Disability in multiple sclerosis. Is MS a more benign condition than previously supposed?

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SUMMARY. Recent data from the Olmsted County MS population based studies further supports the concept that MS is a more benign condition than previously supposed. Most patients are fully ambulatory and continue to work and only 14% are wheelchair bound or restricted to bed. Over a 10 year period most patients remain stable though 30% will progress to needing a cane or worse. Patients with MS for >10 years and an EDSS score ≤2 comprise 17% of MS patients living in the community. This group of patients have a <10% chance of developing worsening disability (EDSS >4) in the following decade. In fact data would suggest that if a patient has had MS >5 years and has no or minimal disability, they are likely to remain well and not progress. This information is important in the counseling of patients and in the shared patient/physician therapeutic decision making process.
Key words: multiple sclerosis, benign condition, ambulatory, disability.

RESUMEN. Datos recientes de estudios basados en la población con EM de Olmsted County permiten pensar que ésta es una enfermedad más benigna de lo que en principio se había supuesto. La mayoría de los pacientes son manejados de forma ambulatoria (no están hospitalizados) y continúan trabajando, y únicamente un 14% necesitan silla de ruedas o están encamados. Después de un periodo de 10 años la mayoría de los pacientes permanecen estables, aunque un 30% progresarán y empeorarán. Los pacientes con EM durante más de 10 años y una puntuación EDSS ≤2 constituyen un 17% de los enfermos con esclerosis múltiple que viven en la comunidad. Este grupo de pacientes tienen <10% de probabilidad de desarrollar un empeoramiento en su discapacidad en la siguiente década (EDSS >4). De hecho, los datos podrían sugerir que los pacientes que han tenido EM durante más de 5 años y no tienen incapacidad, o ésta es mínima, es muy probable que permanezcan bien y no experimenten una progresión de su enfermedad. Esta información es importante para tenerla en cuenta en el consejo que se le ofrece al paciente y para el proceso de toma de decisiones terapéuticas compartidas entre el médico y el paciente.
Palabras clave: esclerosis múltiple, condición benigna, ambulatorio, discapacidad.

Multiple sclerosis is generally perceived as a devastating and disabling disease. Its course is however varied and unpredictable. Natural history studies of MS are very dependent on having good patient ascertainment, such that patients that are doing well are also included otherwise a bias toward poorer outcome would occur. The Olmsted County MS population has been extremely well studied and followed since 1905. The present computerized centralized diagnostic index at the Mayo Clinic, Rochester Minnesota has allowed the study of the natural history of MS patients in a defined geographical area with essentially 100% ascertainment.

We recently reported the levels of impairment, handicap and disability in a population-based cohort of MS patients[1]. The longitudinal studies performed on this cohort have allowed comparison of the levels of disability over a decade[2]. In addition, few studies have performed systematic interviews and examinations and applied well accepted measurement scales to assess the levels of impairment disability and handicap.

Many studies have previously investigated clinical predictive factors in MS, but clinically useful predictors in individual patients are lacking though many are statistically significant in a large patient cohort. The recent Olmsted County studies have added further support to the concept that many patients with MS continue to have no or minimal disability after many years[3].

In this report we will discuss and review the findings from our recent Olmsted County population-based study[1, 3]. With only 25% of patients on immunomodulatory therapies for mean of 14 months, the impact on natural history is likely minimal. Firstly we will describe the levels of impairment, disability, handicap and quality of life. Secondly we will address what happens to people with MS over time. Thirdly we will discuss the issue of benign MS, its frequency, predictors and implications to patient management.

❑ Levels of impairment, disability and handicap for all 201 prevalence cases of MS in Olmsted County

Using the Minimal Record of Disability (MRD) we measured the levels of impairment using the expanded disability status scale (EDSS), disability using the incapacity status scale (ISS) and the environmental sta-

tus scale (ESS) (Appendix 1-3) for 201 patients with definite MS that made up the 2000 Olmsted County prevalence cohort[1, 4, 5].

The levels of impairment as measured by the EDSS for the Olmsted County MS population cohort are shown in (Figure 1). Most (62%) patients were fully ambulatory and only 14% were wheelchair bound or restricted to bed. Employment status is shown in Figure 2. Most patients had no or minimal difficulty (score 0-1) with items on the incapacity status scale, a well accepted measure of disability in MS (Figure 3).

