Assessment of Multiple Aspects of Upper Extremity Function Independent From Ambulation in Patients With Multiple Sclerosis

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ABSTRACT

BACKGROUND: Upper extremity function (UEF) is often compromised in multiple sclerosis (MS), although its importance is regularly underrecognized relative to ambulation. We explored the concurrent presence of impairment in UEF and ambulation by examining various aspects of UEF across different levels of ambulation.

METHODS: The cohort consisted of 247 patients with clinically definite MS or clinically isolated syndrome according to the revised 2010 McDonald criteria. The Nine-Hole Peg Test and the Expanded Disability Status Scale were used to stratify patients into clinically different subgroups. For UEF, cerebellar function (finger-to-nose test), pyramidal function (pronator drift test), and the ability to perform a task of activities of daily living (drinking-from-cup test) were examined. Patient-reported limitations of UEF in daily life were assessed using the Arm Function in Multiple Sclerosis Questionnaire.

RESULTS: Patients in more severely impaired ambulation groups displayed poorer performance on all UEF measures. Although most patients had normal to mild (n = 147) or moderate (n = 46) ambulatory impairment, 87.7% exhibited some level of UEF impairment as defined using the Nine-Hole Peg Test. Most patients had mild UEF impairment (n = 174), accounting for the largest proportion in all ambulation groups (51.9%-77.8%).

CONCLUSIONS: A distinct pattern of impairment was found for ambulation and multiple aspects of UEF. Independent assessment of multiple aspects of disability may be helpful in treatment decision-making and could support the development of rehabilitation strategies that specifically target UEF impairment

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Walking impairment is a common consequence of multiple sclerosis (MS)[1] that is routinely assessed as an indicator of disability progression and to monitor the efficacy of treatment.[2] Although upper extremity function (UEF) is often compromised as well, its importance is underrecognized relative to that of ambulation.[3] Impairment in UEF can impact the ability to use walking aids and is important in maintaining the ability to perform activities of daily living (ADLs). In addition, the magnitude of UE dysfunction was shown to negatively impact the physical domain quality of life (based on the Multiple Sclerosis Quality of Life–54 questionnaire in 31 patients with MS)[4] and was a significant predictor of direct disease-related costs in MS (cohort of 298 patients with MS).[5] Therefore, identifying UEF impairment and characterizing its magnitude and impact is important for MS management.

The traditional end point to rate disability in MS therapeutic trials is the Expanded Disability Status Scale (EDSS), which is heavily weighted on walking ability, especially in the higher range of the scale (ie, 4.0-7.0).[6] The use of UEF-specific measures in clinical trials has increased since introduction of the Multiple Sclerosis Functional Composite, a composite of quantitative measures of UEF with the Nine-Hole Peg Test (NHPT), walking speed with the Timed 25-Foot Walk (T25FW) test, and cognitive function.[7] Although this improved the assessment of UEF, the instrument does not fully capture the broader aspects of function necessary to define the level of severity on more complex tasks, such as ADLs. Furthermore, the incorporation of specific patient-reported outcome (PRO) measures, increasingly being recommended as an integral component in clinical trials,[8] would be valuable to enhance insight into the functional impact of UEF impairment in daily life.

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Recently, data from multiple trials in MS underline the importance of evaluating treatment effects on UEF independent from other motor functions. A large phase 3 trial (A Study to Characterize the Efficacy of Natalizumab on Disability in Secondary Progressive MS [ASCEND]) explored the effect of natalizumab on disease progression in patients with secondary progressive MS (SPMS). Although treatment did not have an effect on ambulation, it reduced progression of UEF impairment as measured using the NHPT.[9] Similar data were presented recently from the ORATORIO trial, demonstrating that ocrelizumab reduced the risk of UEF impairment progression in patients with primary progressive MS.[10] The positive effect of several therapies on UEF indicates that patients with a more advanced stage of MS may benefit from treatment with disease-modifying therapies. Furthermore, UE rehabilitation studies revealed that different types of UE training programs, such as multidisciplinary and robot-based rehabilitation, can improve UE capacity and performance for persons with MS.[11]

Ideally, using both UEF level and ambulation, clinicians would identify subgroups of patients likely to benefit from disease-modifying therapies and, further, select patients who might benefit from rehabilitation strategies. Therefore, the aim of this study was to explore the concurrent presence of UEF and ambulatory impairment in patients with MS by examining various aspects of UEF across different levels of ambulation.

