Hidden Disabilities in Multiple Sclerosis – The Impact of Multiple Sclerosis on Patients and their Caregivers

Gavin Giovannoni,[1] John F Foley[2] and David W Brandes[3]

1. Professor of Neurology, Queen Mary University of London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK; 2. Neurologist and Director, Rocky Mountain Multiple Sclerosis Clinic, Salt Lake City, Utah, US; 3. Neurologist, Hope Neurology, Knoxville, Tennessee, US

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Abstract

Multiple sclerosis (MS) is a heterogeneous condition that presents with a large variety of symptoms. While motor functions including coordination, gait and walking ability are clearly visible to clinicians upon examination, several physical and cognitive disabilities associated with MS are less apparent and are easily missed by clinicians, including MS specialists. These are sometimes termed hidden disabilities and are often overlooked because patients do not mention them in consultations, either because they are embarrassed, do not want to disappoint their family and therefore do not mention the symptoms, or they have not linked the symptoms to their disease. Hidden disabilities in MS include cognition and memory impairment, depression, anxiety and pseudobulbar affect, pain, fatigue, sleep disorders, bowel, bladder and sexual dysfunctions, osteopenia and osteoporosis. These disabilities are associated with a reduced quality of life in patients, their families and caregivers, and affect the ability of patients to function in everyday life. Pharmacological treatments and other interventions are available to manage these symptoms; however, the effectiveness of these interventions in MS is variable. There is need for greater recognition and further research into therapeutic options to reduce the burden of hidden disabilities in MS.

Keywords

Cognitive impairment, depression, fatigue, hidden disability, multiple sclerosis

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Correspondence: Gavin Giovannoni, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, E1 2AT, UK. E: g.giovannoni@qmul.ac.uk

Multiple sclerosis (MS) is an immune-mediated neurological disease affecting the central nervous system (CNS) causing demyelination of nerve fibres resulting in a broad range of neuropathological symptoms and signs. MS is the most common non-traumatic neurological disease to afflict young adults. In the US, the prevalence of MS is approximately 90 per 100,000 population[1] with 200 more diagnosed every week.[2] In Europe, the prevalence is estimated to be 83 per 100,000 population with a mean annual incidence of 4.3 cases per 100,000.[3]

The most common form of MS is characterised by relapses, which are periods of neurological dysfunction related to the site of pathology,[4] followed by a recovery from these episodes. This early phase is known as relapsing–remitting MS (RRMS). RRMS is generally preceded by a clinically isolated syndrome (CIS) in which the patient experiences an attack suggestive of neurological dysfunction but does not yet meet the contemporary definition of MS.[5] Of patients with CIS, 30–80 % go on to develop MS. According to the 2010 McDonald criteria, before a definite MS diagnosis can be made, there must be at least one attack that is supported by findings on a neurological examination, an abnormal visual evoked potential response in patients reporting prior visual disturbance, or a magnetic resonance imaging (MRI) consistent with demyelination in the area of the CNS implicated in causing the original symptoms.[5] Often the disease will eventually progress past the RRMS stage leading to a continuous accumulation of disability over time; this is the secondary progressive MS (SPMS) phase and may or may not be associated with superimposed relapses.

The exact aetiology of MS remains unclear, although there is epidemiological evidence of it being a complex disease due to the interaction of genetic, infectious and environmental factors. Although medications are available to reduce the incidence of relapses and delay progression, there is currently no cure for this disorder. This creates a huge burden for the patients, as well as the family members who care for them.

Manifestations of Multiple Sclerosis

MS is a heterogeneous, multifactorial disorder that presents with a large variety of symptoms, which can change over time and generally differ between patients. As MS is characterised by widespread