The ESS provides an assessment of handicap resulting from MS. The emphasis is on performance or need rather than on ability. Most patients (57%) were working fulltime (score 0-1). Most patients (73%) maintained their usual financial standard without external support (score 0-2) and only 8% of patients were unable to maintain their usual financial standard despite receipt of all available financial assistance. Only 8% of patients had to live in a facility for dependent care. Most (62%) required no changes to their homes, 14% needed to modifications, 5% required major structural alteration and 11% had to move to a satisfactory personal home. 71% required no personal assistance for daily activities. Most patients (72%) were driving with no or minor difficulties (score 0-1). Community services of any sort were utilized by only 7% of patients. Most patients (57%) reported normal or minimal difficulties with social activities (scores 0-1).

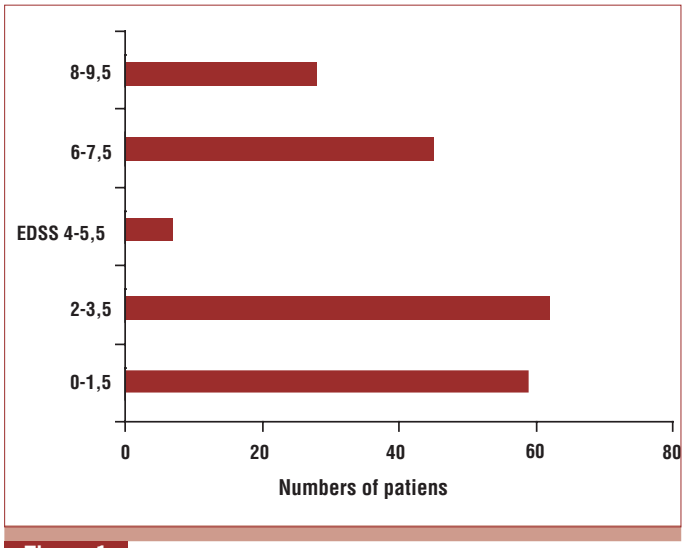

Figure 1 *Frequency distribution of the Kurtzke Expanded Disability Status Scale (EDSS) scores for the Olmsted County MS prevalence-cohort.*

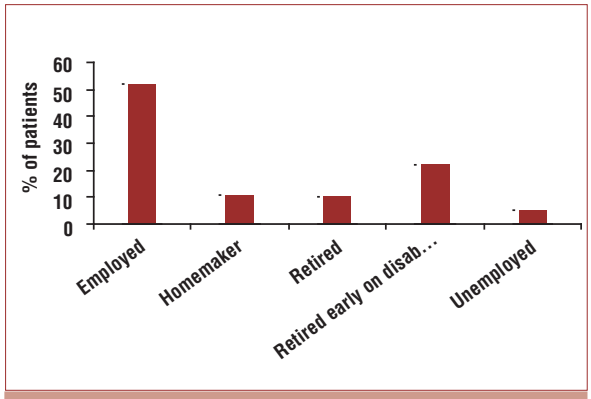

Figure 2 *Employment of patients in the Olmsted County MS prevalence-cohort.*

❑ What happens to people with MS over time?

Data from long term studies have shown that it takes patients a median of 15-20 years to reach the stage at which they need unilateral support while ambulating and a median of 30 years till they can walk only a few steps[6-11]. The median times from MS diagnosis or onset to different levels of impairment as measured by the EDSS for the entire cohort and the different MS subtypes (relapsing remitting (RR), secondary progressive (SP) and primary progressive (PP)) are shown in Table I.

A previous study by Confavreux et al showed that irreversible disability occurred sooner in patients with progressive disease from onset than those with relapsing remission course at onset[11]. However once disability occurred (as defined by EDSS 4) the rate of progressive disability was similar. They showed that once a clinical threshold of irreversible disability is reached, the progression of disability is not affected by relapses either at onset or during progression. Our recent natural history study found similar results, disability progression will progress at a faster rate once a threshold of EDSS 3 is reached but the rate at which a patient reaches EDSS 3 (whether it be 2,5 or 10 years after onset) does not effect the rate of further progression once irreversible disability (EDSS 3) is reached[1].

