,267]. For depressive disorder screening using the BDI was recommended, with a cutoff score of 13[102]. The Chicago Multi-Scale Depression Inventory helped to differentiate cognitive and affective symptoms from MS-associated symptoms[102]. Anxiety was common shortly after the diagnosis[263]. Regarding **bipolar affective disorder,** manic and hypomanic symptoms may occur as part of the physical disorder or secondary to drug treatments, such as Baclofen[183]. Euphoria was associated with greater cognitive impairment and a higher unemployment rate[264] or could be an adverse effect of drug treatment, such as corticosteroids[102]. It correlated with later stages of the disease with EDSS in the upper range. **Behavioral syndromes** included pseudobulbar affect, which was associated with longstanding disease, cognitive impairment and progressive, severe disability[183]. Paranoid symptoms affected patients in advanced stages of the disease. It may be associated with cannabis intake or abuse[183]. Regarding **anxiety**, Dahl[268] (2009) found a higher prevalence of anxiety among women with MS involving fatigue, and among PwMS, with pain and a younger age at the disease's onset[268].

The **pathophysiology** of cognitive disorders was associated with a dysfunction in different CNS pathways caused by axonal diffuse lesions in subcortical tissue, and may have considerable pathology in cortical areas[52,269]. Neuronal dysfunction in the cerebellum was closely associated with cognitive impairment[74]. Functional MRI studies demonstrated the brain's ability to partly compensate for damage associated with the disease. This ability decreased with evolving disease, and cognitive deficits increased accordingly[183]. Depressive disorders proved to have a multifactorial origin, with a complex relation between biological and psychosocial factors[102]. Depressive disorders can be a MS primary impairment, as a consequence of demyelinating disease, or may be a secondary one, as a consequence of psychosocial factors, such as lack of social support or social role and inadequate coping[252,253]. There were controversial results regarding the potential iatrogenic side effect of disease-modifying drugs, especially interferon beta[252,253]. While some authors reported that this drug was associated with depressive disorders[253], other authors pointed out that this association was more related with pre-treatment levels of depressive disorders[102,253].

Summary

The most frequent cognitive disorders in PwMS are delayed recall memory, diminished attention, visual recognition and executive function disorders. Cognitive impairment includes forgetfulness, lack of verbal fluency, impaired attention, slowness of thought processes and impaired ability to manipulate information. Cognitive disorders are associated with severe depression, sexual disorders, a worse functional impairment, poor social and work outcomes, and may interfere in treatment adhesion, in early stages. The most frequent mood and affective disorders are depressive ones. Irritability, anger and somatic disturbances are more common than apathy and withdrawal. Depression disorders are associated with a lower sense of coherence. Depression disorders may interfere in treatment adhesion. They are a major risk factor for suicidal ideation.

17. Voice and speech functions. 398 Structures involved in voice and speech (SIVS), other specified, 399 SIVS, unspecified. Dysarthria and dysphonia.

Results

Epidemiological features. The prevalence of dysarthria among PwMS has generally been identified in 40-50 %[184,185,270]. 31 % of PwMS had mild speech problems, and 9 %, moderate or severe, according to Yorkston[270] (2003). The most common dysphonic phonation pattern was mixed, **spastic** and **ataxic**[141,184,185]. **Clinical features.** The spastic dysphonic phonation pattern involved a strained, harsh and loud phonation; while the ataxic phonation pattern had an appropriate vocal quality, but pitch and loudness control could be often aberrant and variable[271]The most frequent abnormal features were impaired Resp support; harshness; impaired emphasis/stress patterns; impaired pitch variation/control; dysprosodia; imprecise articulation/consonant production; and hypernasality[141,184,185]. It has been reported that in PwMS **velopharyngeal** dysfunction was associated with late disease stages[271].The most commonly reported speech disability was a mild reduction in word and sentence intelligibility[185]. DysA may be present during the course of the disease, mild in early stages, and more severe according to severity of impairment, time from onset and progression of the disease and age[184,185,272]. Severity of impairment was not always associated with DysA[272]. DysA was correlated with other impairments, such as dysphagia, fatigue, depressive and cognitive impairment, mainly memory and executive functions[272-274]. Among progressive MS patients, DysA was closely associated with the cognitive-linguistic function, thus leading to difficulty implementing facilitative strategies and monitoring performance[275].The **pathophysiology** of DysA was related to demyelination in cerebellum, brainstem and connecting pathways[276], and the consequent dysfunction in some or all of the following anatomical structures and function: tongue, lips, velopharynx, larynx, Resp muscle movements and hearing[141,277,278]. **Tongue dysfunction** led to impairment in oral and verbal diadochokinesis; lip dysfunction, to impairment of articulation[184,271]. **Resp muscle movements'** dysfunction included reduced expiratory and/or laryngeal muscle control, resulting in less than adequate pressure for speech production, particularly for speech tasks that require sustained phonation or for connected speech that involves finer control of inspiratory and expiratory timing[279]. Acoustic impairment affected temporal regulation and could lead to dysprosodia (change in rhythm of speech as a result of change in speech[184].

Summary

Dysarthria or dysphonia, or DysA, led to diminished language intelligibility. The most common pattern of DysA is spastic and ataxic. This one shows strained, harsh and loud phonation, but with aberrant and variable pitch and loudness control. Self-awareness is important, regarding communication improvement. DysA correlates with other impairment**,** such as Dysph, fatigue, depressive disorders and cognitive impairment. The association of DysA and cognitive impairment was common among progressive MS patients.

18. b510 Ingestion functions. Dysphagia.

Results

Epidemiological features. The prevalence of Dysph was estimated between 24 and 55 %[141]. Clinical features. The oral and pharyngeal phase of swallowing was considered the most commonly affected one[52,186], especially the pharyngeal stage[280]. The consequences of Dysph may be dehydration, malnutrition, fluids and/or food aspiration, and pneumonia[187,188]. The disability could range from impaired drinking and eating pleasure to malnutrition and breathing difficulty. Dysph was often associated with recurrent cough, sialorrhea, and DysA[52,141]. The frequency of Dysph has been reported to increase with severity of impairment, with EDSS scores 8-9[141]. Occasionally, mildly impaired PwMS have been reported to show a low degree of Dysph[141]. The pathophysiology of Dysph can be explained by disruption of the corticobulbar tracts, cerebellar dysfunction, brainstem, lower cranial nerve involvement and abnormal Resp control and capacity[52,186].

Summary

Dysph is an impairment that affects feeding function and may be life-threatening. It has been correlated with severe disease impairment and co-existence of DysA, and may lead to malnutrition and Resp complications.

19. b440-449 Functions of the Respiratory system. S430 Structure of Respiratory system. Respiratory dysfunction.