Table 1: Common Hidden Disabilities in Multiple Sclerosis

Disability Type	Stage of Disease Hidden Disability is Most Likely to be Observed	Estimated Prevalence (%)	Reference
Cognitive dysfunction	All stages	40–65	7,10,13
Depression	All stages	50	44
Anxiety	Common during the start of a relapse	36	63,158
Pseudobulbar affect	Generally associated with later disease stages (PPMS/SPMS)	10	68,69
Fatigue	All stages, one of earliest symptoms	80	72,73
Sleep disorders	All stages. No evidence to suggest increased incidence at a particular disease stage	30	95,96
Bladder dysfunction	Severity of symptoms often correlate with the degree of spinal cord involvement and, hence, the patient's general level of disability	75	107–110
Sexual dysfunction	All stages. No correlation with bowel dysfunction, duration of disease, disease course or number of exacerbations in the last year	40–90	107,109,117
Bowel dysfunction	Incidence not related to disease duration	54	107,114,115
Pain	Correlation between pain and age, EDSS, disease duration and disease course	55–86	123,159,160
Bone health	Has been correlated to level of disability	27	127

EDSS = Expanded Disability Status Scale; PPMS = primary progressive multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

distribution of lesions throughout the grey and white matter of the CNS, clinical manifestations of MS are variable with a number of symptoms being reported including motor and sensory symptoms as well as neuropsychiatric syndromes.[6] Lesions in the corticospinal tracts cause weakness in the short term and, spasticity with hyperreflexia in the long term. Motor functions including coordination, gait and walking ability are often affected in patients with MS and are clearly visible to clinicians upon examination. However, some physical and cognitive disabilities associated with MS are less evident and can easily be missed by MS specialists. Symptoms also fluctuate with time of day, fatigue, heat or cold, depression and symptomatic management.

Hidden Disabilities

The term 'hidden disabilities' refers to symptoms and disabilities that are not obviously apparent or visible, and patients may not automatically offer information about them to the MS specialist. Hidden disabilities are not easily elicited by a standard history or examination; specific testing or questions are needed to reveal these issues. The standard examination offers its own limitations in that it does not allow enough time to assess and observe the nuances of these 'hidden' symptoms unless the clinician has a heightened awareness and invests the time and energy to look for them. Patients often do not volunteer information regarding these disabilities either because they are embarrassed by them or because they are not aware of them being a problem. Some patients may also not realise that these symptoms are a consequence of MS.

Hidden disabilities include difficulties with cognition, memory, mood, affect, pain, fatigue, sleep, bowel, bladder, sexual function, as well as osteopenia and osteoporosis (see *Table 1*). Frequently, physicians do not assess these symptoms owing to the limited time and resources available to them for patient assessment. Moreover, there is a lack of quick, cheap and widely available standardised tools for evaluation, and physicians are often unaware of the available screening tools. Physicians need to be made more aware of hidden disabilities which can adversely affect an MS patient's health-related quality of life (QoL) and their ability to function at work, at home and in society.

Cognitive Dysfunction

Cognitive impairment is a common problem in MS although mild forms are not readily recognised in routine examinations. Prevalence estimates of cognitive impairment in MS range from 40 to 65 %, depending on the research setting.[7–10] Common cognitive symptoms include deficits in attention, executive functioning, processing speed and memory loss. These symptoms have considerable impact on many aspects of daily life.[11]

Cognitive dysfunction can occur at all disease stages and types of clinical course. A study of patients with benign MS (defined as disease duration ≥15 years and Expanded Disability Status Scale [EDSS] score ≤3) found a high prevalence of cognitive impairment (45 %) in this patient population.[12] Cognitive impairment in CIS was found to be significant and frequent (57 %)[13] although it is generally less frequent in RRMS compared with SPMS. Cognitive impairment is also less frequent in some forms of primary progressive (PP) patients because it tends to be caused by brain rather than spinal cord pathology, the latter being the most prevalent disability in PP patients.[14,15] Early detection often requires significant effort and expertise on the part of the healthcare provider. As a result, detection is a major problem and delays the initiation of therapies to manage it. It is difficult to evaluate this problem routinely and patient reports are often confounded by mood and other subjective factors.[16]

Numerous genetic and environmental factors also contribute to the development of cognitive dysfunction in MS.[17] The heterogeneous nature of MS results in varied presentation of cognitive issues and these can have a large impact on daily activities,[18] neurorehabilitation[19] and work capacity.[20,21] Cognitive dysfunction is also associated with lower QoL,[22] although the extent to which MS patients with cognitive dysfunction can validly self-report their QoL is limited.[23]