Patients appear to do better then was previously suspected. This is likely due to the near 100% case ascertainment, such that patients who are doing well with no or minimal disability are also included in the study. These patients are more likely to get lost to follow up, but the computerized diagnostic index at Mayo Clinic allows capture of any patients ever seen and given a diagnosis of multiple sclerosis. These favorable findings are supported by a recent natural history study in Iceland which reported that 70% of MS patients were fully ambulatory and half of the pa-

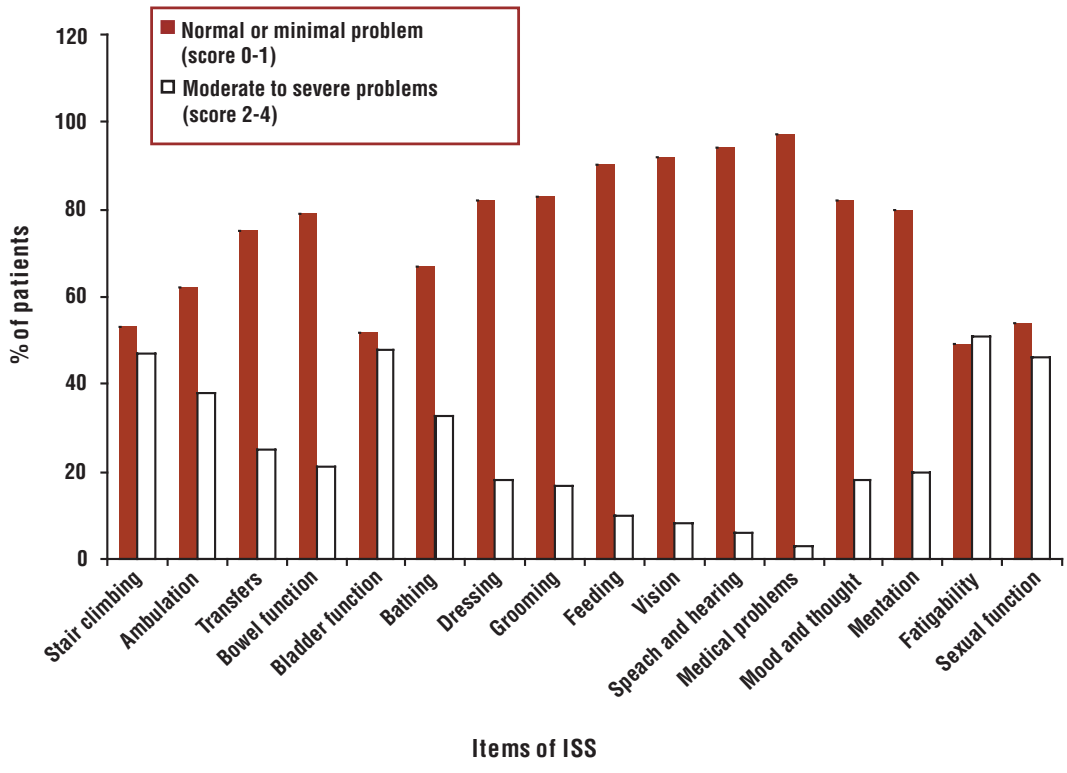

Figure 3 *Incapacity Status Scale (N = 201) scores for 2000 Olmsted County MS prevalence-cohort.*

Table I *Median years to designated endpoint*

Years from	RR	PP	SP	Total
Diagnosis to EDSS 3	49.9	–	3.0	17.3
Diagnosis to EDSS 6	49.9	3.0	10.3	24.5
Diagnosis to EDSS 8	–	25.1	38.0	39.5
Onset to EDSS 3	50.9	–	10.5	23.0
Onset to EDSS 6	50.9	6.3	17.9	28.6
Onset to EDSS 8	–	27.0	42.4	52.0

Median time from MS onset and diagnosis to different levels of impairment for the Olmsted County MS population-based prevalence-cohort. EDSS 3 = fully ambulatory with minimal impairment, EDSS 6 = needs a cane to walk, EDSS 8 = requires a wheelchair. RR-relapsing remitting, PP-primary progressive, SP-secondary progressive, total = entire MS prevalence cohort.

tients were fully ambulatory with no or minimal disability after 30 years[12].

