

Disease Progression in Multiple Sclerosis I. Impaired Mobility and Its Impact on Limitations of Activities and Social Participation

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Abstract

Limitations in activities of daily living are important to an individual's life, and the progressive nature of multiple sclerosis (MS) can have a significant impact on the patient's quality of life (QoL). Monitoring low-level limitations of activities during the early stages of MS should be encouraged, as it can indicate advancing neurological damage. Clinical data and survey evidence from numerous research groups suggest that impaired mobility is a large contributory factor to diminished QoL. Although these studies have demonstrated the negative effect of reduced mobility, there remains a substantial need for greater recognition of the presence and effects of disabilities, including reduced mobility, fatigue, pain, depression and spasticity, and the need for targeted treatments for specific impairments. In this review, literature describing the impact on the lives of patient is presented; because of the variability in speed of progression and prognosis with early mobility loss, the need for early, continuous and consistent assessment is suggested.

Keywords

Multiple sclerosis, walking ability, mobility, activity and social participation, determination of walking ability

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Patients with multiple sclerosis (MS) typically present with a clinically isolated syndrome (CIS), which eventually develops into relapsing–remitting MS (RRMS); after a varying number of years, most patients transform into secondary progressive MS (SPMS). An alternative course is primary progressive MS (PPMS), which develops more rapidly from onset and is also inevitably accompanied by some decline in walking ability.¹ In early MS, the prognosis after disease onset is highly variable and the time taken to progress to irreversible disability is generally unpredictable.

A number of studies have shown that disease onset in later life generally results in more rapid progression. This was shown in a study of 1,844 patients with MS in France, which found that individuals who were diagnosed with MS at up to 29 years of age took a median of 33 years to progress to a disability status score of 7 (unable to walk more than 10m without rest and/or support), whereas in patients diagnosed at over 50 years of age, a similar progression was seen in a median of only 17 years (see *Figure 1*).² In the same study, progression from RRMS to SPMS was estimated to occur in about 2.5% of patients per year and the median time to conversion was 19.1 years.³ These findings also indicate that increasing disability in MS occurs at widely varying rates, but it is inevitable that over periods of many years, the abilities of patients will decline and they will require increasing levels of support.

Most clinical trials and studies of patients with MS have focused on RRMS. As a consequence, there is a large body of information available on this phase of the disease, but less on progression and disability during later stages of MS. This deficiency needs to be addressed. In SPMS, disability is more apparent, severely restricting the functions and activities of patients, and it is more difficult to treat than at earlier phases of the disease. Interventions designed to stop or more effectively delay progression of disability in MS are a substantial unmet clinical need.

The currently available treatments for MS are targeted primarily at reducing inflammation, and have been shown to reduce relapse rates and pathological activity as detected by magnetic resonance imaging (MRI). However, these treatments are not sufficient on their own, as they do not address decreasing axonal function.⁴ Managing MS must therefore also involve managing the symptoms of disease progression, in particular limitations of activities and social participation, an area of research that continues to require development.^{4–7}

Of all the limitations of activities that can affect patients with MS, the loss of walking ability is the most feared.⁸ Walking ability normally declines during the course of MS; this decline may even be present,

although less perceptibly, in the early stages of the disease, including in patients with CIS. Since the onset of MS occurs most often between 20 and 30 years of age, when individuals are likely to be otherwise fit and leading productive lives, the loss of mobility has a more severe impact than it might if it were to develop in older persons already living a more sedate lifestyle.⁹⁻¹¹ As discussed above, age at onset of MS affects prognosis: in younger patients the disease generally progresses more slowly, but also leads to greater disability than does onset later in life.¹²

Despite the long-established recognition of mobility impairments in MS, the ability to walk is generally not sufficiently nor specifically assessed by therapists or physicians, and quantitative measures are frequently not used to determine and continuously monitor the impact of this disability on patients and their care-givers. This review aims to identify the impact of decreased walking ability on patients' lives. An accompanying article in this issue considers the various methods used to assess both general disability and specific aspects of walking ability in MS (see pages 61-8).

