Effect of a strong desire to void on walking speed in individuals with multiple sclerosis and urinary disorders

Claire Hentzen, Nicolas Turmel, Camille Chesnel, Audrey Charlanes, Frédérique Le Breton, Samer Sheikh Ismael, Gérard Amarenco

Effect of a strong desire to void on walking speed in individuals with multiple sclerosis and urinary disorders

Claire Hentzen [1], M.D., Nicolas Turmel [1], M.D., Camille Chesnel [1], M.D., Audrey Charlanes [1], M.D., Frédérique Le Breton [1], M.D., Samer Sheikh Ismaël [1], M.D., Gérard Amarenco [1], Ph.D.

[1] Sorbonne Université, GRC 001, GREEN Groupe de Recherche Clinique en Neuro-Urologie, AP-HP, Hôpital Tenon, F-75020 Paris, France

Abstract

Background. Lower urinary tract symptoms, especially overactive bladder, are frequent and disabling in individuals with multiple sclerosis (IwMS). An association with gait disorders is common, which could aggravate continence difficulties and affect quality of life. The association between the need to void and walking has never been studied in this population. **Objective.** The primary aim of this study was to assess the effect of a strong desire to void (SDV) on walking speed in IwMS and lower urinary tract symptoms. The secondary aim was to identify clinical or urodynamic factors associated with walking speed impairment at SDV in this population.

Methods. We included IwMS with urinary disorders and Expanded Disability Status Scale score < 7 in this observational study. Individuals underwent 3 10-m walk tests (10MWT) and one Timed Up and Go (TUG) test at SDV and at post-void (PV).

Results. Among the 72 IwMS included (mean [SD] age 50.6 [11.6] years; 46 [64%] females), the mean (SD) speed for 10MWT was 1.00 (0.31) $m.s^{-1}$ at SDV and 1.07 (0.30) $m.s^{-1}$ at PV

(p<0.0001). Time for TUG was also increased when individuals felt SDV: mean 11.53 (4.6) sec at SDV versus 10.77 (3.8) sec at PV (p=0.004). No predictors of greater impairment of walking speed at SDV were identified.

Conclusion. This study suggests a clinical impact of bladder sensation on walking speed in IwMS and urinary disorders. None of the individual characteristics could predict greater decrease in gait velocity at SDV.

Keywords: Multiple sclerosis, Walking speed, Gait, Urination, Lower urinary tract symptoms

Introduction

Multiple sclerosis (MS) causes demyelinating lesions and could be responsible for a number of symptoms, including motor or sensitivity disorders, cognitive impairment, visual disturbances, and urinary and bowel disorders. Gait difficulties are the most visible disability, and about 70% of patients report a psychological impact due to their walking impairment[1]. Different neurological presentations can be observed in different individuals: spastic, ataxic, cerebellar, and pyramidal forms, depending on the topography of the cerebral or medullar lesions. Lower urinary tract symptoms (LUTSs) are also very common, with a prevalence of 32% to 86%[2]. Overactive bladder with urgency, increased bladder frequency and urgency urinary incontinence is the most common symptoms. Obstructive symptoms are also frequent and may coexist with storage symptoms. Detrusor overactivity is the most frequent urodynamic profile, but the correlation between clinical symptoms and urodynamics data is not perfect. Other urodynamic profiles exist: bladder oversensitivity, detrusor-sphincter

dyssynergia, and neurogenic detrusor underactivity, but urodynamics can be normal for 1% to 34% of patients with LUTSs[2,3]. Despite a correlation between frequency and severity of LUTSs and severity of incapacity assessed by Expanded Disability Status Scale (EDSS) [4] or with number of falls[5], no strict relationship can be demonstrated between type of LUTS, urodynamics profile and type of neurological presentation (pyramidal, with or without major spasticity, cerebellar etc.)[4,6].

The role of bladder filling and need to void on gait has been poorly studied and only in healthy populations. Yet, some hypotheses could support a link between these 2 parameters. The need to void is a sensory stimulus, integrated in different cerebral areas, including insula, periaqueductal gray, cingulate cortex, hypothalamus and prefrontal area[7,8]. A modification in gait velocity with emotions was demonstrated. Jousse et al. showed a decrease in attentional skills with a strong desire to void (SDV)[9]. These 2 studies may suggest a possible impact of the need to void on gait velocity, as a new sensory phenomenon to integrate and modulate, as a function of the locomotion task.