❑ Benign MS

There is much controversy regarding the existence of the entity "benign" MS. The question is complicated by differing definitions and terminologies such as "no restriction of activity for normal employment and domestic life"[13] or "slight disability"[14] after at least 10 years or the ability to work after 20 years[15]. Others have used different expanded disability status scales (EDSS) scores with cut off at 4[16] or 3 and minimum disease duration of 10[17] and 14 years[18]. An international survey of clinicians involved with MS defined benign MS as "disease in which the patient remains fully functional in all neurologic systems 15 years after disease onset"[19].

In large part, the controversy arises from the fact that a certain proportion of patients defined as having benign MS subsequently develop significant permanent impairment and disability. In a 10-year follow up study of Irish patients with benign MS (defined as EDSS ≤3 for >10 years) eight of 11 patients with

EDSS score ≥2.0 in 1986-7 (duration >10 years) still had EDSS ≤3 a further 10 years later[17]. In a US army study the best predictor of later course (next 10 years) was the 5-year DSS (Kurtzke *et al.*, 1977)[20]. Of 53 patients with DSS of 0-2.0, 5 years after onset, 66% remained with EDSS 0-2 and only 11% required a cane or worse 10 years later. In a hospital-based study of MS patients, McAlpine found a high percentage of patients (32%) had "unrestricted" disability at ≥10 years but 15% were significantly more disabled 5 years later[13, 21].

Further insight into benign MS has come from our recent Olmsted county follow up study in which 49 patients with Benign MS in (EDSS <4, for >10 years) 1991 were followed up in 2001[22]. Patients with EDSS 0-2 for >10 years in 1991, were highly likely (>90% chance) of remaining with EDSS ≤3 a decade later. This group of patients accounts for nearly 1 in 5 MS patients. Patients with EDSS 2,5-4 for 10 years, did not do so well when examined a further 10 years later. About half had gone on to develop EDSS >4, with some requiring a cane to walk and others having entered the secondary progressive course of the disease.

When we assessed the impact of duration of disease from onset on disability progression, our findings agreed with previous observations. Patients with no or minimal disability for <5 years had a 30% chance of developing significant disability a decade later. However once duration of disease was >5 years, and EDSS was 0-2 then there was minimal risk of developing significant disability 10 years later. For patients with EDSS 2.5-4, the risk of developing significant disability after 10 years was similar for those patients with disease duration <5 years and >5 years (Figure 4).

❑ Are there other early predictors of a benign outcome?

For the purposes of this analyses we considered, benign patients those with MS >20 years and EDSS ≤4 and those with non benign MS as those with MS >20 years and EDSS >4. The frequency of different patient characteristic variables and odds ratios for the benign versus non-benign MS patients are shown in Table II. Patients with benign MS in 1991 who remained benign in 2001 (EDSS ≤4) were considered "confirmed benign" (n = 34). Those patients with non-benign MS in 1991 (n = 68) as well as those classified as benign in 1991who had EDSS >4 in 2001 (n = 14) were considered "ultimately non-benign". The non benign group were significantly more likely to have a motor pathway deficit at onset of disease compared with the benign group (33% *vs* 12%, p <. 05).

No differences between groups were identified for other neurological at onset, degree of recovery (> or <80% recovery) from initial attack, mono vs poly

Figure 4 ***The impact of duration of disease from onset, stratified by EDSS in 1991, on progression of disability in 2001***

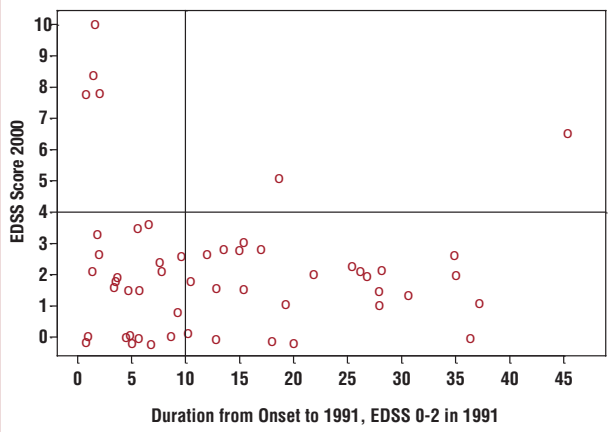

Figure 4 (A): *Effect of duration of disease from onset for all patients with EDSS ≤2 in 1991 on further change in EDSS over 10 years.*