METHODS

The data reported herein are part of a larger study to develop the ASSESS MS system, a multinational project of large European MS centers.[12-16] ASSESS MS is being designed to automatically quantify motor dysfunction in MS with the goal of providing a consistent and fine-grained measure of motor ability. Movements of patients with MS were recorded noninvasively using Microsoft Kinect, a 3D depth-sensing and color camera (Microsoft Corporation), and analyzed using machine learning algorithms. Written informed consent was obtained from all patients before participation, and the study was approved by the ethics committees of participating centers in Amsterdam, Basel, Bern, and Lucerne.

Patients

All patients from the original ASSESS MS project were used for this study. In total, 247 patients from 4 outpatient clinics were included: 165 females; mean ± SD age, 47.3 ± 13.0 years; median disease duration, 13 years (interquartile range, 6–21 years); median EDSS score, 3.5 (range, 0–7.0); with clinically definite MS (181 relapsing-remitting, 42 SPMS, 14 primary progressive MS) or clinically isolated syndrome (n = 10) according to the revised 2010 McDonald criteria.[17] Further inclusion criteria required patients to have a Neurostatus-EDSS score between 0 and 7.0,[18] to be older than 18 years, and to be without additional diseases that contributed to disability. Exclusion criteria were inability to follow procedures or read the consent form due to psychological disorders, dementia, or language barriers.

Ambulation and UEF Measures

All patients received a standardized EDSS assessment according to the Neurostatus definitions on the day of recording.[18] Furthermore, the NHPT and the T25FW test were performed, as implemented in the Multiple Sclerosis Functional Composite.[7] For the T25FW test, the performance of 2 trials was averaged for each patient. For the NHPT, the averaged value of 2 trials was taken for the dominant and nondominant hands, which was determined by asking the patient. Three UEF movements from ASSESS MS were chosen. Two movements were based on the classic neurologic examination: the finger-to-nose test (FNT) to evaluate the level of ataxia (tremor/dysmetria) and the pronator drift test (PDT) to evaluate the level of pyramidal dysfunction. The third movement was the drinking-from-cup test (CUP), which evaluates the level of motor dysfunction affecting ADLs.[19] For the CUP, patients were asked to take a sip of water from a standardized three-quarters–filled plastic cup on a table in front of them at arm's length. The Arm Function in Multiple Sclerosis Questionnaire[20] and the 29-item Multiple Sclerosis Impact Scale (MSIS-29)[21] assessed activity limitations due to impaired UEF and the perceived physical and psychological impact of MS from the patients' perspective, respectively.

Video Rating of Movements

A comprehensive description of the methods used for video rating can be found elsewhere.[19,22] In short, all color videos of the movements of patients were rated by 2 neurologists (C.E.P.vM. and M.D'S.) with broad experience in MS. Predetermined rating scales were used for the FNT and the PDT based on the Neurostatus-EDSS functional system scoring definitions, which are rated on 5-point (0 = none to 4 = severe limb ataxia) and 3-point (0 = none to 2 = evident pronation and downward drift) Likert scales, respectively.[18] For the CUP, a 5-point Likert scale was created (0 = normal performance to 4 = impossible to perform). Using an algorithm that takes into account individual rater bias, the videos were subsequently assigned a consensus score.[15] This consensus score was used in the statistical analysis. Videos of insufficient quality and videos of tests not performed according to the protocol were primarily excluded from the analysis.

Classification of Ambulation and UEF Impairment Groups

The EDSS was chosen as a surrogate measure for ambulation because of its wide acceptance and familiarity in MS clinical practice and trials. Although it primarily indicates the level of disability, the EDSS is heavily weighted toward ambulation and thus seems suitable as a surrogate marker. To verify this association, we compared T25FW test performance between ambulation groups. Based on the Neurostatus-EDSS scoring definitions, patients can be divided into 3 clinically different ambulation