Cognitive impairment is apparent from tests measuring attention and information processing speed, working memory, verbal and visuospatial memory, and executive functions.[24] Standardised neuropsychological tests are needed to provide a more valid determination of cognitive dysfunction in patients including visual and spatial processing, memory and mental processing speed. A number of assessment tools are available (see *Table 2*) including the Selective Reminding Test (SRT),[25] 7/24 Spatial Recall Test[26] and the Paced Auditory Serial Addition Test (PASAT).[27] Also available are the Symbol Digit Modalities Test (SDMT), which is becoming commonly used in MS trials,[28] the online tool NeuroTrax (www.neurotrax.com) and the MS Neuropsychological Screening Questionnaire (MSNQ).[29] A new initiative, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) has been optimised for small centres, with one or few staff

Table 2: Summary of the Major Assessment Tools Used to Evaluate Cognitive Dysfunction

Test	Description	Reference
Selective Reminding Test	Provides 12 words, which are selectively rehearsed by the subject until they are memorised	25
7/24 Spatial Recall Test	Tests spatial memory by placing seven poker chips on a board. After a ten-second exposure the patient attempts to recreate the pattern	26
Paced Auditory Serial Addition Test	Tests working memory, attention and arithmetic capability. The patient is given a number every three seconds and asked to add the number they just heard with the number they heard before	27
Symbol Digit Modalities Test	Patient substitutes a number, either orally or written, for randomised presentations of geometric figures	28
Neuro Trax (MindStreams®)	Computerised test taking approximately 30–45 minutes to complete – contains tests for memory, attention, executive function, visual spatial processing, verbal skills, information processing speed and cognitive motor skills	29
Neuropsychological Screening Questionnaire	Self-administered questionnaire, which asks patients to assess frequency of cognitive problems	29
Brief International Cognitive Assessment for Multiple Sclerosis	Recommendations comprise Symbol Digit Modalities Test, if only five minutes was available, with the addition of the California Verbal Learning Test® – Second Edition and the Brief Visuospatial Memory Test	30

members who may not have neuropsychological training.[30] Batteries of tests have also been developed, such as the Brief Repeatable Battery of Neuropsychological Tests (BRB-N).[31] Certain paraclinical parameters may serve some utility in assessing cognitive endpoints. The main MRI predictors of cognitive impairment are baseline brain damage and progressive central brain atrophy in the two years following MS diagnosis.[32]

There is currently no consensus as to which screening tests for cognitive dysfunction should be used routinely and on a large scale in MS patients, though several tests exist.[33–35] It has been suggested that single, predominantly speed-related cognitive tests are preferable to extensive and time-consuming test batteries.[36] With reliable methods of evaluation, decline in cognition may be used as a clinical measure of disease progression.[17] While some studies have found an association between physical disability and cognitive disability,[36] they do not share a causal link since pathology in different areas of the CNS drives the different clinical manifestations of MS.

Although there are no recommended effective treatments for cognitive dysfunction in MS, several products have been used off-label for this indication. Limited evidence suggests that L-amphetamine sulphate may improve cognition in patients,[37] particularly memory.[38] Drugs employed in the treatment of Alzheimer's disease such as donepezil and memantine have been used in MS but randomised controlled trials (RCTs) have failed to demonstrate their superiority over placebo.[39,40] In an RCT, gingko biloba was found to improve cognitive impairment but the effect was not statistically significant.[41] There is evidence from single-case or small group studies that memory rehabilitation can be beneficial for patients with MS but findings from RCTs and systematic reviews have been inconclusive.[42] Recent data has found that short-term treatment with natalizumab may significantly improve cognitive performance in patients with RRMS.[43] There remains a substantial need for more effective therapies and improved management strategies.