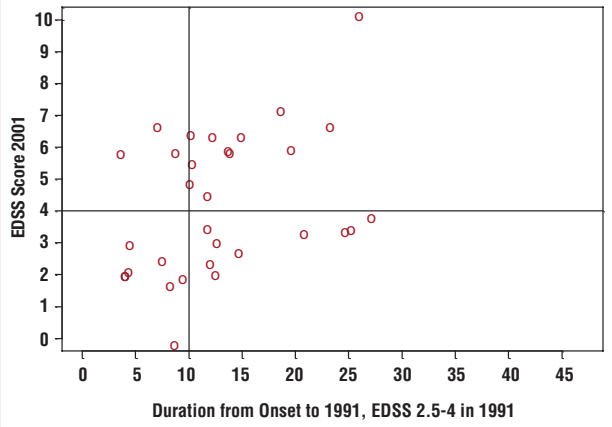

Figure 4 (B): *Effect of duration of disease from onset for all patients with EDSS 2.5-4 in 1991 on further change in EDSS over 10 years.*

regional symptoms at onset, number of attacks in the first year or age at onset or diagnosis.

A multiple logistic model revealed that patients with a motor pathway deficit at onset (odds ratio (OR) 0.25, p = 0. 02) and longer duration of MS in 1991 (OR 0.75, p <. 01) were significantly less likely to be in the benign group.

❑ How does this effect current clinical decision making?

Patients with MS often have minimal disability, impairment or handicap. Though 36% of patients in a community-based sample of MS required an aid (cane

Table II *Patient Characteristics by Benign status. In 1991 116 patients had MS >10 years. In 2001 these patients had MS >20 years. Those with EDSS ≤4, after 20 years were considered benign (n = 24), those with EDSS >4, after >20 years were considered non-benign (n = 82).*

			No. (%)*				OR (95% CI)	P-value
		N	Non-Benign		Benign			
Overall		116	82	(71%)	34	(29%)		
Gender	Female Male	88 27	62 19	(77%) (23%)	26 8	(76%) (24%)	1.00 (0.39, 2.58)	0.99
Cerebral	No Yes	113 3	80 2	(98%) (2%)	33 1	(97%) (3%)	1.21 (0.11, 13.83)	0.88
Optic neuritis	No Yes	87 29	64 18	(78%) (22%)	23 11	(68%) (32%)	1.70 (0.70, 4.14)	0.24
Sensory	No Yes	54 62	40 42	(49%) (51%)	14 20	(41%) (59%)	1.36 (0.61, 3.05)	0.46
Motor	No Yes	85 31	55 27	(67%) (33%)	30 4	(88%) (12%)	0.27 (0.09, 0.85)	0.2
Brainstem	No Yes	89 27	62 20	(76%) (24%)	27 7	(79%) (21%)	0.80 (0.30, 2.12)	0.66
Cerebellum	No Yes	108 8	76 6	(93%) (7%)	32 2	(94%) (6%)	0.79 (0.15, 4.13)	0.78
Gait difficulty	No Yes	88 28	59 23	(72%) (28%)	29 5	(85%) (15%)	0.44 (0.15, 1.28)	0.13
Sphincter dysfunction	No Yes	112 4	78 4	(95%) (5%)	34 0	(100%) (0%)		
Mono polyregional symptoms	*vs* Mono Poly	102 14	72 10	(88%) (12%)	30 4	(88%) (12%)	0.96 (0.28, 3.30)	0.95
Recovery from initial attack	No Yes	13 103	12 70	(15%) (85%)	1 33	(3%) (97%)	5.66 (0.71, 45.35)	0.10
IMT†	No Yes <1 yr. >1 yr.	102 14 6 7	68 14 6 7	(83%) (17%) (7%) (9%)	34 0 0 0	(100%) (0%) (0%) (0%)		
Number of attacks in the first year	<=1 >1 PP	72 33 11	49 22 11	(60%) (27%) (13%)	23 11 0	(68%) (32%) (0%)	1.07 (0.44, 2.56)	0.89
Age at onset		116	31.2 (11.5)‡		29.6 (9.2)‡			0.49
Age at diagnosis		116	36.1 (11.2)‡		35.0 (9.7)‡			0.59
Age in 1991		116	54.9 (13.2)‡		49.4 (10.8)‡			0.03
Follow-up (yrs)**		116	33.0 (11.3)‡		28.8 (8.1)			0.05
Duration of MS in 1991		116	18.7 (10.6)‡		14.3 (7.9)‡			0.03