TABLE 1. Demographic, Clinical, and UEF Measures of the Ambulation Subgroups

Measure	Impairment[a]			*P* value			
	Normal to mild (N-M) (n = 147)	Moderate (M) (n = 46)	Severe (S) (n = 54)	Overall	N-M vs M	M vs S	N-M vs S
Demographic data							
Age, mean ± SD, y	43.2 ± 11.1	50.9 ± 15.1	53.5 ± 10.9	<.001	<.001	NS	<.001
Sex, F/M, No.	104/43	29/17	32/22	NS	NA	NA	NA
Disease type, R/P, No.	142/5	34/12	15/39	<.001	<.001	<.001	<.001
Disease duration, median (IQR), y	10 (4-16)	18 (9-27)	20 (12-31)	<.001	<.001	NS	<.001
Outcome measures							
T25FW test, median (IQR), s	4.6 (4.0-5.2)	5.7 (4.9-6.9)	11.8 (8.5-15.9)	<.001	<.001	<.001	<.001
MSIS-29 score, median (IQR)	42 (33-57)	73 (56-84)	74 (62-95)	<.001	<.001	NS	<.001
NHPT D, median (IQR), s	19.9 (18.3-22.4)	25.0 (21.7-30.2)	33.0 (25.8-41.4)	<.001	<.001	NS	<.001
FNT D score 0/1/≥2, No.	82/36/11	9/20/13	5/17/24	<.001	<.001	NS	<.001
FNT ND score 0/1/≥2, No.	78/41/13	6/21/14	2/22/26	<.001	<.001	NS	<.001
PDT score 0/≥1, No.	124/15	27/14	21/29	<.001	.001	.040	<.001
CUP D score 0/1/≥2, No.	100/30/5	10/23/8	4/17/26	<.001	<.001	.002	<.001
CUP ND score 0/1/≥2, No.	101/30/5	15/22/7	1/24/24	<.001	<.001	<.001	<.001
AMSQ score, median (IQR)	33 (31-40)	50 (38-74)	81 (54-89)	<.001	<.001	.006	<.001

AMSQ, Arm Function in Multiple Sclerosis Questionnaire; CUP, drinking-from-cup test; D, dominant hand; FNT, finger-to-nose test; IQR, interquartile range; MSIS-29, 29-item Multiple Sclerosis Impact Scale; NA, not applicable; ND, nondominant hand; NHPT, Nine-Hole Peg Test; NS, not significant; P, progressive (ie, secondary and primary progressive multiple sclerosis); PDT, pronator drift test; R, relapsing (ie, clinically isolated syndrome and relapsing-remitting multiple sclerosis); T25FW, Timed 25-Foot Walk; UEF, upper extremity function.

[a]Normal to mild ambulatory impairment: Expanded Disability Status Scale (EDSS) score of 0 to 3.5; moderate ambulatory impairment: EDSS score of 4.0 to 5.5; severe ambulatory impairment: EDSS score of 6.0 to 7.0.

groups: normal to mild ambulatory impairment (able to walk ≥500 m; EDSS score, 0-3.5), moderate ambulatory impairment (limited ambulation, ≥300 m without an aid; EDSS score, 4.0-5.5), and severe ambulatory impairment (assistance required when walking, able to take a few steps; EDSS score, 6.0-7.0).

The NHPT of the dominant hand (despite disability due to MS) was used to stratify patients into clinically different UEF groups: normal UEF (<18 seconds), mild UEF impairment (³18 seconds and <33.3 seconds), and severe UEF impairment (≥33.3 seconds). The lower benchmark was chosen based on work by Kierkegaard et al[23] that provided evidence that 18 seconds on the NHPT differentiated patients with MS with no impaired UEF from patients with minimally impaired UEF who were at risk for activity limitations and participation restrictions. The upper benchmark was derived from the cutoff value in the study by Lamers et al,[24] who used a median split of the NHPT score of a large MS sample (n = 105), which differentiated between mild and marked to severe UE dysfunction based on various measures of UEF (eg, assessment of strength, tremor, spasticity, pain) and participation level. Patients who were unable to perform the NHPT due to MS-related impairment were categorized as severely impaired. This classification resulted in 9 clinically different groups stratified according to the level of ambulatory and UEF impairment.