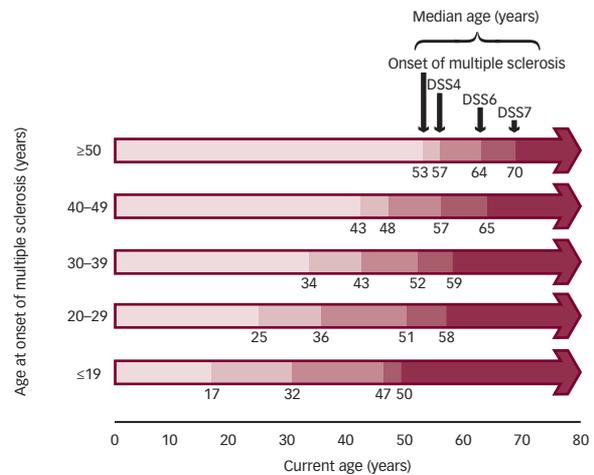
Impaired Mobility Limits Activities and Social Participation – An Important Part of the Burden and Impact of Multiple Sclerosis

As noted above, MS often leads to significantly impaired abilities. Recently, the International Classification of Functioning (ICF) produced by the World Health Organization (WHO) proposed terms related to disability and handicap that aim to avoid negative connotations. What used to be called 'disability' is now described as 'activities', and instead of 'handicap' the emphasis is on 'participation in social life'. Core sets of terms related to MS were developed by the ICF at an International Consensus Conference following established rules. In some current and older publications, however, the former terms disability and handicap are used, and when referring to literature this article has retained the reported terminology.

The general decrease in levels of activities and social participation that accompanies the progression of MS pathology, the loss of walking ability in particular, gradually reduces a patient's functional capacity – both in employment and in his or her private and social life. Data from studies over the past two decades show that after disease onset, the median time until a patient has some limitation in walking ability is eight years, the median time until the patient needs some support, such as a walking stick, is 20 years and the median time until the patient is confined to a wheelchair is 30 years.¹³ Loss of walking ability can also negatively influence the quality of life of family members.

Various studies have highlighted the burden caused by MS, with most showing motor disability to be the most feared by patients. In recent work, walking in particular was shown to be the faculty most valued by patients and its loss was regarded as one of the worst consequences of the disease.¹⁴⁻¹⁶ In a survey in the UK that included 84 patients who had MS of a duration greater than five years and a further 82 patients with MS of a duration greater than 15 years, participants were asked to rank 13 of their faculties in order of importance.⁸ Approximately 37% with short-duration MS and 27% with long-duration MS rated walking to be the most important (see Figure 2). Surprisingly, this was greater than the numbers rating visual function (16 and 24%), thinking and memory (8 and 15%) or even lack of pain (11 and 9%) as their most important domains. On the basis of these findings, it was concluded that patient-centred scales, tailored

Figure 1: Age at Onset of Multiple Sclerosis and Age at Reaching Major Disability Scores Among 1,844 Patients with Multiple Sclerosis