Results

Epidemiological features. Although Resp dysfunction does not often entail clinical symptoms, such as dyspnoea, during the course of the disease[281], **Resp complications** become a major cause of morbidity and mortality in PwMS, in late stages[63,191]. Pneumonia has been the most frequent contributory cause of mortality[52,62]. **Clinical features**. Progressive breathlessness, orthopnoea and obstructive sleep apnea were considered signs of impending Resp failure[189]. PwMS often had an ineffective cough[282], which might predispose them to **Resp complications**[191]. The association with Dysph and/or DysA may increase the risk of aspiration and lower Resp tract infection[189]. Regarding the **relationship between** Resp **dysfunction, and disability** in PwMS, it was reported that inspiratory and expiratory muscle weakness - the latter being more severely affected[191] - and ineffective coughing were common among those that were confined to a wheelchair or bedridden[190], or with upper limb weakness[189,279], correlating to severity of disease[189,283,284]. Ambulatory PwMS could have expiratory muscle weakness, related to reduced exercise capacity and clearing pulmonary secretions[191]. This group of PwMS had decreased PE_{max} and normal values of PI_{max}, forced vital capacity (FVC), and MVV, expressing an early impact of the disease on expiratory muscle tests (PE_{max}), but not on pulmonary functional tests (FVC, MVV)[189]. Wheelchair-bound and especially bedridden PwMS had decreased PwMS PI_{max}, $PE_{max,}$ FVC, and MVV, and thus impairment in Resp muscles and pulmonary function[189]. The Tiffenau index (FEV1/FVC) was nearly under normal values, indicating a restrictive pattern[189,284]. These features were common with those of a neuromuscular disease.

There was an increased drive response at rest and normal drive response to CO_2 in clinically stable, moderate-to-severe PwMS, whilst there was a lower ventilatory response to CO_2 [189]. **Pathophysiology**. Several causes of Resp dysfunction have been reported, such as Resp muscle weakness, bulbar dysfunction, obstructive sleep apnea, Resp control abnormalities, and paroxysmal hyperventilation[189]. Progressive breathlessness might be the result of atelectasis, aspiration and pneumonia[189]. Orthopnoea can be the result of a weak diaphragm. Acute Resp failure [189]might be the result of demyelinating lesions of Resp centers of the brainstem and cervical spinal cord, leading to Resp muscle weakness[191]. Impaired expiratory muscles diminished the strength and velocity of airflow, and therefore, the effectiveness of coughing[282]. It was suggested that increased drive response at rest and normal drive response to CO_2 were a Resp control mechanism compensating for Resp muscle weakness[189], and also that impaired ventilatory response to CO_2 could be a consequence of muscle weakness, and of changes in mechanical properties of the chest[189]. Deconditioning could increase muscle weakness[190]. The association with Dysph and/or DysA may increase the risk of aspiration and lower Resp tract infection[189]. Aspiration, pneumonia secondary to aspiration or immobility, or even acute ventilator failure may ensue[190].

Summary

An ineffective cough, especially if associated with Dysph, and/or DysA, and/or immobility, may lead to aspiration, atelectasis and pneumonia, the latter being a main cause contributing to mortality. Cough effectiveness depends on expiratory muscle function. Functional assessment is useful to detect Resp dysfunction, at different stages in the disease, especially among wheelchair-bound and bedridden patients.

20. b134 Sleep functions. Sleep disorders.

Results

Epidemiological features. The prevalence of sleep disorders can reach as much as 54 % of PwMS[224,285], and is three times more frequent than among the general population[52,211], insomnia being the most prevalent one[224]. **Clinical features**. Insomnia, narcolepsy, and circadian rhythm disorders led to daytime sleepiness[192], restless leg syndrome led to daytime sleepiness, depressive disorders, insomnia, and fatigue[193]), sleep apnea led to central alveolar hypoventilation[192]. Sleep disorders have been **related to other impairments,** such as fatigue[93,192,285], especially pain[224], anxiety and depressive disorders[224]. Insomnia could be a consequence of the adverse effects of drugs, such as amantadine[211]. Women were at a higher risk of sleep disorders, and men had these more severely[285]. Sleep disorders were more prevalent among PwMS with more severe disease and worse disability status[224]. **Pathophysiology.** Sleep disorders could be a consequence of demyelinating lesions in the upper cervical medulla or bulbar dysfunction[52,211]. Sleep disorders could be a consequence of interfering impairment, including pain and depressive disorders, and of disability, as in other chronic disabling disorders[224].

Summary

Sleep disorders have been reported as frequently associated with fatigue, anxiety, depressive disorders, and especially with pain. They can be primary related to the MS disease or be secondary to other impairment, and to some drugs' adverse effects. Sleep disorders are more prevalent among women and more severe among men. PwMS with sleep disorders tended to have a more severe disease and disability condition.

IV. Impact of body function and body structure impairment on activities, participation, HRQoL and QoL

Introduction

The body function and body structure impairment previously described had an impact on activities, participation and HRQoL and QoL of PwMS. Resp dysfunction had an effect on life expectancy.

Aim

The aim was to describe the impact of body functions and body structure impairment on activities, participation and HRQoL QoL of PwMS.

Results

In the domain of activities and participation, the ones that were most frequently affected were mobility[87,286-288], domestic life[87,287], community and social activities[87,287], principal areas of life, such as remunerative employment[87] and economic life[289,290], interpersonal relationships[87], self-care[87,287], learning and applying knowledge[87]. Communication results have been included due to being closely related to interpersonal relationships and scored as relevant by PwMS[123].

1. Regarding **mobility,** walking was the most frequent limitation of activities mentioned by PwMS, ranging from 91 to 100 %[87,287]. Limitations for walking ranged from 28 %[88] to 50 %[291]. In a survey in Finland, it was reported that 16 % of PwMS were wheelchair-bound, and 7 % were bedridden[88]. Limitations to walking, especially long distances, were reported as having an extreme impact by 77 % of the participants in a survey of

PwMS with EDSS scores of 2-7.5 and cognition 0-2, in Kurtzke Functional System[287]. Limitation of walking distance and the need for walking aids are related to progression of the disease and irreversible disability[48]. Fatigue and lower health-related physical fitness had an impact on mobility[89,195]. Muscle weakness, sensory and visual impairment[52], spasticity [98,228] and ataxia may lead to BD and to GD[200228]. BD and GD could predict limitation in mobility in a mild-moderate PwMS sample[89]. Reduction in visual acuity interfered in activities, such as mobility [239], including driving [166]. Dexterity was affected by tremor[148]. **Changing and maintaining body position** could be affected by spasticity, ataxia, BD and PCD, leading to difficulty in transfers and wheelchair propulsion[98,145,148,227].