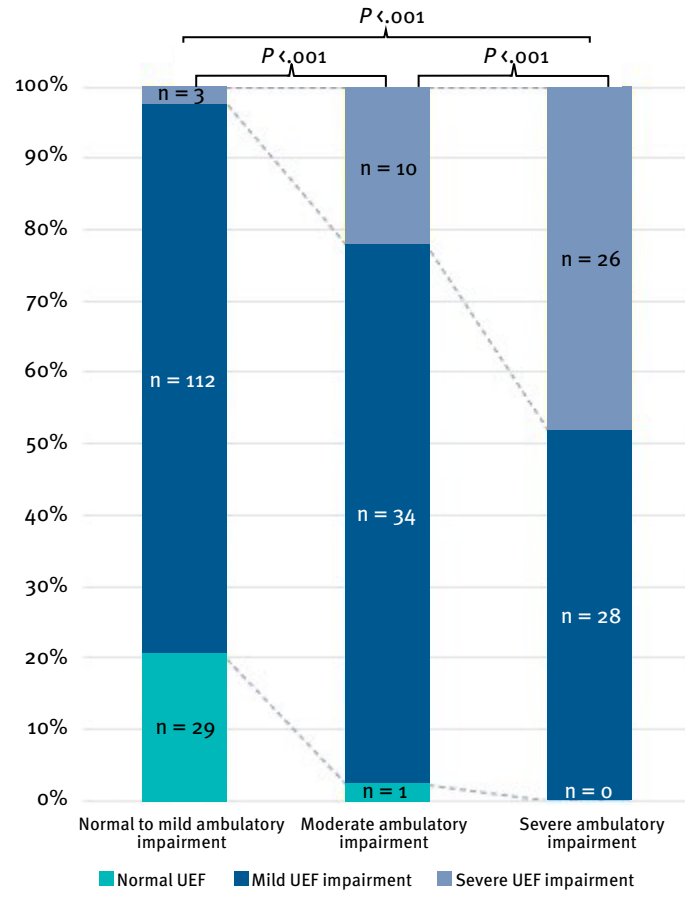
To identify different aspects of UEF at various levels of ambulation, the following variables were compared between the aforementioned patient groups: FNT, PDT, CUP, Arm Function in Multiple Sclerosis Questionnaire (AMSQ), and MSIS-29, along with demographic and disease-specific characteristics (age, sex, disease type, disease duration, T25FW test). Disease type (ie, relapsing/progressive) and PDT (ie, 0/≥1), FNT (0/1/≥2), and CUP (ie, 0/1/≥2) scores were further categorized for ease of interpretation.

To explore the relationships between the NHPT, FNT, PDT, and CUP scores, comparison Venn diagrams with multiple overlapping closed curves were created, each representing a set of patients with abnormal performances (score ≥1) on either of the tests. Patients were included in the final analyses only if they completed all 4 tests.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics, version 24.0 (IBM Corp). A $P < .05$ was considered statistically significant. The normality of each variable was assessed using histograms and normality plots. For variables with a normal distribution, mean ± SD values were calculated, and for variables with nonnormal distributions, median (interquartile range) values were calculated. Variables following a normal distribution were compared between groups

FIGURE 1. Distribution Among the Clinically Different UEF and Ambulation Subgroups



A, ambulation; EDSS, Expanded Disability Status Scale; NHPT, Nine-Hole Peg Test; UEF, upper extremity function.
Normal to mild A/UEF impairment: EDSS score, 0 to 3.5; NHPT less than 18 s.
Moderate A/UEF impairment: EDSS score, 4.0 to 5.5; NHPT 18 seconds to less than 33.3 s.
Severe A/UEF impairment: EDSS score, 6.0 to 7.0; NHPT 33.3 s or longer.

using analysis of variance models, as appropriate, whereas categorical variables were compared using Mann-Whitney *U* and χ^2 tests. The Bonferroni correction was applied. The distribution of patients across the EDSS- and NHPT-defined ambulation and UEF groups, respectively, was compared using a χ^2 test.

RESULTS

Ambulation Groups

The median EDSS score of the total cohort was 3.5 (range, 0-7.0). Based on the Neurostatus-EDSS, 147 patients were categorized as having normal to mild ambulatory impairment, 46 as having moderate ambulatory impairment, and 54 as having severe ambulatory impairment (**TABLE 1**). All groups were similar in terms of sex distribution (*P* = .26). Subgroup comparisons revealed that patients with worse levels of ambulatory impairment were older and had more progressive MS phenotypes, longer disease durations, higher MSIS-29 scores, and longer T25FW durations. These differences were significant between all groups (overall *P* < .001); however, age, disease duration, and MSIS-29 did not differ between the moderate and severe ambulatory impairment groups (*P* = .17, .62, and .81, respectively).

A similar trend was observed for all UEF measures, with a worse level of UEF performance along with a worse level of ambulatory impairment (all group differences overall *P* < .001) (**FIGURES S1** and **S2**, available online at IJMSC.org).

Distribution of UEF Groups

FIGURE 1 shows the results of the 9 clinically different ambulation and UEF impairment groups, as defined by the EDSS and NHPT benchmarks. Four patients were excluded from the analysis because the NHPT was missing due to reasons not related to MS: 3 in the normal to mild ambulatory impairment group and 1 in the moderate ambulatory impairment group. Overall, the cohort consisted of relatively few patients with normal UEF (n = 30) and 29 with normal to mild ambulatory impairment. Most patients had mild UEF impairment (n = 174), accounting for the largest proportion in all ambulation groups (77.8%, 75.6% and 51.9%, respectively). We

PRACTICE POINTS

In 247 persons with multiple sclerosis or clinically isolated syndrome, we explored the concurrent presence of impairment in upper extremity function (UEF) using multiple clinical and self-report measures and ambulation using the Expanded Disability Status Scale.