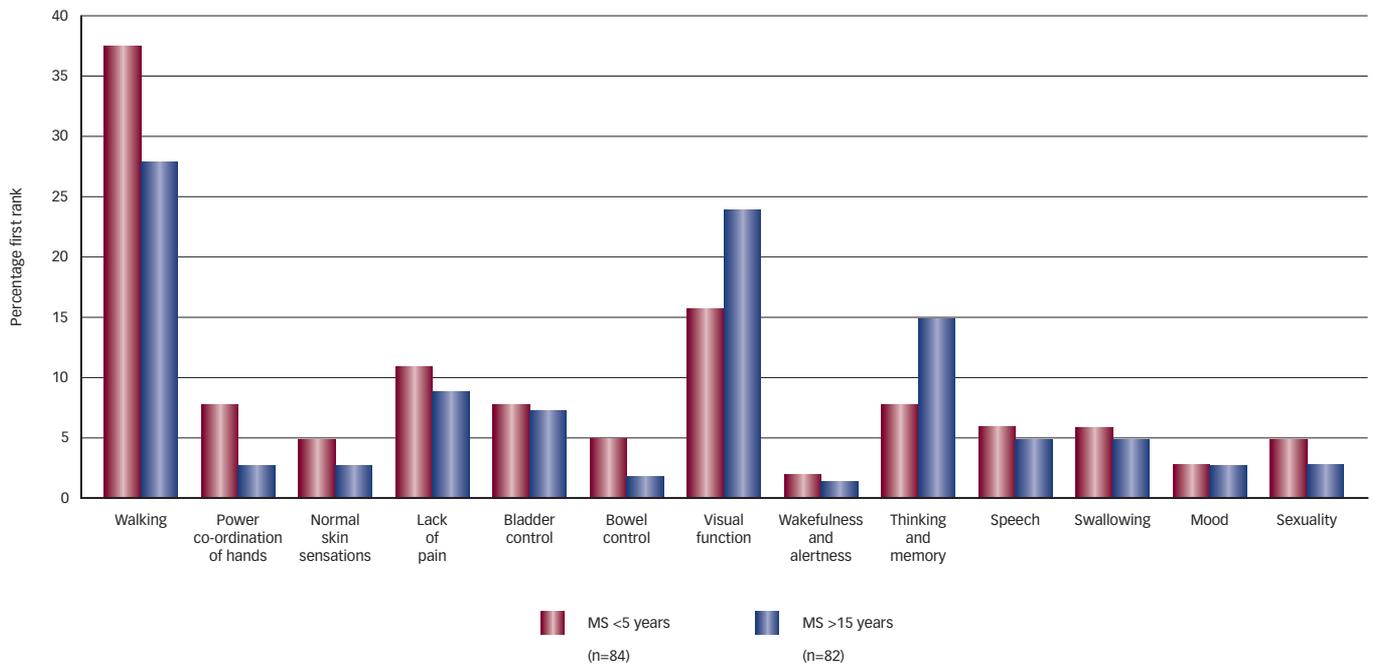
DSS = disability status scale. A score of 4 indicates limited walking ability but able to walk without aid or rest for more than 500m, a score of 6 indicates the ability to walk with unilateral support for no more than 100m without rest and a score of 7 indicates the ability to walk no more than 10m without rest while leaning against a wall or holding onto furniture for support. A given score of disability was defined as irreversible when a patient had had that score or more for at least six months, excluding any transient worsening of disability related to relapses. Source: Confavreux and Vukusic, 2006.²

to the value of these abilities, should be major outcome criteria for the assessment of any therapies in MS.

Further work highlighting the importance of walking included the Canadian Community Health Survey (CCRS), which compared a variety of health-related quality of life (HRQoL) parameters in 302 patients with MS (age range 46.6-50.8 years) with those in 109,741 individuals without MS (age range 44.7-44.8).¹⁴ HRQoL was determined using the Health Utilities Index Mark 3 (HUI3) score based on vision, hearing, speech, walking, cognition, dexterity and pain. Among these, walking had the greatest difference relative to the general population in HUI3 score (difference 0.26; p<0.05), with pain showing the second-largest difference (difference 0.14; p<0.05). The difference between the MS patients and control subjects was markedly greater for walking than for vision, hearing, speech, dexterity, emotion and cognition (see Table 1). The magnitude of this burden was concluded to be severe relative to the general population.

The effects of MS symptoms, impact on QoL, costs and burden of disease were analysed in a recent literature search of clinical studies published up to January 2009.¹⁶ Results from the identified clinical studies showed that impaired mobility was considered to be of high concern among many patients. For example, in one chosen study, a postal survey of 1,992 patients with MS in the UK, >90% of patients reported mobility as a concern and pain was reported by >80% of patients; among patients receiving disease-modifying treatments (DMTs), only 52% reported improvement in mobility.^{16,17} In another study, spasticity was reported to affect the life of 44% of patients.¹⁸ The authors of the review concluded that there is a need for greater recognition of disability and its effects in MS as well as a need for targeted treatments for specific impairments to improve QoL and reduce indirect costs.¹⁶ Another literature search covering the period 1980-2008 found that, across a number of studies, the prevalence of impaired mobility ranged from 50 to >90%.¹⁵ This variability was attributed to differences in the methods employed, definitions used

Figure 2: Rating of Most Important Functions by Multiple Sclerosis Patients Grouped by Two Disease Durations