*Benign MS is defined as EDSS ≤4 and at least 20 years of follow up. Non-Benign is defined as EDSS >4 and at least 20 years of follow up. **Length of follow-up: Time from MS onset to exam date. †IMT = Immunemodulatory treatments, interferon b1-a or b or glatiramer acetate. ‡mean (standard deviation) for continuous variables.

or wheelchair) or were unable to walk, 62% were fully ambulatory. In addition a majority of patients had no or minimal problems with all items on the Minimal Record of Disability a measure of disability and handicap.

The rates of progression of disability for the entire MS cohort, for those that remain relapsing remitting and for those with secondary progressive MS are more favorable than previously reported. This data is helpful in counseling patients.

Benign MS (EDSS ≤4, duration of MS >20 years) presently accounts for approximately one fifth of the Olmsted county 1991 population-based cohort. In recent years disease modifying agents including interferon β-1a and 1b and glatiramer acetate have become available for RRMS[23-30]. The US Food and Drug Administration (FDA) recently approved the use of interferon β1a for use in patients with a clinically isolated syndrome and a MRI suggestive of MS on the basis of the CHAMPS study[31]. These drugs have been shown to have modest benefits in the relative short term though they are expensive and associated with side effects. In Olmsted County, half of all patients started on a disease modifying medication stopped because of lack of perceived efficacy or side effects.

Therefore, one fifth of patients who might be advised to take disease-modifying agents at onset of disease for an indefinite period would be expected to remain benign regardless of treatment. Such patients would be considered 'drug-responders' even though this was merely the result of benign natural history.

Drug intervention in this benign group could alter the immune repertoire and possibly even impact the factors that maintain the benign state. The biological factors that account for the variability in disease course are unknown. One hypothesis is that the benign phenotype is due to a neuroprotective profile that promotes remyelination with axonal protection and preservation. The non-benign phenotype on the other hand may be due to a neurotoxic profile characterized by T cell cytotoxicity and failure of neurotrophic support of axons from death of myelinating oligodendrocytes as a consequence of demyelination[32].

The early biological cut-off of EDSS >2 as a predictor of future disability may be explained by the fact that a fixed deficit on examination reveals at an early point in the disease that a neurotoxic profile characterized by an axonal vulnerability and impaired repair capacity exists in an individual.

We propose that patients with MS for 10 years or more who have EDSS ≤2 should be considered 'truly benign' because they have a very low likelihood of developing significant disability. Patients with EDSS 2.5-4 after longer than 10 years, have a significant chance of developing disability and a secondary progressive course over the subsequent 10 years albeit less frequently than patients with EDSS >4 within first 10 years of disease. The favorable impact of EDSS ≤2 seems to be established once the duration of MS exceeds 5 years.

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Appendix 1

Expanded Disability Status Scale[5]: The scale ranges from 0-10 in 0.5 increments. The scores from grades 0-4 are derived from Functional System (FS) scales that evaluate dysfunction in 8 neurologic systems, including pyramidal, cerebellar, brainstem, sensory, bladder and bowel, vision, cerebral, and "other"