2. In the domain of **domestic life**, **household tasks** were the most frequently affected aspect[87]. 47 % of participants in a survey in Finland required some assistance[88]. Limitation for shopping was mentioned as being a great impact for 35.6 % of PwMS, in a survey of mild-moderate impaired (EDSS < 8) and mild-moderate cognitive impaired PwMS[287]. **Fatigue**[89]**,** severe **pain**[143]**, continence problems,** especially UI[112], **cognitive dysfunction**[91], and **depressive disorders**[89] had an impact on domestic life, including household tasks. Executive functions, processing speed and new learning could predict the degree of independence in activities of daily living (ADL) performance, including householding[91]. Self-awareness of functional status could predict better instrumental ADL performance (IADL), including householding[292], while **visual impairment** associated with cognitive affection led to lower IADL performance[293].

3. Regarding **community and social activities, recreation and leisure** were reported to be affected for 90 % of PwMS[87] and had an extreme impact on 42.6% PwMS[287].

Reduced **mobility**[294], **pain**[225], **spasticity**[229], **continence problems**, especially UI[295], and **cognitive dysfunction**[91] interfered in social activities.

4. **Remunerative employment**, as one of the main areas of life, was considered a problem in 75 % of PwMS in a multicenter study[87]. It was considered of extreme influence by over 50 % of PwMS[287]. There has been general agreement that PwMS display higher unemployment rates[296], and a higher loss of employment after diagnosis[290,294] than the general population. Early disability pension has been reported as being obtained by up to 30 % of PwMS, in the first 5 years after diagnosis, while it was 3 % among the general population, increasing up to 78 % after 20 years, while the controls gave 14 %[290]. In a survey in Finland, 60 % of PwMS were either retired or receiving disability pension[88]. **Fatigue**[297], **pain**[225], **spasticity**[229], **cognitive dysfunction**[91,294], and **depressive disorders**[298] revealed an impact on the ability to work. Although working memory was reported to be the cognitive domain that best predicted work status[91], other authors did not observe any relationship between cognition and employment[299]. Disability status was correlated with loss of employment, and premature retirement for the more severely disabled [294].

5. Among **interpersonal relationships**, **intimate relationships** were reported as being a problem by 54 % of PwMS[87], and were considered to be extremely affected by 54 % of PwMS[287]. Complex and particular personal interactions were affected in up to 18 %[87]. There was a greater risk of break-up of the same partners' relationship, which increased over time and with the worsening of disability status[300], but there was no general agreement on this issue. Hakim[294] (2000) found that there were no significant differences regarding divorce and separation compared with the general population. Cognitive impairment and economic pressure caused distress in relationships, especially

within the family[294,301]. **Pain**[225] and **continence problems**[112] interfered in interpersonal relationships. **Sexual dysfunction** was a hindrance in intimate relationships[245].

6. **Communication** and related problems could be considered in a context, such as initiating, maintaining, developing or ending personal interactions or relationships[273]. Baylor[302] (2010) reported that **communication** restriction was related to fatigue, slurred speech, cognitive dysfunction, depressive disorders, employment status, and social support.

7. **Self-care** was commonly affected[87], according to the severity of the disease, ranging from 18 % in a mild-moderate PwMS-impaired sample[88] to over 50 %[291]. Most PwMS with self-care limitations had previously experienced domestic life limitations [89]. **Fatigue**[89]**, spasticity**[229], **continence problems**[112] and c**ognitive dysfunction**[91] had an impact on self-care.

8. **Learning and applying knowledge** was reported as being a common problem[87,303], leading to difficulty in performing cognitive-based ADL[91]. **Cognitive dysfunction**, involving difficulty in the initial acquisition of information, was reported as the primary reason for this limitation[304].

9. **Economic life,** among **the main areas of life,** was affected, since overall standards of living declined after MS diagnosis, according to loss of employment of PwMS and restrictions on informal caregivers' own employment [289,294,300], an increase in both actual and opportunity costs[289,294]. These costs were related to medication, home help, equipment and adaptations to housing[289]. Perception of financial strain rather than financial situation could predict poor psychological wellbeing[305].

10.**Health-related quality of life and quality of life**

MS has a greater impact on QoL than in the general population[306-308] and in other diseases[119]. Fatigue has been seen to have an impact on HRQoL, in physical[194,308], mental functioning[308,309], and on QoL, in social functioning[308,309]. Higher levels of health-related fitness have been related to enhanced HRQoL and QoL[218,310]. Pain has been observed to have a detrimental impact on HRQoL[104,136], in physical functioning, body pain[194,311,312], and mental health[104]. Spasticity has displayed an impact on physical health[194,308]. Visual impairment was associated with lower scores for vision-specific HRQoL[166,194,308]. NLUTD[112], NBD[311] and sexual dysfunction have been shown to have an impact on QoL, in social functioning[194,245,311]. NeuroPsy impairment was seen to have an effect on physical and mental domains of HRQoL; and on QoL, in social functioning[194,308,311,313]. Depressive disorders and anxiety had an adverse effect on HRQoL scores[194,292,306,312], depressive disorders being a significant predictor of poor QoL[292]. Decreased self-awareness appears to act as a buffer for distress[313]. DysA was associated with poor mental health[194,308]. Sleep disorders were shown to have an impact on different domains of HRQoL, and on QoL, in social functioning, poor sleep being a predictor of decreased HRQoL[194,224].

Duration of disease[194,308,314], severity of impairment[239,314], including number of impairments[312], have displayed a negative correlation with HRQoL, EDSS scores being a predictive factor of HRQoL, and especially concerning mobility[312,315].

Limitation in activities due to physical limitations proved to be higher than in other disabled populations, and negatively correlated with HRQoL[316]. Physical limitations have been shown to have a higher impact on HRQoL than mental disorders[306,307].

Mobility and especially limitation in ADL have been seen to have an impact on social QoL[194,239]. It should be highlighted that limitation in mobility in PwMS with low EDSS scores has displayed a greater effect on HRQoL and QoL than increasing limitation between moderate and severe PwMS[119,307]. It has been suggested that this may be due to response shift[119] or to EDSS being a better surrogate for physical dimension of HRQoL in earlier than in later stages of the disease[307]. Unmet needs for ADL and IADL have been associated with waning QoL[308].

Loss of remunerative employment and lower household income have been associated with lower QoL[239,307]. Economic pressure was found to be a predictor of poor QoL among PwMS[289,301,305]. Cutbacks in spending were considered the most relevant conditioning factors of the ones leading to economic pressure[289].