Depression, Anxiety and Pseudobulbar Affect

Another category of neuropsychiatric symptoms that is commonly seen in patients with MS regards those affecting mood and behaviour.[44] Depression is the most common neuropsychiatric disorder encountered in MS. The lifetime prevalence rates of depression in MS patients are around 50 %, approximately three-times higher than in the general population.[45–47] A similar prevalence has been reported in patients with benign MS.[12] Early recognition and management of depression in MS is important because it may be linked to morbidity, mortality, decreased QoL, disease exacerbations, adherence to disease-modifying drugs and suicide risk in the patient, as well as the caregiver's distress and QoL.[44,48] Suicide ideation has been found to be common in MS patients,[49] although a recent Danish study found no increased risk for suicide attempts in MS compared with the general population.[50] Depression severity has been found to be the most important risk factor for suicide ideation.[51]

Depression is commonly underdiagnosed and undertreated in MS patients[52] since it is not readily detected.[53] Symptoms of depression such as fatigue and social isolation are also associated with greater cognitive impairment.[54,55] Since depression is common in the general population, a proportion of MS patients are likely to have endogenous depression and they would have been depressed whether or not they had MS. However, the high prevalence of depression in MS patients relative to the general population suggests that it is disease-related as well. Furthermore, there is a higher rate of depression in MS than in other diseases. Depression in MS can be organic, a result of structural brain abnormalities,[56] or situational, a reaction to poor prognosis or recurring symptoms such as fatigue, weakness and pain. Symptoms of post-traumatic stress disorder have been reported following a diagnosis of MS.[57] Another factor in depression in MS is the use of disease-modifying drugs. Interferon beta (IFNβ) treatment may exacerbate depression and, in rare cases, increase suicidal tendencies,[58,59] although older studies have associated depression with discontinuation of IFNβ treatment.[60]

Despite the number of tests available (Beck Depression Index, Hamilton Depression Rating Scale, Hospital Anxiety and Depression Index), these instruments are not routinely used in most clinical settings. Again, this is often because of time and resource limitations during office visits. Management strategies include medication, counselling and psychotherapy.[44,61] Patients with MS may also have a poorer treatment response to antidepressant medication. Cognitive impairment, particularly executive functioning, has been found to be a predictor of response to antidepressant treatment.[62]

Anxiety is also associated with MS and seems to progress according to the severity of the disease.[63] There are fewer studies on anxiety than depression in MS. A recent study (n=198), using the Hospital Anxiety and Depression Scale, found that the prevalence of anxiety (44.5 %) was higher than that of depression (18.5 %).[64] Another study (n=140) found

that the lifetime prevalence of any anxiety disorder was 35.7 %, with panic disorder (10 %), obsessive compulsive disorder (8.6 %) and generalised anxiety disorder (18.6 %), being the most common diagnoses. Risk factors for anxiety include being female, a co-morbid diagnosis of depression and limited social support.[65] It has been suggested that MS patients suffering from anxiety disorders may benefit from additional therapeutic support specifically targeting anxiety.[66]

Another under-recognised symptom of MS is pseudobulbar affect, which is characterised by sudden outbursts of uncontrolled laughter or crying that are disproportionate or incongruent to a patient's feelings or surroundings.[67] Approximately 10 % of MS patients are affected by this condition,[68,69] most commonly during the later stages of disease. Some rating scales for pseudobulbar affect have been developed, including the Center for Neurologic Study-Lability Scale (CNS-LS)[70] but it is still often missed during consultations. Dextromethorphan co-administered with quinidine (Neudexta®) has shown efficacy in improving the symptoms of pseudobulbar affect in MS patients[70,71] and has now been approved by the US Food and Drug Administration (FDA) for treating this condition.

Fatigue and Sleep Disorders

Fatigue is often found to be the most common symptom in MS and can be the first manifestation of the disease.[72] It has a prevalence of up to 80 %, and 30–40 % of MS patients consider it the most disabling symptom of the disease.[73–77] Significant fatigue has also been reported in 49 % of patients with benign MS.[12] The consequences of fatigue include loss of work hours and in some instances, loss of employment.[78] MS-related physical fatigue may obscure other forms of fatigue, including mental fatigue, psychological fatigue and daytime sleepiness. Fatigue in MS patients may be multifactorial – MS is associated with an increased prevalence of other conditions that contribute to fatigue, including depression and sleep disorders. Primary causes of fatigue in MS include increased levels of cytokines, endocrine causes and axonal loss.[72] Basal ganglia and frontal/parietal cortical atrophy has also been associated with fatigue in RRMS.[79] Fatigue may also be caused by co-morbidities such as anaemia, hypothyroidism, as well as being a common side effect of medication.