Although more severely impaired ambulation was overall associated with worse UEF, most patients had mild UEF impairment regardless of ambulation level.

Because the severity of UEF limitations does not consistently match the severity of ambulatory impairment, it is important to assess UEF to get a more comprehensive picture of multiple sclerosis–related disability. ■

observed a decline in the proportion of patients with normal UEF across the level of ambulatory impairment (20.1% [normal to mild ambulatory impairment], 2.2% [moderate ambulatory impairment], and 0% [severe ambulatory impairment]) and a concurrent increase in the proportion of patients with severe UEF impairment (2.1%, 22.2%, and 48.1%, respectively).

Combination of UEF Tests

FIGURE S3 shows the Venn diagrams revealing the overlapping of patients (total number) with abnormal performance on the different UEF tests. Fifty-six patients were excluded from the analyses due to missing values on any of the tests: 4 on the NHPT, 23 on the CUP, 30 on the FNT, and 17 on the PDT (74 missing tests in total). Of the 191 remaining patients, 165 (86.4%) had abnormal performances on the NHPT, 105 (55.0%) on the FNT, 49 (25.7%) on the PDT, and 91 (47.6%) on the CUP. Most patients who had abnormal performances on the NHPT also performed abnormally on the other tests.

DISCUSSION

In a cohort of people with MS, this study explored the concurrent presence of UEF and ambulatory impairment and examined various aspects of UEF across different levels of ambulation. We found distinct patterns of UEF and ambulation impairment. Although most patients exhibited only mild UEF deficits, this was already a prominent sign in patients with no obvious ambulatory restrictions. Patients with moderately or severely impaired ambulation also displayed poorer performance on the UEF measures than patients with less impaired ambulation. Strikingly, many patients with severely impaired ambulation (EDSS score, 6.0-7.0) displayed only mild UEF impairment. Our observations underscore the importance of considering a patient's UEF impairment independent of ambulation. Because the severity of UEF limitations does not consistently match the severity of ambulatory impairment, it is important to assess UEF to get a more comprehensive picture of MS-related disability.

In the present study, more than 80% of patients exhibited some level of UEF impairment as measured with the NHPT, in line with previous findings.[25] To identify the relevant underlying constructs of UE dysfunction, we examined the relationship between the NHPT and the FNT, PDT, and CUP using Venn diagrams. Although the 9HPT is often used as a performance-based measure of manual dexterity, the present results indicate that it may also identify patients with pyramidal dysfunction and UE ataxia, as well as diminished ability to perform ADLs. Patients with abnormal NHPT performances also had abnormal performances on the clinical tests. This is in line with an earlier report on a largely similar cohort of patients that revealed that a large percentage of NHPT variance was explained by the combination of UEF movements, of which the CUP contributed most in all regression models.[19] However, additional studies are needed to determine the utility of the NHPT as a performance-based measure of additional functional aspects for patients with MS.

In previous studies, the NHPT seemed to be a good outcome measure for differentiating the levels of severity of UE dysfunction.[23,24,26] Implementation in clinical practice and trials of MS has been recommended given its good psychometric properties. Furthermore, the NHPT shows high convergent validity with other manual dexterity tests as well as more comprehensive UEF measures.[26] To date, it is still not clear which cutoff values on the NHPT should be applied. For the present study, we used the proposed cutoff values published by Kierkegaard et al and Lamers et al for the lower and upper benchmarks because of their supposed relationship to real-life anchors and functional independence.[27] Longitudinal and larger studies are needed to confirm the clinical utility and relevance of these proposed NHPT benchmarks and to parse out whether there are additional benchmarks in the lower and higher ranges of performance.

Previous studies have reported relative patterns of UEF and ambulatory impairment in patients with MS that are largely complementary to the present findings.[25,28-30] A cross-sectional study explored UEF and ambulation across different levels of disability using the NHPT and the T25FW test to stratify patients into different UEF and ambulation

groups (>1 SD worse than age- and sex-related norms).[25] Disability was defined as mild (EDSS score, 1.0–3.5), moderate (EDSS score, 4.0–5.5), or severe (EDSS score, 6.0–9.5), resulting in a distribution of 71%, 92%, and 97% of patients with UEF impairment and 22%, 89%, and 100% of patients with walking impairment, respectively. The authors concluded that most patients with MS experienced several concurrent disabilities. Although these findings are in line with the present data, the authors did not provide detailed insight into the broader aspects of UEF.