Summary

Mobility, including walking and changing body position, is the most frequent limitation of activities. Restrictions in walking distance and need for walking aids have been related to progression of the disease. Fatigue, decreasing health-related physical fitness, muscle weakness, sensory and visual impairment, spasticity, ataxia, BD and GD are factors closely associated with mobility limitation. Domestic life is also regularly limited. Fatigue, severe pain, continence problems, especially UI, cognitive dysfunction, and depressive disorders, visual impairment - if associated with cognitive dysfunction - are the background of domestic life constraints. Community and social activities, recreation and leisure are frequently affected. Limitation of mobility, pain, spasticity, continence problems, especially UI, and cognitive dysfunction hampered social activities. Remunerative employment was seen to drop as compared with the general population. Early disability pensions are common. A disadvantaged economic life is found in most PwMS. Impact on interpersonal relationships may be a consequence of an impaired economic life. Pain, continence problems and sexual dysfunction are factors that get in the way of interpersonal relationships. Sexual dysfunction particularly interferes with intimate relationships. Communication restriction is closely associated with fatigue, slurred speech, cognitive dysfunction, depressive disorders and employment status. Social support acts as a facilitator. Self-care limitation usually develops after a growing restriction in householding. Learning and applying knowledge is closely related to cognitive dysfunction. Economic life undergoes the adverse effect of loss or restriction of employment, either of PwMS and/or of their significant others.

MS has an impact on HRQoL and on QoL. Fatigue, pain, spasticity, visual impairment, NLUTD, NBD, sexual dysfunction, cognitive impairment, anxiety, depressive and sleep disorders, duration of disease, severity of impairment, limitation in mobility, in ADL and IADL, loss of employment status, heightening economic pressure, and unmet needs on ADL and IADL have a detrimental impact on HRQoL and on QoL, displaying a negative correlation with their scores. Health-related fitness has a positive correlation with HRQoL.

V. Impact on significant others and caregivers

Introduction

The impact of MS may be felt by every member in the family, from an emotional point of view[317]. Informal caregivers, such as family and friends[318], have been the primary resource for keeping PwMS integrated in their natural environment[319]. Males and spouses, mainly husbands, were reported as being the most frequent caregivers, followed by females and other relatives, mostly daughters [320,321]. Formal caregivers were employed and not related to the patient[319]. Since the most commonly found MS type has been RR MS, with women being the most frequently affected individuals, disability has increased according to progression, and this to lifetime, caregivers' profile being predominantly older male – spouses – and young women – daughters[320].

Aim

The aim was to report the impact of being the significant other of a PwMS or a caregiver.

Results

Partners showed increased disease-related distress and anxiety shortly after the MS diagnosis, with a decrease in disease distress throughout the following five years, but with anxiety not improving [263]. Other complaints referred to were feeling depressed, tiredness and back pain[294].

The activity mostly associated with caregiving was task performance. The tasks for which assistance was most often provided were mobility-related[319] and included transportation, household, moving around inside the house, and getting dressed[319,320,322]. Managing bowels and bladder, transfers, grooming and feeding were less commonly required[319]. Cognitive impairment of the care recipient required more hours of care[320].

Being the caregiver of a PwMS has been a challenge regarding the difficulty that tasks may involve. The most challenging tasks were transportation and helping PwMS move around inside the house[320]. Managing bowels and bladder was not considered as challenging by spouses but was for non-spouses[320]. A lack of specific skills for undertaking these tasks was reported by most caregivers[319,320].

Other problems arising from caregiving were of psychological and emotional origin, relationships and other problems, such as scheduling difficulties and curtailment of employment or limited finances[323]. Psychological aspects perceived by the caregiver included the ones stemming from the care recipient, such as distress at the time of diagnosis, anxiety associated with the variability of impairment over time, the uncertainty about of their lifetime; also emotional aspects, as a result of the challenge of the disease, such as feeling helpless and under emotional strain; and furthermore the psychological and emotional problems produced by the care recipient's impairment, such as mood swings, personality changes[323]. Relationship problems included change of role (e.g., shifting the relationship as a couple towards a care recipient and caregiver relationship). Scheduling difficulties were related to restrictions on time either for oneself or for other relatives (e.g., young women taking care of their mother and children)[320,323]. Adjustment to caregiver role was variable[317] and so was the demand for support, which rose with the care recipient's growing disability[317,320].

The effect of MS on caregivers correlated with their own health problems, as well as with their physical and mental health[319]. Tiredness, depressive and sleep disorders, back pain and sexual relation misadjustment have been reported among caregivers[319]. Caregivers reporting high levels of caregiver strain, such as demands on caregiver time, changes in personal plans, and loss of the care recipient's independence, have led to waning QoL[321].

On the other hand, life outlook and reflection among caregivers may lead to a change in values and insights into life in a positive way[317].

Summary

Impact of MS on significant others and caregivers displayed several common features, which was understandable, since informal caregivers are the most usual helpers of PwMS. Regarding specific impact on caregivers, this has been related to added caregiving tasks, due to the increasing constraints on the care recipient's activities, mainly as regards mobility. These tasks are a challenge and may require specific skills. The psychological impact and the restriction of participation, such as employment, and environmental limitations, such as finance, require an adjustment to the new life's circumstances, and external support. Caregivers' comorbidity and reduced QoL are common.

VI. Conclusions

As shown by the results, we may conclude that MS is a paradigm of disease leading to limitation in activities and participation, and with an impact on HRQoL and QoL. We may conclude that ICF domains reflect the dimension of the disease's impact either on body functions and body structure, or on activities and participation. Contextual factors may play a major role on this impact, modulating how each individual can effectively act and take part in society. Further review of environmental factors for PwMS continues to be an opportunity for the authors. On the other hand, ICF does not reflect features relating to HRQoL and QoL which would complete a full picture of PwMS' health status in a individual-environment interacting system.

We conclude that the perceived problems of PwMS partially converge with professionals' perspective of what is most relevant for PwMS. Assuming service delivery in a client-oriented system, we infer that PwMS should be envisaged more as customers than as recipients of care, and that there is a need to steer health care and non-care systems' service delivery towards clients and their significant others' most important perceived problems. This means a huge learning process for both the client and RHB professionals.

We may conclude from the results that body function and body structure impairment have displayed an association between each other as clusters, although no causal relationship between the different impairments can be seen from the evidence. The body function and body structure impairment associations or clusters that can be supported from the results are as follows:

- Cluster 1. Fatigue, NeuroPsy impairment, depressive disorders, PS, and sleep disorders.
- Cluster 2. Weakness, spasticity, reduced tolerance to exercise and CV and Resp dysfunction (health-related fitness), ataxia, PCD and GD.
- Cluster 3. Sensory disorders and PS.
- Cluster 4. Visual impairment and PS.
- Cluster 5. PFM dysfunction, NLUTD, NBD, and sexual dysfunction.
- Cluster 6. AD, fatigue, decreased tolerance to exercise and CV and Resp dysfunction (health-related fitness), PFM dysfunction, NLUTD, NBD, and sexual dysfunction.
- Cluster 7. NeuroPsy impairment, depressive disorders, and sexual dysfunction.
- Cluster 8. DysA, Dysph, fatigue, NeuroPsy impairment, and depressive disorders.
- Cluster 9. DysA, Dysph, and Resp dysfunction.