Data on the impact of the disease-modifying drugs on fatigue vary. It has been suggested that most disease-modifying drugs do not have a significant effect on MS-related fatigue,[80] although evidence has suggested that glatiramer acetate (GA) improves fatigue symptoms in MS.[81,82] On the other hand, a recent observational study reported fatigue as the most common adverse affect associated with GA treatment.[83] A study suggested that the prevalence and severity of fatigue during natalizumab treatment was lower compared with treatment with IFNβ or GA.[84] Furthermore, recent data have demonstrated that short-term treatment with natalizumab may significantly improve fatigue in patients with RRMS.[43]

Despite its high prevalence, fatigue in MS is not very well understood and has been difficult to define and quantify because of its complex and subjective nature.[72,85] Unlike the occasional fatigue observed in otherwise healthy individuals, MS patients report fatigue that comes on easily, affects their ability to perform tasks and persists, preventing sustained physical functioning.[75,86] Several rating scales have been developed such as the Chalder Fatigue Scale,[87] Fatigue Severity Scale (FSS),[88] the Modified Fatigue Impact Scale (MFIS),[89] Checklist Individual Strength (CIS20R) (173133914) and the Multidimensional Fatigue Inventory (MFI).[90–92] However, a study that compared the FSS, MFIS and CIS20 found that these questionnaires are not very responsive to change in patients with MS and suggested that future trials should monitor profiles of fatigue by repeated measurements rather than pre-post assessments alone.[93] Treatment options for fatigue in MS include the off-label use of amantadine, pemoline, non-amphetamine stimulants (i.e. modafinil) and non-pharmacological interventions such as exercise and cognitive behaviour therapy.[72] Amphetamine stimulants (i.e. methylphenidate) are also used off-label for this indication.

Sleep disorders are important among many contributing factors to fatigue in MS. Sleep disorders not only disturb sleep at night, but also result in impaired performance during the day. MS patients who experience unsatisfying sleep may have lower QoL and increased depression.[94,95] A large study (n=1,063) of subjective sleep disturbances found mild, moderate and severe problems in 13.3 %, 21.5 % and 30.0 % of the MS population, respectively, with women at higher risk of sleep disturbance than men.[96] Insomnia occurs commonly in MS patients and may arise secondary to pain, spasticity, depression, anxiety, nocturia, medication, or primary sleep disorders such as restless leg syndrome (RLS) and periodic limb movement disorder (PLMD).[72,95] The majority of patients with RLS have PLMD but the reverse is not true.[97] The prevalence of RLS among MS patients is approximately 3–5 times that of the general population.[98] Obstructive sleep apnoea is also common in MS patients and has been associated with fatigue.[99] Recent data found a predisposition for obstructive sleep apnoea and accompanying central apnoeas in patients with MS, particularly those with brainstem involvement.[100] Nocturia was reported as the primary reason for middle-of-the-night insomnia.[101] Narcolepsy, a chronic neurological disorder in which the brain is unable to regulate normal sleep–wake cycle, leading to fleeting urges to sleep, has also been reported by MS patients as well.[102,103]

Unless patients and partners are directly questioned about sleep, the diagnosis of sleep disorders is often missed. Patients themselves are often unaware of many sleep disorders that only occur when the patient is asleep such as snoring, sleep apnoea and PLMD. Furthermore, sleep disorders are associated with increased morbidity and mortality.[104,105]

Poor sleep hygiene and subsequent fatigue are often associated with other aspects of disease such as spasticity, pain and bladder problems, therefore treating these underlying issues can improve sleep and, in turn, fatigue. More than one sleep disorder can occur in a single patient. As a result, considerable time during a clinical evaluation may be necessary to elicit the full range of problems, and a sleep study may be required. Patients on chronic IFNβ or GA therapy have shown lower sleep efficiency than patients without therapy,[106] but, this refers to an off-label side effect.