At the medullar stage, a modification of the H-reflex was demonstrated at SDV in healthy individuals[10]. The H-reflex is considered to reflect motoneuronal excitability. The impact of motoneuronal excitability on gait is not clearly established, but some studies revealed a modification of the H-reflex with gait velocity[11,12]. The H-reflex is also used as an indirect measure of spasticity, but its expression is not correlated with spasticity severity[13]. The modulation of the medullar reflex with bladder sensation, and perhaps with bladder filling or detrusor overactivity, with a possible impact on gait may explain a link between gait and the need to void.

The consequences of the need to void on other tasks have been little studied and only in healthy populations; however, alterations in attentional condition[9], gait velocity[14] and

balance[15] performance were shown. Assessing the effect of the need to void in a neurologic population with frequent gait disorders and LUTSs could be pertinent to better understand the pathophysiological mechanisms and evaluate whether an intervention for one condition may improve the other, with the hypothesis that an appropriate management of LUTSs could lead to an improvement in some locomotor parameters.

The primary aim of this study was to assess the effect of an SDV on gait in individuals with multiple sclerosis (IwMS) and LUTSs. The secondary aim was to identify clinical or urodynamic factors (EDSS, symptom severity, detrusor overactivity, cystometric capacity) associated with greater gait impairment.

Material and methods

Participants

Individuals over age 18 who were consulting for LUTSs linked with MS in the neuro-urology department of a university hospital between February 2017 and March 2017 were invited to participate in this observational study. Individuals who agreed to participate were included where they were admitted for a consultation or urodynamic assessment, and all tests were performed on the same day.

Inclusion criteria were MS with EDSS score 1 to 6.5 and LUTSs secondary to MS (storage or voiding symptoms). Participants had to be able to walk 50 m without human help and to hold urine for 5 min, the time required to perform the tests. They could be taking medication for MS or LUTSs. All types of MS were accepted. We excluded individuals with urinary tract infections, relapse of MS in the last 7 days, or severe cognitive impairment (Mini Mental State Examination [MMSE] score < 10).

93

94 Measures and procedure

95 Gait was assessed by 2 clinical tests approved for MS. The same tests were performed under 2
96 conditions: first when the individual felt an SDV, and then immediately after micturition,
97 spontaneously or with self-catheterization (post-void [PV]).

98 The primary outcome was gait velocity assessed by a 10-m walk test (10MWT)[16]. Three
99 trials were recorded, as per Booth et al. [14]. Individuals were instructed to walk the 10 m at a
100 comfortable speed. Maximum speed was not recorded to limit the impact of fatigue on test
101 repetition, because maximal speed improves energetic cost. Only the 6 intermediate meters
102 (meters 2 to 8) were recorded, to limit the effect of acceleration and deceleration. Tests were
103 recorded with a manual chronometer by the same examiner for each individual, with 30 sec of
104 rest at most between each trial.

105 Secondary outcomes were time on the Timed Up and Go Test (TUG)[17,18] and gait
106 variability assessed by the coefficient of variation (CoV) of the 3 trials of 10MWT. The trial
107 began with a non-recorded TUG to understand instructions and to limit the learning effect, but
108 only one trial was recorded to limit the test duration and fatigue induced by the get up
109 exertion.

110 Medical history, treatment, and anthropometric data were collected. An MMSE was
111 administered to identify memory impairment. Urinary symptoms were assessed by the
112 questionnaire Urinary Symptom Profile (USP) with 3 aspects: “stress urinary incontinence”
113 (/9), “overactive bladder” (/21) and “low stream” (/9)[19]. Data for the last cystometry were
114 collected (retrospectively if cystometry was not planned on the day of inclusion): detrusor
115 overactivity, volume at first detrusor contraction, SDV during filling, and cystometric
116 capacity. MS severity was assessed by the EDSS, a score based on measures of impairment in

8 functional systems, and on walking ability[20]. Individuals with an EDSS score > 4 complained of gait difficulties. Each participant was asked if they had urine leakage during the tests. PV residual volume was measured with a mobile transabdominal ultrasound apparatus (Bladder Scan®); 3 measures were taken, and the highest was recorded. Secondary analyses were planned to identify clinical or urodynamic factors associated with greater gait impairment: age, EDSS score, need for a walking device, severity of overactive bladder on USP score, spontaneous void or self-catheterization, cognitive impairment assessed by the MMSE, detrusor overactivity during the last cystometry, and PV residual volume.