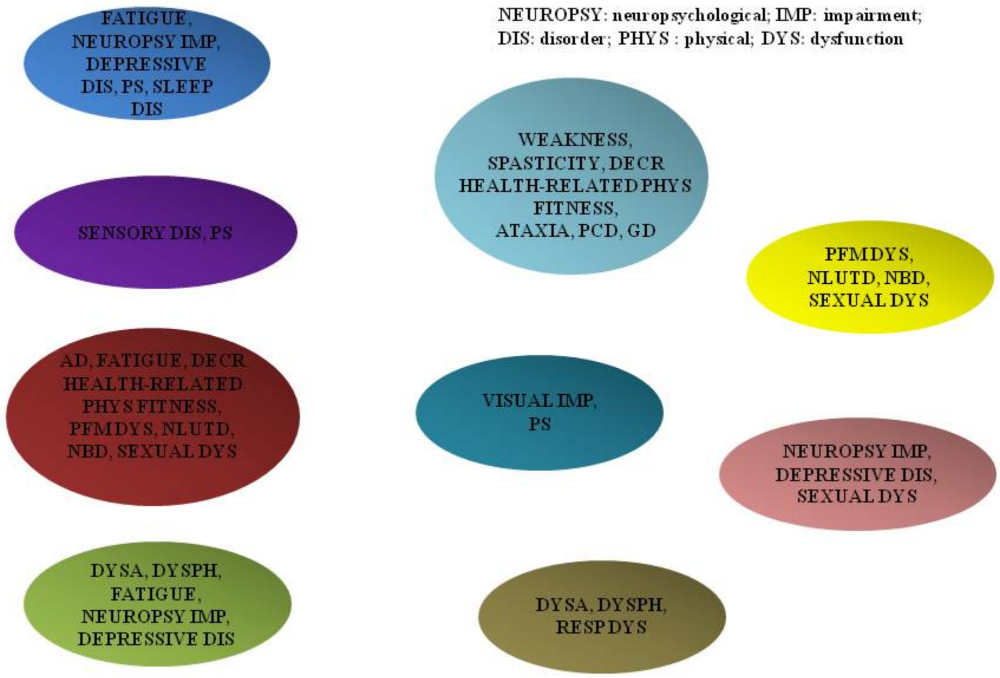
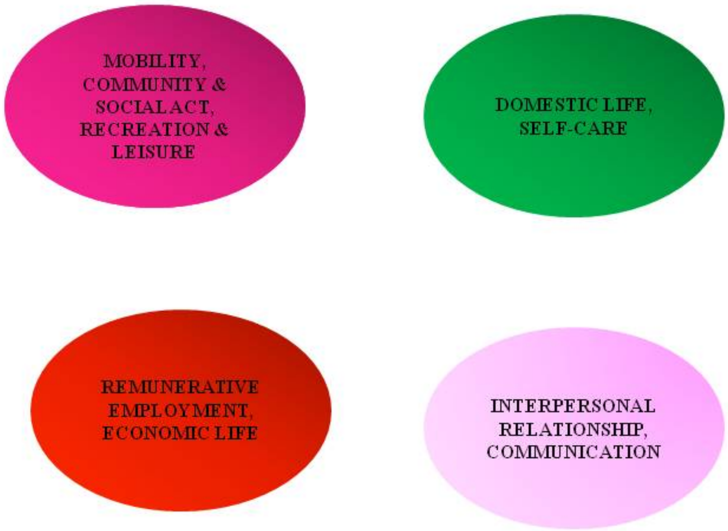


Fig. 1. Body function and body structure impairment clusters

The following clusters were observed as regards limitations of activities:

- Mobility, community and social activities, recreation and leisure.
- Domestic life, self-care.
- Remunerative employment, economic life.
- Interpersonal relationships, communication.



ACT: activities

Fig. 2. Activity limitation clusters

These body function and body structure impairment clusters displayed several impairment coincidences among them, and an impact on HRQoL and QoL: Cluster 1, 2, 3, 4, 5, 6, 7.

1: FATIGUE, NEUROPSY IMP, DEPRESSIVE DIS, PS, SLEEP DIS.

2: WEAKNESS, SPASTICITY, DECR HEALTH-RELATED FITNESS, ATAXIA, PCD, GD.

3: SENSORY DIS, PS.

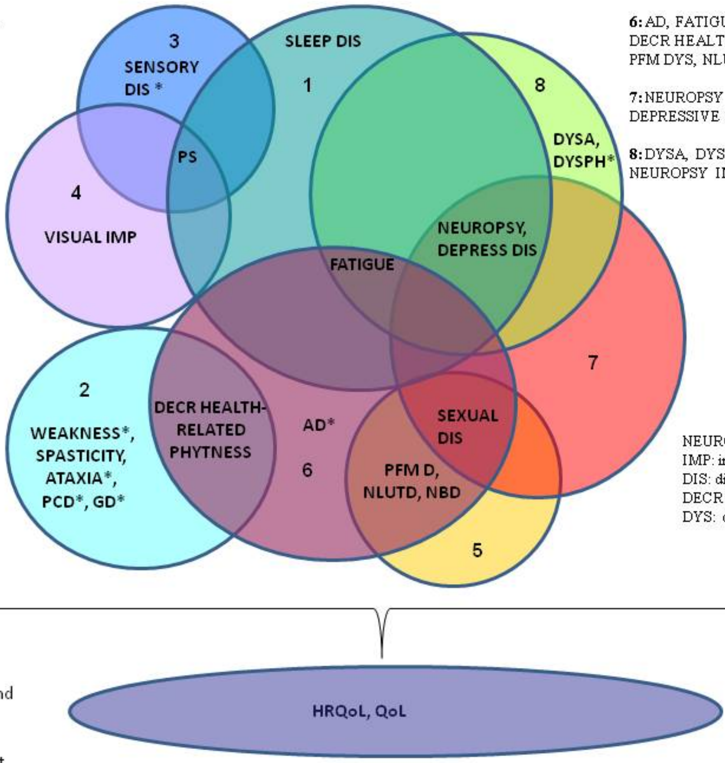
4: VISUAL IMP, PS.

5: PFM DYS, NLUTD, NBD, SEXUAL DYS.

6: AD, FATIGUE, DECR HEALTH-RELATED FITNESS, PFM DYS, NLUTD, NBD, SEXUAL DYS.