Bladder, Bowel and Sexual Dysfunctions

MS patients often experience bladder, bowel and sexual problems, which are frequently hidden from physicians, perhaps by the patients themselves owing to their embarrassing nature. These problems warrant greater attention because they affect QoL and patients' abilities to participate in daily and social activities.[107] The prevalence of urinary dysfunction is high (over 65 %) and symptoms include urgency, infection, neurogenic detrusor overactivity, and detrusor sphincter dyssynergia,[108] and occur at early disease stages.[109] Several therapeutic options are available for urinary tract disorders including anticholinergics, clean intermittent self-catheterisation and the use of desmopressin, and

intradetrusor botulinum neurotoxin type A.[110,111] Although a recent Cochrane review found no evidence to support the efficacy of anticholinergics in MS patients.[112] Self-catheterisation may be difficult for women, people with upper limb dysfunction, spasticity, weakness, poor sitting balance, or cognitive impairment, and in such individuals an indwelling catheter (suprapubic or urethral) may be required.[113]

Constipation and faecal incontinence are the two most frequently observed bowel symptoms in MS, and result from dehydration, anal inhibitory reflex and paradoxical contractions.[114] A recent literature review reported a prevalence of constipation and faecal incontinence of 40 %. Anorectal dysfunction significantly affected patients with nearly one in six patients limiting social activities or even quitting work because of symptoms.[115] The pattern of bowel symptoms does not necessarily correlate with urinary disturbance, the duration of MS, or the degree of disability. Management strategies to address constipation in people with MS may involve ensuring adequate fluid intake other than caffeinated options and a high fibre diet. Treatment is generally symptomatic although gut-focused behavioural treatment (biofeedback) has been found to be beneficial in patients with limited disability and a non-progressive disease course.[116]

Sexual dysfunction associated with MS is frequently overlooked. Sexual dysfunction is linked to a reduced QoL and is a cause of marital and relationship problems. Sexual dysfunction may not only be due to lesions affecting the neural pathways involved in physiological function, but also result from general physical difficulties or psychological and emotional issues.[117] Partners may not recognise the link between fatigue or decreased libido and the MS disease process. The prevalence of sexual dysfunction in MS patients is higher than that reported in other chronic diseases and affects 50–90 % of men and 40–80 % of women.[107,117–121] The most frequent dysfunctions include anorgasmia or hyporgasmia, decreased vaginal lubrication and reduced libido in women, and impotence or erectile dysfunction, ejaculatory dysfunction and/or orgasmic dysfunction and reduced libido in men.[117] Treatment options for sexual dysfunction in MS are limited. Specific pharmacotherapy is only currently available for erectile dysfunction and a recent Cochrane review found limited evidence to support the effectiveness of sildenafil citrate for erectile dysfunction in MS.[122]

Pain

The prevalence of pain symptoms in MS varies between studies but has been estimated to be as high as 86 %.[123] In a Canadian study of MS patients, 55 % of participants reported acute or chronic pain syndrome.[124] In a postal survey of MS patients, 66 % of the respondents reported pain, 25 % of whom reported severe pain. Persons with pain reported an average of 6.6 distinct pain sites.[125] A variety of pain symptoms are experienced in MS; neuropathic pain includes trigeminal neuralgia, L'Hermitte's sign (an electrical sensation that runs down the back and into the limbs) and dysaesthesic pain. Somatic pain includes painful muscle spasms and lower back pain. Headache (tensive headache and migraine) is also frequently reported.[126] Treatments are the same as those employed with patients who do not have MS, since there are few specific options.

Bone Health

MS patients may have an increased risk of osteoporosis. People with MS have reduced mobility, a known risk factor for osteoporosis, and are susceptible to falls. Reductions in bone mineral density (BMD) have been detected at the lumbar spine, hip and total body in MS patients, the greatest degree of reduction being at the hip. There is also a correlation between the disability level, measured by the EDSS and BMD at the lumbar spine and femoral neck. The rate of loss of BMD also correlates with the level of disability.[127] In a study of the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry (n=9,346), 27.2 % of respondents reported low bone mass, 15.4 % reported osteoporosis and 17.1 % reported osteopenia. A history of fracture after age 13 years was reported by 16 % of respondents.[128] A recently devised risk score for estimating the long-term risk of osteoporotic and hip fracture includes MS as a risk factor.[129] Criteria for screening MS patients for osteoporosis have yet to be established.