Grade	Definition
0	Normal neurologic examination (all grade 0 in FS, cerebral grade 1 acceptable).
1.0	No disability, minimal signs in 1 FS (i.e., grade 1 excluding cerebral grade 1).
1.5	No disability, minimal signs in more than 1 FS (more than 1 grade 1 excluding cerebral grade 1)
2.0	Minimal disability in 1 FS (1 FS grade 2, others 0 or 1).
2.5	Minimal disability in 2 FS (2 FS grade 2, others 0 or 1).
3.0	Moderate disability in 1 FS (1 FS grade 3, others 0 or 1) or mild disability in 3 or 4 FS (3/4 FS grade 2, others 0 or 1) though fully ambulatory.
3.5	Fully ambulatory but with moderate disability in 1 FS (1 grade 3) and 1 or 2 FS grade 2, or 2 FS grade 3, or 5 FS grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid; self-sufficient; up and about some 12 h/d despite relatively severe disability, consisting of 1 FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest approximately 500 m.
4.5	Fully ambulatory without aid; up and about much of the day; able to work a full day; may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of 1 FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest for approximately 300 m.
5.0	Ambulatory without aid or rest for approximately 200 m; disability severe enough to impair full daily activities (e.g., to work full day without special provisions; usual FS equivalents are 1 grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
5.5	Ambulatory without aid or rest for approximately 100 m; disability severe enough to preclude full daily activities (usual FS equivalents are 1 grade 5 alone; others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0).
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk approximately 100 m with or without resting (usual FS equivalents are combinations with more than 2 FS grade 3+).
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk approximately 20 m without resting (usual FS equivalents are combinations with more than 2 FS grade 3+).
7.0	Unable to walk beyond approximately 5 m even with aid; essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about approximately 12 h/d (usual FS equivalents are combinations with more than 1 FS grade 4+; very rarely, pyramidal grade 5 alone).
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair (usual FS equivalents are combinations with more than 1 FS grade 4+).
8.0	Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms (usual FS equivalents are combinations, generally grade 4+ in several systems).
8.5	Essentially restricted to bed much of the day; has some effective use of arms; retains some self-care functions (usual FS equivalents are combinations, generally 4+ in several systems).
9.0	Helpless bed patient; can communicate and eat (usual FS equivalents are combinations, mostly grade 4+).
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow (usual FS equivalents are combinations, almost all grade 4+).
10.0	Death due to MS.

Appendix 2

16 items (abbreviated) of the incapacity status scale (ISS)[4]

1.- Stair climbing refers to ascending and descending 12 steps	**2.- Ambulation** refers to ability to walk 50m without rest on level
0 = Normal.	0 = Normal.
1 = Some difficulty but performed w/o aid.	1 = Some difficulty but performed w/o aid.
2 = Need for aid (cane, brace, banister).	2 = Need for aid (cane, brace, banister).
3 = Need human assistance.	3 = Need human assistance.
4 = Unable to perform.	4 = Unable to perform, includes perambulation in a WC or motorized WC.
3.- Bathing refers to how independent getting into and out of the tub or shower?	**4.- Dressing**
0 = Normal.	0 = Normal.
1 = Some difficulty with washing and drying self though performed without aid.	1 = Some difficulty clothing self completely in standard garments but accomplished by self.
2 = Need for assertive devises in order to bathe self; or need to bathe the self outside of tub or shower.	2 = Specifically adapted clothing or devices required to dress self.
3 = Need for human assistance in bathing parts of the body or in entry/exit.	3 = Need for human aid to accomplish but performs considerable portion by self.
4 = Bathing performed by others	4 = Need for almost complete assistance.
5.- Grooming	**6.- Feeding**
0 = Normal.	0 = Normal.
1 = Some difficulty but no aids required.	1 = Some difficulty but performed without aid.
2 = Need for adaptive devices but performed without human aid.	2 = Need for adaptive devices or special preparation to feed self.
3 = Human aid to perform some tasks.	3 = Need for human aid in the delivery of food; or dysphagia preventing solid diet; e.g., esophagostomy or gastrostomy maintained and utilized by self; or tube-feeding performed by self.
4 = Almost all tasks performed by another person.	4 = Unable to feed self or maintain ostomies.
7.- Bladder function	**8.- Bowel function**
0 = Normal.	0 = Normal.
1 = Occasional hesitancy or urgency.	1 = Bowel retention not requiring more than high fibre diets, laxatives, occasional enemas or suppositories, self administered.
2 = Frequent hesitancy, urgency or retention.	2 = Bowel retention requiring regular laxatives, enemas or suppositories, self administered in order to induce evacuation; cleanses and disinpacts self.
3 = Occasional incontinence.	3 = Bowel retention requiring regular laxatives, enemas or suppositories, administered by another.
4 = Frequent incontinence.	4 = Frequent soiling.