Another report provided more detailed insight into the UEF of patients with MS across different EDSS score subgroups.[28] In this cross-sectional study, various measures of UEF were included to assess strength, spasticity, and sensation, and the NHPT and a PRO measure were also incorporated. Findings indicated a concurrent deterioration of UEF on all aspects with disability accrual, which is in line with the present data; however, a small proportion of patients was reported as being impaired on the NHPT, perhaps due to the use of a different definition of abnormal.

No inference can be made on deterioration of UEF and ambulation longitudinally based on this study's data. Two earlier longitudinal studies investigated these patterns. In the first study, changes in performance on the 10-m timed walk test and the NHPT were assessed in 156 patients within 10 years of diagnosis.[30] The authors concluded that ambulation deteriorates earlier and more rapidly than UEF. This difference was much clearer in the smaller group with a progressive onset (n = 28). In the second study, the primary goal was to improve the assessment of disability accrual in patients with SPMS using the EDSS-Plus, a composite end point adding the T25FW test and NHPT scores to the EDSS score. They found that once the T25FW test time deteriorated by 20% or more, UEF deteriorated more gradually than ambulation in the subsequent 2 years, especially in the most severely disabled group (EDSS score, 6.0-6.5).[29]

Other studies confirm the presence of UEF impairment early in the disease course. Data from questionnaires of 35,000 patients collected in the North American Research Committee on Multiple Sclerosis registry revealed that in the first year after onset, 52% of patients reported minimal to mild UEF impairment and 40% perceived no problems.[31] For ambulation, these values were 35% and 50%, respectively. An important limitation of this study was that function was assessed with short 6- or 7-item questionnaires only, and no additional physician- or performance-based measures were used. Two other studies of patients with MS found subtle UEF impairments in the early disease course that were not detected with standard neurologic examination.[32,33] Abnormalities were found in movement smoothness, speed profile, and lifting tasks. These limitations were noticed by patients and had an effect on their ability to perform ADLs.[32]

Several neurobiological explanations for different patterns of ambulatory and UEF impairment are possible. One hypothesis to explain the finding that a significant proportion of patients with severe ambulatory impairment have only mild UEF impairment is that changing functional networks that compensate for increasing structural damage are more robust in UEF than in ambulation. This might lead to slower deterioration of UEF. A similar phenomenon has been described in the preservation of cognition in patients with MS.[34] The cognitive reserve hypothesis postulates that genetic and environmental factors attenuate the negative effect of disease burden on cognitive decline.[35] Another hypothesis for the UEF and ambulation difference is that of a central length-dependent axonopathy.[36] In this mechanism, longer neurons to the lower extremities are more vulnerable to accumulating focal damage, which causes secondary neurodegeneration. Clinically, this would lead to faster deterioration of ambulation than of UEF.

The present study has some limitations. To define the level of ambulatory impairment, EDSS cutoff values were used. According to the Neurostatus-EDSS definitions,[18] a patient with unrestricted ambulation (able to walk >500 m) can have an EDSS score between 0 and 4.0, depending on impairment of other functional systems. As a result, we cannot rule out the possibility that other patterns of disability contributed to the classification of ambulation in this cohort. Furthermore, in patients with an EDSS score lower than 2.0, walking and balance can already be impaired, which should be considered when interpreting these findings. Well-known floor and ceiling effects for the EDSS and any choice of classification scheme probably affected the findings. Nonetheless, we have chosen the EDSS because of its familiarity in clinical practice and trials, which allows other researchers to form a mental picture of the clinical status of the subgroups. Another limitation was that patients with MS included in the study were relatively mildly disabled (median EDSS score, 3.5), which limits the generalization of the data to more severely disabled patients. However, the sample was representative of a general MS population visiting an outpatient clinic.

To conclude, this study emphasizes the importance of wider incorporation of performance-based and PRO measures as adjuncts to the EDSS score in clinical practice and trials. We provided data on the relative patterns of UEF and ambulatory impairment and explored the concurrent presence of a variety of functional aspects of UEF. Further stratifying patients according to UEF, beyond ambulation, will enhance patient selection for future treatment and support the development of rehabilitation strategies specially targeted toward UEF impairment. ■

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