7: NEUROPSY IMP, DEPRESSIVE DIS, SEXUAL DYS.

8: DYSA, DYSPH, FATIGUE, NEUROPSY IMP, DEPRESSIVE DIS.



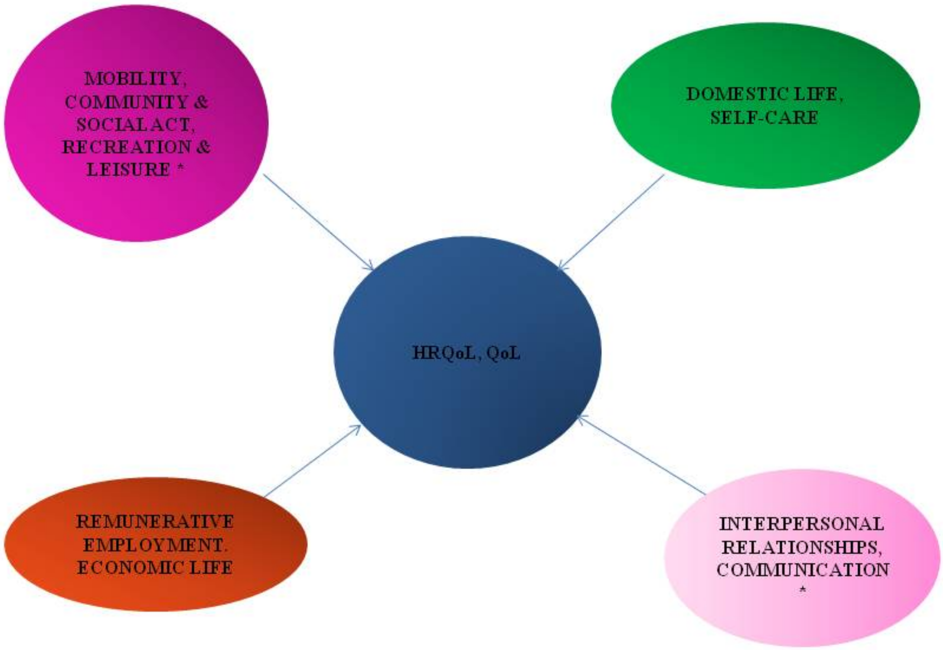
NEUROPSY: neuropsychological
IMP: impairment
DIS: disorder
DECR: decreased
DYS: dysfunction

Fig 3. Body function and body structure impairment clusters' correlation and impact on HRQoL and on QoL.

*:Not associated with HRQoL, QoL

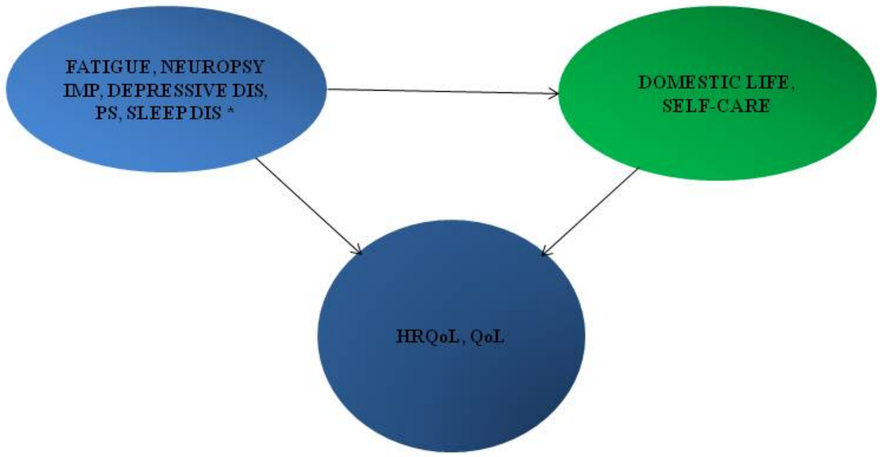
The following activity limitation clusters have had an impact on HRQoL and QoL:

- Mobility, community and social activities, recreation and leisure.
- Domestic life, self-care.
- Remunerative employment, economic life.
- Interpersonal relationships, communication.



ACT: activities
•Not associated with HRQoL, QoL
•Fig. 4. Activity limitation clusters' impact on HRQoL and on QoL

Cluster 1 (except sleep disorders, that have not revealed any association with domestic life and self-care) is related to the *domestic life and self-care* cluster and both prove to have an impact on HRQoL and QoL.

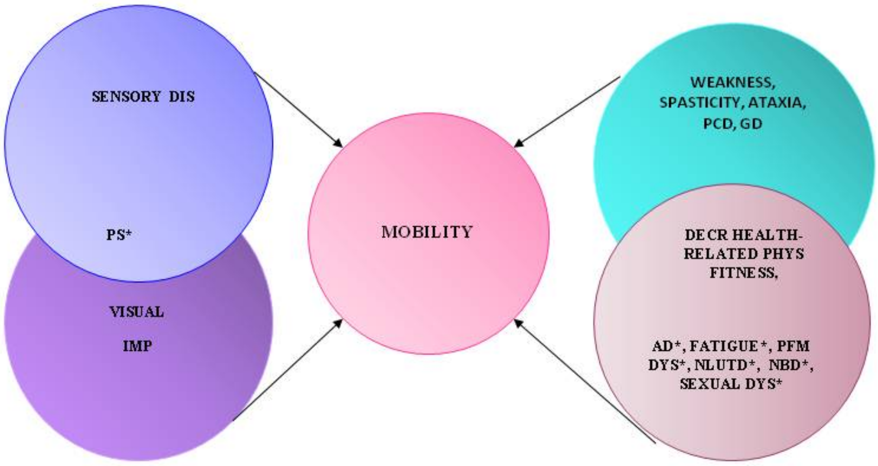


NEUROPSY: neuropsychological; IMP: impairment; DIS: disorder.

•Not associated with domestic life, self-care.

Fig.5. The Fatigue, NeuroPsy impairment, depressive disorders, PS, and sleep disorders cluster and the domestic life and self-care cluster, and its impact on HRQoL and on QoL.

Cluster 2, cluster 4 (except PS that has not displayed any association with reduced mobility), and cluster 6, (except AD, fatigue, PFM dysfunction, NLUTD, NBD, and sexual dysfunction that have not displayed any association with reduced mobility) are related to reduced mobility.