9.- Transfers refers to ability to position oneself and arise from a regular toilet, chair, bed, and wheelchair	**10.- Vision**
0 = Normal.	0 = Normal. Can read print finer than standard newspaper.
1 = Some difficulty but performed without aid.	1 = Cannot read print finer than standard newspaper or complains of double vision.
2 = Need for adaptive or assistive devices.	2 = Magnifying lenses or large print necessary.
3 = Need for human aid.	3 = Can only read very large print.
4 = Must be lifted.	4 = Legal blindness.
11.- Speech and hearing	**12.- Medical problems**
0 = Normal.	0 = No significant disorder present.
1 = Impaired, not interfering with communication.	1 = Disorder not requiring active care, may be on medication.
2 = Deafness sufficient to require hearing aid and/or dysarthria interfering with communication.	2 = Disorder requiring occasional monitoring by physician or nurse.
3 = Severe deafness and/or severe dysarthria compensated for by sign language.	3 = Disorder requiring regular attention (at least weekly) by physician or nurse.
4 = Severe deafness and /or dysarthria without effective compensation.	4 = Disorder requiring daily attention by physician or nurse.
13.- Mood and thought disorder	**14.- Mentation**
0 = No observable problem.	0 = No observable problem.
1 = Disturbance is present at time but does not interfere with day to day functioning.	1 = Disturbance is present but does not interfere with day to day functioning.
2 = Disturbance does interfere with day to day functioning but person can manage without professional assistance except for occasional visits to maintain medication.	2 = Disturbance interferes with performance of everyday activities, but manages without help from others.
3 = Disturbance does interfere with day to day functioning and consistently requires professional intervention (requires psychotherapy or hospitalization).	3 = Disturbance is severe enough to require prompting or assistance from others for performance of everyday activities.
4 = Despite medication and /or other intervention disturbance is severe enough to preclude day to day functioning.	4 = Disturbance preclude the performance of most everyday activities.
15.- Fatigability	**16.- Sexual function**
0 = No fatigability.	0 = Sexually active as before and/or not experiencing some sexual problems.
1 = Fatigability present but does not interfere with baseline physical function.	1 = Sexually less active than before and/or now experiencing some sexual problems but not concerned.
2 = Fatigability causing intermittent and transient impairment of baseline physical function.	2 = Sexually less active than before and/or now experiencing some sexual problems and concerned.
3 = Fatigability causing intermittent and transient loss or frequent moderate impairment of baseline physical function.	3 = Sexually inactive and concerned.
4 = Fatigability which generally prevents prolonged or sustained physical function.	4 = Sexually inactive and not concerned.

Appendix 3

7 items of the Environmental Status Scale (ESS)[4]

1.- Work	**2.- Financial/Economic status**
0 = Normal or retired for age.	0 = No MS related financial problems.
1 = Works full time but in less demanding position.	1 = Family maintains usual financial standard without external support despite some financial disadvantages resulting from MS.
2 = Works more than half time at work, housework or school.	2 = Family maintains usual financial standard with aid of some external financial support.
3 = Works between one quarter and one half time at work, housework or school.	3 = Family maintains usual financial standard by receiving basic disability pension.
4 = Works less than one quarter time at work, housework or school.	4 = Family maintains usual financial standard only because receiving all available financial assistance.
5 = Unemployed, not able to do housework or to attend school at all.	5 = Family is unable to maintain usual financial standard despite receipt of all available financial assistance.
3.- Personal residence/Home	**4.- Personal assistance** re daily activities
0 = No change necessary.	0 = None.
1 = Minor modifications necessary.	1 = Minor help.
2 = Moderate modifications necessary.	2 = Up to 1 hour per day.
3 = Major structural alteration.	3 = Up to 3 hours per day.
4 = Must move to satisfactory personal home.	4 = More than 3 hours per day but can live at home and does not need a constant attendant.
5 = Must live in facility for dependent care.	5 = Constant attendant or care in institution, cannot be left alone for more than 2-3 hours.
5.- Transportation	**6.- Community Services**
0 = No problems.	0 = None required.
1 = Uses all form of transportation despite minor difficulties or drives with minor difficulty (handicapped parking).	1 = Requires service once per month or less frequently.
2 = Uses some public transportation despite difficulties or needs hand controls to drive.	2 = Requires not more than 1 hour per week.
3 = Cannot use public transport but can use private transport, cannot drive but may be driven by others.	3 = Requires not more than 1 hour per day.
4 = Requires community transportation in wheelchair.	4 = Requires 1-4 hour per day.
5 = Requires ambulance.	5 = Requires more than 4 hours per day.
7.- Social activity	
0 = Social activity as before.	
1 = Maintains usual pattern of social activity despite some difficulties.	
2 = Some restrictions on social activity.	
3 = Significant restriction of social activity.	
4 = Socially inactive except for the initiative of others.	
5 = So social activity.	