Ethics approval

The study protocol and data collection were conducted in accordance with the ethical standards of the national research committee and the Declaration of Helsinki. This study was approved by the local ethics committee (registration no. 2015-A00125-44). All participants gave their consent to participate. This study was registered on ClinicalTrials.gov: NCT03204747.

Statistical analysis

Statistical tests were performed with R for Windows (Rx64 3.2.3). In a previous study of healthy individuals, the only one assessing the effect of the need to void on gait, Booth et al. [14] showed a mean difference on gait velocity of 0.05 $m.s^{-1}$ between SDV and PV. In IwMS, we expected a slightly greater mean difference between the 2 conditions. Thus, based on this previous study, for an expected mean difference of 0.06 $m.s^{-1}$, a standard deviation of 0.17 (SD 0.18 to 0.19 in the Booth et al. study) and 80% power, we needed 65 participants. Mean gait velocity at SDV and PV were calculated for the 3 trials of 10MWT. Variability of the 3

trials was assessed by the CoV (standard deviation/average). The temporal parameters of gait for 10MWT, TUG and CoV data were normally distributed. Thus, these were analyzed by Student's *t* test for paired samples. The effect size was calculated with Cohen's d formula. The impact of clinical and urodynamic parameters on the mean difference between TM10 at SDV and PV were analyzed by Student *t* test for qualitative variables and Spearman correlation for quantitative variables. Significance was considered at $p < 0.05$. Missing data were not replaced.

Results

We included 72 individuals (mean [SD] age 50.6 [11.6] years; 46 [64%] females). Characteristics are summarized in Table 1. Three individuals performed only 2 trials of the 10MWT for each condition because of physical tiredness. The mean speed for 10MWT was 1.00 (0.31) $m.s^{-1}$ at SDV and 1.07 (0.30) $m.s^{-1}$ at PV ($p<0.0001$; effect size 0.79). Maximal improvement on mean 10MWT was 0.34 $m.s^{-1}$ (5.03 s). Only 10 (14%) participants had a lower performance at PV than SDV. These 10 participants and the others did not differ in EDSS score, use of a walking device, existence of detrusor overactivity, or age. The distribution of gait velocity change between SDV and PV is presented in the Figure. The individual variability of the 3 trials of 10MWT, assessed by the CoV, was significant (mean [SD] 5.2% [3.9] vs 4.2% [3.6], p=0.048). Between the first and second try, 47% of participants showed improved gait velocity at SDV and 40% at PV. Between the second and third try, 68% of participants showed improved gait velocity at SDV and 63% at PV. Mean time for TUG was also increased when individuals felt SDV: 11.53 (4.6) sec at SDV versus 10.77 (3.8) sec at PV (p=0.004, effect size 0.35). Only one participant reported a leak during the test.

Secondary analysis did not identify any predictors of impaired walking speed at SDV among the features explored (Tables 2 and 3).

Discussion

The results of this study showed an increase in gait velocity after voiding as compared with velocity during an SDV in lwMS and urinary disorders. This finding suggests a negative impact of an urgent need to void on walking speed in IwMS and urinary disorders. We found no clinical or urodynamic factors that predicted reduced gait performance.

In their study, Booth et al.[14] proposed that "the experience represents a dual task or divided attention situation" to explain the difference in the SDV and PV situation in healthy individuals. The authors introduced for the first time bladder sensation as a divided attention situation. The role of dual tasks is well established, particularly in older adults and with a risk of falling. The effect of dual tasks, in particular in gait, has been widely studied and demonstrated in IwMS. In a recent review, the presence of cognitive motor interference appeared more frequent in IwMS than in healthy individuals during gait analysis [21]. Individuals with mild cognitive impairment seemed more sensitive to the influence of a cognitive task on walking speed[22]. Moreover, emotional perception of the need to void could also influence gait velocity.

Functional MRI shows activation of different areas during bladder filling (insula, periaqueductal gray, cingulate cortex, hypothalamus and prefrontal area, amygdala). Most of these cerebral areas are implicated in emotional control, and functional MRI studies found less activation or deactivation of some of these areas in individuals with overactive bladder as compared with healthy individuals, which suggests a lack of control of this unpleasant sensation[23]. A modification of gait velocity has been found correlated with emotion in

healthy individuals[24]. In IwMS, only the fear of falling has been studied, but other emotions could also affect gait. We found no relationship between severity of symptoms and greater difference between the 2 conditions. However, the proportion of individuals with regular leaks was higher (no statistical analysis) in individuals with a difference of > 0.1 m/s between SDV and PV, which supports a possible distractible effect of the urge to void and the role of emotional control.