MS = multiple sclerosis. Source: Heesen et al., 2008.⁸

Table 1: Impact of Disabilities on Quality of Life in Multiple Sclerosis

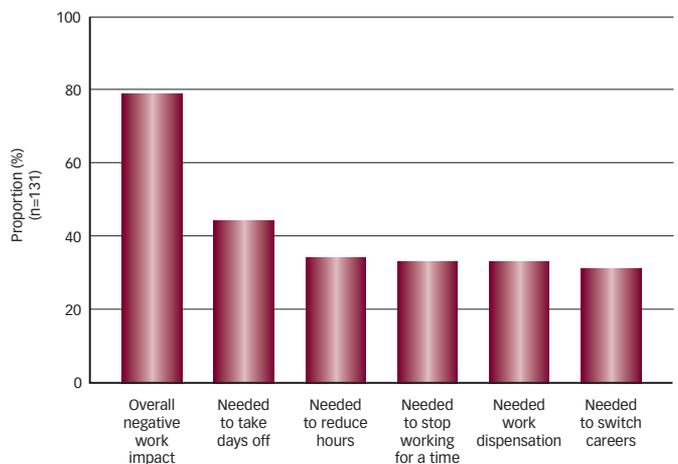
Adjusted* Mean Overall and Single Attribute Utility Scores (HUI3)			
	MS Population (n=302)	General Population (n=109,741)	Mean Difference (CI)
Overall	0.58	0.84	0.25 (0.20–0.31) [†]
Vision	0.94	0.96	0.03 (0.01–0.05) [†]
Hearing	0.99	0.99	0.00 (-0.01–0.004)
Speech	0.99	1.00	0.01 (-0.003–0.006)
Walking	0.72	0.98	0.26 (0.20–0.32) [†]
Dexterity	0.93	1.00	0.06 (0.03–0.10) [†]
Emotion	0.92	0.95	0.03 (0.01–0.05) [†]
Cognition	0.89	0.94	0.05 (0.02–0.09) [†]
Pain	0.77	0.91	0.14 (0.09–0.19) [†]

*Adjusted for age, sex, education, marital status, social assistance and number of medical conditions other than multiple sclerosis; [†]p<0.05 based on the Bootstrap Variance Estimate for between-group difference after adjustment for covariates. CI = confidence interval. Source: Jones et al., 2008.¹⁴

and patient populations included in the studies reviewed. Impaired mobility was also shown to be associated with reductions in QoL and activities of daily living and productivity, and was regarded as a concern for loss of independence. These findings highlighted the need for more comprehensive and consistent assessments of walking impairment and further evaluation from a patient’s perspective.¹⁵

A number of other studies have confirmed the importance of mobility impairment on various aspects of the lives of patients. In a recent large-scale survey (conducted in the US by Harris Interactive for the National MS Society and Acorda Therapeutics), which included 1,011 MS patients, 41% of responders needed assistance in walking, including 12% who required a wheelchair and 17% who needed support when crossing a room.¹⁹ Among patients with walking difficulties, 58% reported that this difficulty had caused them to miss

Figure 3: Impact of Walking Difficulty on Productivity Among Multiple Sclerosis Patients with Difficulty Walking or Inability to Walk Who Were Employed