More studies are required to assess the impact of supplementation on loss of BMD in patients with MS, as no recommendations currently exist. Despite recent studies suggesting that vitamin D plays a role in MS, there appears to be no correlation between vitamin D levels and bone health in MS.[127] A small Phase II trial found that supplementation with 20,000 IU vitamin D a week did not prevent BMD loss.[130]

Burden of Multiple Sclerosis

Not surprisingly, hidden disabilities, together with other physical symptoms of MS, create a huge burden for patients. This burden can extend to their families and caregivers causing them distress and potentially straining the relationships between patients and their relatives, caregivers and partners.[131] As MS progresses, patients are often decreasingly able to perform many of their normal daily functions; they become unable to continue working and their social life is often restricted. Unfortunately, healthcare providers are often not aware that failure to treat hidden disabilities appropriately has consequences well beyond the patient's clinical parameters.

Impact on Employment

Numerous data have demonstrated the impact of MS on patients' ability to remain in employment,[78,132–134] with as many as two-thirds of MS patients unable to maintain employment.[135] Specific symptoms such as fatigue and cognitive performance have been associated with increased odds of becoming unemployed.[133] In one study, 90 % of MS patients who reduced their working hours, reported that fatigue was responsible for their work status change.[78] The severity of depression has also been correlated to unemployment.[135] Aspects such as a flexible work schedule are important to enable MS patients to remain in the workforce. The MS work difficulties questionnaire has been devised as a measure of workplace difficulties in MS.[136]

Loss of employment results in financial insecurity which adds to the burden of MS. In an American survey of 983 working-age MS patients, 27 % reported that, since being diagnosed with MS, health insurance concerns had affected their employment decisions. Furthermore, 16 % had experienced considerable difficulty paying for healthcare, 27 % postponed seeking healthcare because of cost and 22 % delayed filling prescriptions, skipped medication doses or even split pills because of costs. Worries about the cost of basic necessities such as food and housing were reported in 27 % of the patients.[137]

Quality of Life and Patient-reported Outcome Measures

Measurements of QoL are becoming increasingly important in determining treatment efficacy in chronic illnesses and should be

used for the follow-up of patients with MS. Many such tools are available and include the Short Form 36 general health survey (SF-36), the MS Impact Scale 29 (MSIS 29), Functional Assessment of MS (FAMS) and the Sickness Impact Profile (SIP), Life Satisfaction Questionnaire (LSQ) and Quality of Well-Being Scale (QWBS)[138] but these are rarely used on a regular basis in a clinical setting.

To assess wellbeing, physicians and other healthcare providers often simply ask about the average day of a patient to gain information about their QoL, using their own common sense and critical judgement rather than specific tests. Furthermore, MS specialists are becoming more aware of QoL and so there is perhaps a trend towards more routine QoL evaluation and monitoring and patient-reported outcome measures. However, further education is needed, both in general and by the referring healthcare provider. The role of the clinical nurse specialist is vital in the management of hidden disabilities in MS. With correct training, nurses can diagnose and assess many of these symptoms.[139,140] Cognitive impairment can also impact on patient-reported outcomes, patients with higher cognitive reserve were more likely to report lower levels of perceived disability.[141]

Hidden disabilities contribute to a decline in the QoL of an MS patient. Cognitive impairment affects daily functioning even during the early stages of disease and may be considered the most devastating symptom for patients and their families.[142] It is clearly associated with decreased QoL.[143] QoL is also correlated with psychological distress and depression.[144,145] Other symptoms of MS including fatigue, bladder, bowel and sexual dysfunction also adversely affect a patient's wellbeing.[146]

Addressing disabilities that contribute to a decrease in QoL is important to allow MS patients to continue performing their everyday routines, remain employed and to psychosocially interact with others. Successful treatments for physical and neuropsychiatric disease symptoms will clearly improve the QoL for MS patients.