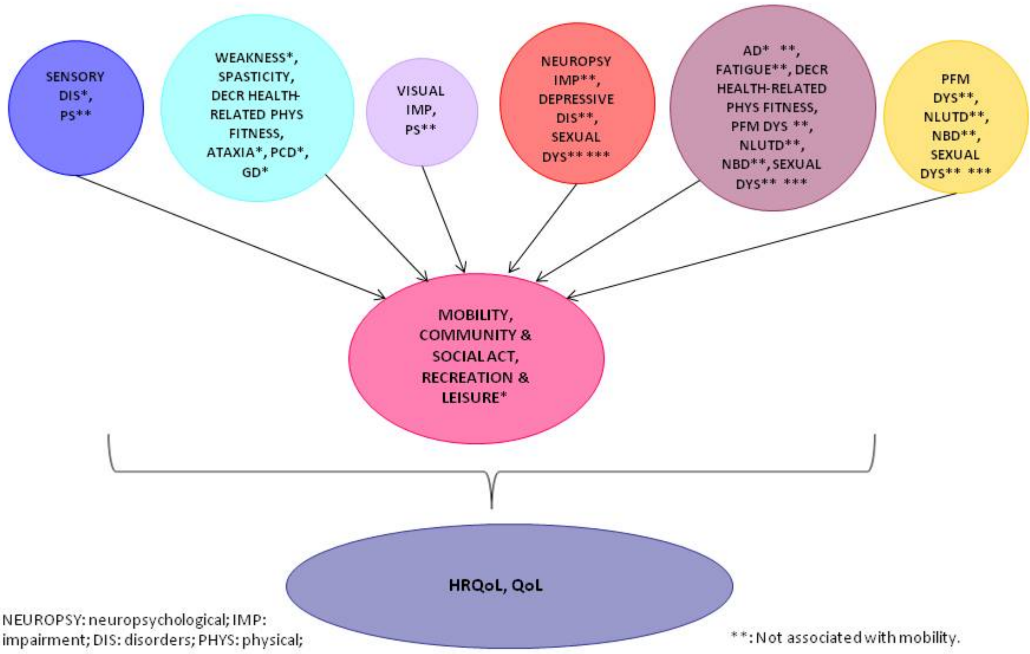


IMP: impairment DIS: disorders DECR: decreased

*: Not associated with mobility

Fig. 6. Body function and body structure clusters limiting mobility.

Cluster 2, cluster 4, cluster 5, cluster 6 (except AD, fatigue, PFM dysfunction, NLUTD, NBD, and sexual dysfunction that have not displayed any association with reduced mobility), and cluster 7 (except sexual dysfunction that has not been reported in association with community and social activities, recreation and leisure) are related to the *mobility*, *community and social activities*, *recreation and leisure* cluster and display an impact on HRQoL and QoL. However, in cluster 2, only *health-related fitness* and *spasticity* have shown any impact on HRQoL and QoL.



NEUROPSY: neuropsychological; IMP: impairment; DIS: disorders; PHYS: physical; DYS: dysfunction; ACT: activities.

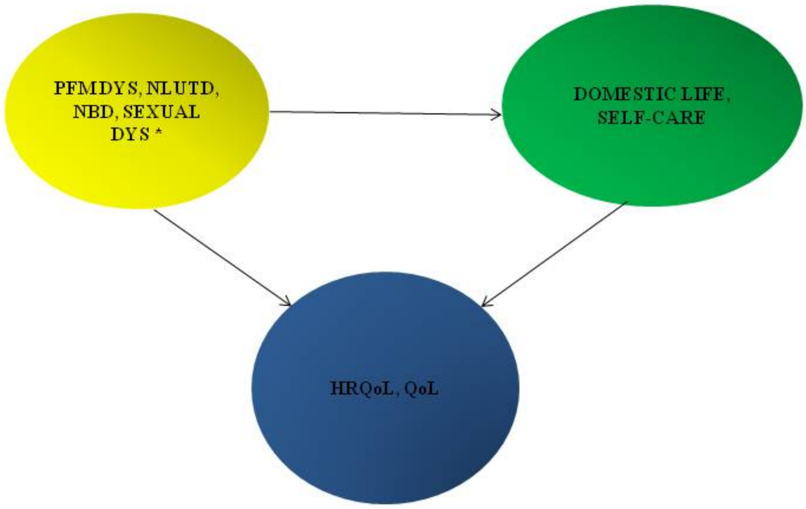
*: Not associated with HRQoL, QoL.

**: Not associated with mobility.

***: Not associated with community & social act, recreation & leisure.

Fig. 7. Body function and body structure impairment clusters associated with mobility, community, and social activities, recreation, and leisure clusters and its impact on HRQoL and on QoL

Cluster 5 (except sexual dysfunction that has not been associated with domestic life and self-care), and the *cluster 6* (except AD and sexual dysfunction that have not been associated with reduced domestic life and self-care) are related to the *domestic life and self-care* cluster and have an impact on HRQoL and QoL.

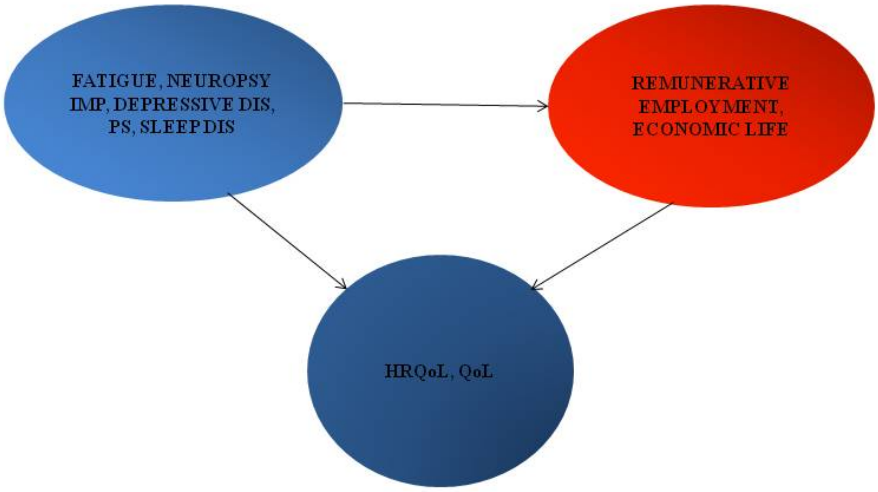


DYS: dysfunction

•Not associated with domestic life and self-care.

Fig.8. The PFM dysfunction, NLUTD, NBD, and sexual dysfunction cluster associated with the domestic life and self-care cluster, and its impact on HRQoL and on QoL.

Cluster 1 (except sleep disorders that have not shown an association with remunerative employment, economic life) is related to the *remunerative employment, economic life* cluster and both have an impact on HRQoL and on QoL.



NEUROPSY: neuropsychological; IMP: impairment;
DIS: disorder.

•Not associated with remunerative employment and economic life.

Fig.9. The Fatigue, NeuroPsy impairment, depressive disorders, PS, and sleep disorders cluster associated with remunerative employment, economic life cluster and its impact on HRQoL and on QoL.