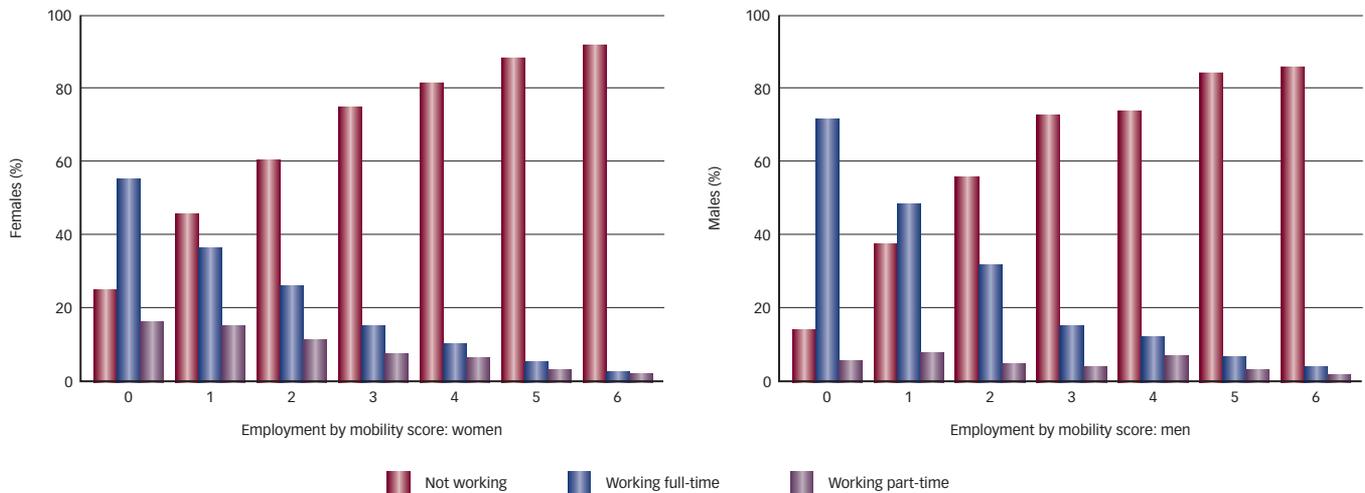


Source: Cheo and Larocca, 2009.¹⁹

major personal events (vacations, weddings, birthdays, etc.), 74% said that their walking difficulty had increased household responsibilities among family members and 70% agreed that this was the most challenging aspect of their disease. Respondents who had walking difficulty and were also employed (n=131) reported a substantial impact on work. Among these, 79% reported that walking difficulty had a negative impact on their employment, and this was a result of specific needs such as taking time off (44%), reducing working hours (34%) or switching careers (31%) (see Figure 3).

The impact of MS-associated walking impairment on care-givers has also been investigated. A study of 445 patients with clinically definite MS and their care-givers (n=445) conducted in Italy examined QoL in

Figure 4: Employment by Mobility Score in Men and Women with Multiple Sclerosis Using the NARCOMS Six-point Mobility Performance Subscale in the NARCOMS 2007 Registry Study



n=8,180. Employment decreased significantly with increasing mobility scores in both men and women (p<0.0001 for both). Association with unemployment was significant even at low mobility scores of 0, 1 and 2 (mild gait disability) (p<0.0001 for all). In the total cohort, income was significantly correlated with mobility (p<0.0001). NARCOMS = North American Research Consortium on Multiple Sclerosis. Source: Salter et al., 2010.²¹

both groups of individuals.²⁰ Although QoL was comparatively worse in the MS patients than in their carers, care-giving was associated with reduced mental health, vitality and general health and lower measures of QoL; these measures worsened with the condition of the patient. The authors concluded that better supportive strategies for MS care-givers are warranted.

A notable investigation of the socioeconomic effect of MS is the North American Research Consortium on Multiple Sclerosis (NARCOMS). This is a self-reported registry of persons with MS who are assessed twice yearly using both paper and web-based questionnaires.²¹ The study assesses the effect of mobility performance, scored on a six-point scale (0 = no disability to 6 = total disability), on aspects of life. A recent analysis of 8,180 persons with MS in this registry showed that, in both men and women, employment decreased significantly with decreasing mobility performance (p<0.0001 for both sexes) (see Figure 4). Interestingly, this association was significant even at low mobility scores of 0, 1 and 2 (mild gait disability; p<0.0001 for all). Furthermore, for the total cohort, paid income was significantly correlated with mobility (p<0.0001). The greatest reductions in all income measures occurred at the lowest level of mobility impairment (0 to 1; minimal gait disability), suggesting that small decreases in walking ability have a severe effect on employment capability. Reductions in income levelled off at higher mobility scores. The authors suggested that this showed that many persons with MS cease employment during early stages of the disease when they have less severe mobility impairment.²¹

The impact of MS on employment had already been demonstrated in an older study of 602 persons with MS (430 women and 172 men) conducted at neurological treatment centres across Canada.²² In total, 66% of the participants were unemployed and 78% of these believed their unemployment was related to MS symptoms. The most frequent patient-reported MS-related reasons for unemployment were walking difficulties (41%), fatigue (39%) and memory and vision problems (12%). A multivariate analysis of covariance showed that significant correlates of unemployment were mobility problems (p=0.001), age (p=0.001) and perceived

cognitive problems (p=0.001). The study by Salter et al. described above therefore provided further evidence that walking is critical for employment among MS patients and maintaining walking ability is vital for preserving the patient’s normal life and independence at early stages of the disease.²¹

Overall, clinical trial and survey evidence from numerous research groups worldwide suggests that impaired mobility is a large contributory factor to diminished QoL. Although these studies have demonstrated the negative effect of reduced mobility, there remains a substantial need for greater recognition of the presence and effects of disabilities encompassing immobility, fatigue, pain, depression and spasticity and a need for targeted treatments for specific impairments.¹⁶

The Impact of Multiple Sclerosis on the Individual Patient – The Importance of Monitoring Mobility Loss

Assessments of the impact of MS or the effect of treatment on mobility impairment describe general population trends. Although providing valuable measures of overall mobility, these assessments fail to convey the devastating impact that losing the ability to walk has on the individual and the loss of freedom and increased dependency accompanying these changes. The scores from these tests also fail to convey the impact of measures that improve the circumstances of the individual coping with MS. A number of case reports have examined the effect of declining mobility on both individual MS patients and on their partners or care-givers.