Impact on Family and Caregivers

The burden and problems associated with MS affect not only the individual with the disease but also their family members.[147] MS results in psychological, emotional, social and financial issues that impact the whole family and lower their overall wellbeing and QoL.[148] The relationships and balance within a family of an MS patient are liable to negatively change as a result of the disease.[149]

While each family member is affected by the disease in different ways depending on their role within the family as well as individual coping methods, it is the partners of patients that tend to experience the most distress and anxiety, and endure the greatest decline in QoL compared with other categories of caregivers.[150] Chronic illness creates stress and strains a relationship, potentially leading to marital problems and divorce.[151] One study found a six-fold increase in the risk of divorce among patients with MS or cancer following diagnosis if the woman was diagnosed versus the man (20.8 versus 2.9 %).[152] However, the opposite trend was observed in another study of MS patients, which also demonstrated a greater probability of divorce and separation among MS patients relative to the background population. This study found that five years after onset, the cumulative probability of remaining in the same relationship was 86 % in MS patients versus 89 % in controls. However, at 24 years the probability was 33 % in MS patients versus 53 % in controls.[153]

Table 3: Therapeutic Strategies for Treating Hidden Disabilities

Disability	Treatment	Reference
Cognitive impairment	L-amphetamine sulphate	37
	Memantine	40
	Gingko biloba	41
Depression	Desiparime	61
	Paroxetine	61,160
Anxiety	Benzodiazepines including alprazolam, temazepam, diazepam	161
	Buspirone	161
	SSRIs	161
Pseudobulbar affect	Dextromethorphan with quinidine (Nuedexta®)	70,71
	SSRIs, tricyclic antidepressants	67
Fatigue	Amantadine	72
	Pernoline	72
	Modafinil	72,162,163
Bladder dysfunction	Anticholinergics	112
	Desmopressin	164
	Botulinum toxin A	165,166
Sexual dysfunction	Treatments for erectile dysfunction including sildenafil, alprostadil	122,167
Pain	Sativex®	168
	Gabapentin, pregabalin, Lamotrigine, tricyclic antidepressants	169

It should be noted that many of these indications are off-label. SSRIs = selective serotonin reuptake inhibitors.

Burdens on both the individual and the caregiver contribute to the indirect costs of MS as one or both of them may be unable to work.[151] More attention is needed in this area, especially in the general clinical setting with the well-known time limitations and a very complicated disease process. Future research should focus on the diagnosis and treatment of specific MS-related problems, as well as identifying family members at risk of depression, and finding psychotherapeutic interventions and support for them.[149]

Management Approaches for Hidden Disabilities

A number of medications are employed in the treatment of hidden disabilities in MS with varying levels of success, although almost all are not specifically indicated or approved for use in MS patients (see *Table 3*). There have been developments in the treatment of MS symptoms, most notably dalfampridine (formally called fampridine-SR and 4-aminopyridine), which has been approved for specific use in MS patients to improve walking speed.[154,155]

Physical and cognitive therapies are available for the management of hidden disabilities in MS, although studies have resulted in variable outcomes.[156,157] Family communication and counselling can also be important for improving QoL as can addressing psychological issues such as the stress, uncertainty and burden of MS. Various resources may be available to MS patients but are limited to specific patient issues – these include: MS societies, social workers and rehabilitation facilities. However, many healthcare workers are not specifically trained to help MS patients and may need further education.

Summary and Conclusion

Patients with MS can present with a complex range of symptoms, such as fatigue, cognitive dysfunction, bladder, bowel and sexual

dysfunction, and mood disorders. These symptoms can affect the success of therapeutic interventions and must be suitably managed in order to optimise treatment outcomes. Many of the symptoms associated with MS are not evident upon physical evaluation and are not volunteered by the patient. Partners and caregivers are often aware of deficits but are not in the room during an examination. Such symptoms are considered hidden disabilities and are frequently overlooked as a result of the limited time and resources available to clinicians for patient assessment. There is a need for quick, cheap and widely available standardised tools for evaluation. The ability to recognise and manage these symptoms can have a significant and beneficial impact on the QoL of MS patients and their partners and caregivers. Clinicians should actively screen for hidden disabilities, refer to specialists where necessary and educate patients, their families and caregivers about the potential therapeutic options available to them.

Effective multidisciplinary management strategies can alleviate the burden of many of the hidden symptoms in MS. However, many therapeutic strategies for the management of these disabilities are not specifically indicated in MS. Following the approval of dalfampridine in the improvement of walking speed for some patients with MS, there is a substantial need for more research and evaluation of other symptomatic treatments. This and the development of new therapies could greatly reduce the negative effects of MS and improve the QoL and economic impact of the disease both for patients and their caregivers. ■

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