Cluster 1 (except for sleep disorders that have not displayed any association with interpersonal relationship and communication), cluster 5, cluster 7, and cluster 8 (except Dysph that has not been associated with interpersonal relationships and communication), are related to limitation in *interpersonal relationships and communication* and have an impact on HRQoL and QoL (except for communication that has not been reported in association with HRQoL and QoL).

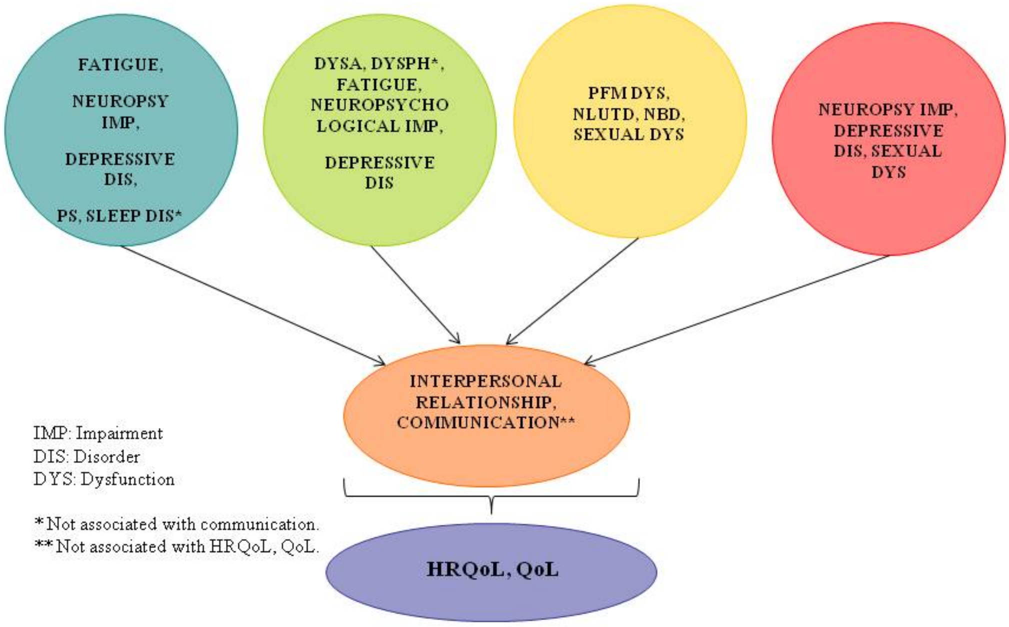


Fig. 10. Body function and body structure impairment clusters associated with interpersonal relationships and communication, and its impact on HRQoL and on QoL

The results thus support the hypothesis that different body functions and body structure clusters among PwMS may have a direct impact on HRQoL and on QoL. However, decreased mobility itself, rather than the impairment that limits this activity, has an impact on HRQoL and QoL.

Compensating strategies are a result of body function mechanisms and of skills acquired to avoid co-morbidity, such as falls, and growing impairment, such as de-conditioning. Some body function and body structure impairment may interfere with compensating strategies, such as visual impairment interfering with visual compensating strategies among PwMS with BD and PCD; or AD interfering with TE performance among PwMS with lower tolerance to exercise and cardiovascular and respiratory dysfunction.

The impact of MS on caregivers has included:

- Fatigue, Psy impairment, PS, and sleep disorders.
- Detrimental remunerative employment and economic life.
- Interpersonal relationship changes.
- Reduced HRQoL and QoL.

The effect of the duration, the day-to-day and individual variability, and the relative unpredictability of the disease completes the broad scope of its impact on PwMS and their caregivers' health status.

Strengths of this study: This overview is underpinned by a review of the literature that has included 2 Cochrane systematic reviews, 1 meta-analysis, 1 systematic review, 6 consensus guidelines, 6 consensus documents, and 5 RCTs. Most of PwMS body function and body structure impairment, most of the limited activities and participation, and impact on HRQoL and QoL have been reported with a broad perspective.

Limitations of this study: Not being a systematic review, the selected database and language may have induced bias, regarding included and excluded articles' relevance. Vertigo, pressure sores, seizures and co-morbidities were not included. Environmental factors have not been extensively reviewed.

Implications for research. Further research is needed on genetics and pathophysiology. On genetics, to define disease-mediating variants in regions of linkage disequilibrium in the genome, and contributions from copy number variants and rare or private mutations[19]; and the environmental factors that interact with gene products and pathways and contribute to disease development[19]. On pathophysiology, to identify potential pathways and its biomarkers, by means of animal models[19,27], cellular and molecular in vivo imaging[27], proteomics techniques to identify protein molecules to be tested in animal models[27], genotype-based epidemiological studies to examine pathogenic pathways[19], including the identification of mechanisms involved in the onset of disease progression. Further research is needed on internationally agreed outcome and assessment tools, such as for assessing fatigue, and visual impairment, and for detecting minimal significant perceived and smaller real changes in improvement due to RHB interventions; on pathophysiology of impairment such as fatigue, on the predictive role of impairment, such as depressive disorders, on other body function impairment; on the epidemiology of PFM dysfunction and on Resp dysfunction; on the impact of DysA, Dysph, Resp dysfunction and reduced communication on HRQoL and QoL; on the impact of MS on keeping the same partner; of sick-listed PwMS on their economic life; of MS on strengthening PwMS and their significant others' relationship. Further evidence-based studies are needed with larger and stratified population samples according to the different MS types, to impairment and to limitation of activities and participation levels, including the more severely impaired (EDSS > 7), and with longer lifetime evolution as target population. Further analysis of environmental factors is also required.

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VIII. APPENDIX

2005 REVISIONS TO THE "McDONALD CRITERIA"

Source: Pohlman[324] 2005, Pohlman[4] 2008

AREAS OF McDONALD CRITERIA MODIFICATION	2005 REVISIONS OF THE "McDONALD CRITERIA"
Modified MRI dissemination in time criteria	1. There are two ways to show dissemination in time using imaging: a. 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 b. 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
Modified MRI dissemination in space criteria	A spinal cord lesion can be considered equivalent to a brain infratentorial lesion, but not for a periventricular or justacortical lesion; an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and to a double lesion to fulfilling the criteria; and individual spinal cord lesions, together with individual brain lesions can contribute to reach the required number of T2 lesions to satisfy Barkhof criteria as modified by Tintoré.
PP MS diagnostic criteria	One year of disease progression (retrospectively or prospectively determined) and

	2. Two of the following: a. Positive brain MRI (nine T_2 lesions or four or more T_2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T_2 lesions) c. Positive CSF (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both).

VEP: visual EP

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