In one report, the effects of MS on two separate married couples were considered and showed an increasing awareness of change in abilities over time.²³ In one of the couples, a woman 53 years of age who had been diagnosed with SPMS 20 years earlier stated that during the course of the disease her “horizons had shrunk”. She needed a walker and was increasingly dependent on her husband for everyday functions. Prior to MS onset, she had enjoyed activities such as walking, rock climbing and swimming. When she had been

forced to stop these activities due to her MS, her lifestyle had been severely curtailed. Six years previously she could manage to walk four blocks, but now she could only manage two and that would take 40 minutes. Another couple told a similar story. The husband, who was 71 years of age, had been diagnosed with MS 38 years earlier and had been confined to a wheelchair for 20 years. He and his wife, who was his care-giver, had previously enjoyed dancing and family activities, but these had gradually stopped due to his progressive MS. On one occasion while alone in the house, the man had slipped from his wheelchair and had to crawl on his elbows and stomach down his hallway to reach the telephone to get help; it had taken him two hours to cover the short distance. Both couples reported declining social activity and increasing isolation, largely resulting from decreased walking ability and mobility.

The value of improved monitoring and support in MS patient mobility is also illustrated in a report of a 40-year-old man who had a 10-year history of MS.²⁴ He increasingly relied on a wheelchair for mobility, but was too weak to propel it outdoors. He had decreasing levels of endurance and this severely restricted his walking ability. He was concerned about his inability to go outside and was becoming isolated. He was hospitalised with ataxia and increasing tremors that resulted from his efforts to move about. In the hospital, his mobility needs were assessed and a treatment plan was formulated. He was allocated a powered wheelchair with tremor-dampening electronics and postural and wrist support. He was also given physical therapy that aimed to increase endurance, stretching, strength and sitting balance. These measures substantially improved his life and functional status.

Assessment of mobility in MS is therefore important for an individual patient both at the time of diagnosis and during the course of the disease, and provision of lifestyle interventions associated with recognition of an individual's mobility status can provide significant benefits. Addressing individual needs, such as providing assistance and physiotherapy or appropriate equipment, enables patients to be less dependent and more able to cope as their disease progresses. This is an important contribution to the life of any individual MS patient and should not be overlooked when considering management strategies. However, such interventions require extensive resources

and are expensive; consequently, many healthcare organisations are currently unable to provide them.

Future Developments in Mobility Assessment and Management in Multiple Sclerosis

In the coming years, the importance of impaired mobility in MS will be increasingly recognised and is likely to be monitored more closely by neurologists. Currently, data assessing the impact of mobility impairment in MS are limited both in scope and in the numbers of patients involved. As a consequence, walking ability, which is the most significant aspect of overall mobility, is an insufficiently monitored aspect of the impact of MS. In fact, as in many other diseases, we are only just beginning to recognise the difference between what patients and clinicians consider important. Studies in larger populations of MS patients using general purpose and more specific methods for assessing mobility will contribute to a better understanding of the clinical meaningfulness of mobility data in MS. Data from these studies are likely to result in recommendations and guidelines that specify this faculty be more accurately assessed as part of both the diagnostic process and continuous monitoring throughout the disease course.

Awareness of walking and mobility impairment as a particularly serious consequence of MS, in terms of its contribution to decreased capacity for employment and normal day-to-day functioning, is likely to increase among neurologists, general physicians, patients and care-givers. Demand for more intensive mobility assessment may therefore increase, and continued monitoring throughout the course of MS may allow findings to be used to better assess patient needs.

Increasing recognition of impaired mobility by physicians as a major factor in MS will drive interventions to address patients' needs and significantly improve many aspects of patients' lives. It will also encourage the development and use of treatments that improve neurological function, in turn contributing to the achievement of greater independence for patients, increasing their confidence and improving their self-efficacy and overall wellbeing for more extended time periods than would be possible without such interventions. ■

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