A second explanation is the effect of bladder sensation on motoneuronal excitability. Previous studies of individuals with spinal cord injury evoked a gait spinal central pattern generator[25,26]. Furthermore, the H-reflex, which is a spinal motoneuronal response to electrical stimulation, is considered to reflect motoneuronal excitability. Variation in H-reflex amplitude reflects modified spinal cell excitability [27]. During gait, some studies showed an increase in H-reflex amplitude, which suggests an increase in motoneuronal excitability, with variation in function of gait cycle. A proportional increase in the amplitude of the H-reflex as a function of walking speed has been demonstrated[11,12]. Thus, a role of motoneuronal excitability in gait velocity can be supposed, and a decrease in motoneuronal excitability could affect walking speed. A decrease in H-reflex in the soleus muscle occurs at SDV in healthy individuals[10]. However, no study has examined the impact of the need to void on motoneuronal excitability in IwMS, whereas in individuals with spinal cord injury, bladder filling tends to increase H-reflex amplitude[10]. Application of these findings in IwMS is difficult, as far as lesion localizations at cerebral or medullar level could affect H-reflex variability, and a specific study would be necessary.

Another possible explanation is that pelvic and trunk muscle activation is modified by bladder filling: the activation of pelvic floor muscles decreases when the bladder is moderately full, and the obliquus internus abdominis and rectus abdominis activation is increased. Bladder fullness also influences balance: an increase in center-of-pressure motions on a force plate

was demonstrated when the bladder was full in healthy individuals[15]. These 2 parameters could participate in gait velocity decrease at SDV.

Our results agree with the Booth et al.[14] study of healthy individuals (continent, International Prostate Symptom Score 0-7). The authors used a GAITRite® walkway and showed an impairment of 0.05 $m.s^{-1}$ at SDV as compared with PV. Results in our study were obtained with clinical (not instrumental) tests. A potential limitation of the primary outcome is that fast speed usually has better reliability in 10TMW than comfortable speed, but energetic cost is improved at maximal speed. We chose not to record this measure to limit the impact of fatigue on the different tests.

Several measures were established to limit bias in recording walking tests. Participants underwent 3 trials for the 10MWT under each condition, to limit intra-individual variability and to observe whether this variability is modified by SDV, as previously described[14]. To prevent inter-judge variation, all tests were recorded by the same examiner using a standardized protocol and the same time-measuring tool. A recent study did not find a significant difference between 3 consecutive short walk tests (Timed 25-Foot Walk) [28], which suggests no spontaneous improved performance with repeated tests. Thus, to reduce the impact of tiredness on recording, we did not randomize by order of condition, and clinical tests at PV were always performed after those at SDV. This minimization of bias is also a potential limitation for highlighting a greater difference between the 2 conditions, because fatigue induced by the first tests can affect subsequent performance with a limited rest time between the 2 conditions. Individuals could also take a rest between the tests to reduce this bias. Our results did not reveal a progressive improvement in performance with the repetition of tests during the same condition. This suggests that the difference shown between SDV and PV is not related to a spontaneous improvement due to the repetition of the same exercise. For the TUG test, the learning effect was limited by a first non-recorded trial to verify

comprehension of instructions. Instructions were repeated before each trial to facilitate their memorization.

Our study has several limitations. Clinical tests are less precise than instrumental tests, and some gait parameters such as stride length, swing time, and duration of single support could not be studied. The examiner was not blinded to condition (PV or SDV), but participants did not know the expected results and were not informed of the time performed in each test. The sequence of the test after urination can have a negative impact on performance, by the fatigue induced by the first tests and by the fatigue induced by urination, with the different stages of undressing, sitting, etc. This could influence the identification of factors associated with a greater impact of the need to void on walking speed. Moreover, because of the design of the study, the negative impact of the urgent need to void is derived from the interpretation of the increase in speed after urination. An evaluation without the need to void but away from urination could have been interesting to free oneself from possible neurological reflexes induced by micturition, especially in individuals with detrusor overactivity. In secondary analyses, an evaluation of executive functions would have allowed a more specific analysis, in the hypothesis of “dual task” impact, because the MMSE does not properly evaluate these functions.

The difference between SDV and PV we found is less than the minimally clinical relevant differences described in the literature, but these have been defined with small numbers of participants with high EDSS score or using a modification of EDSS score as a relevant clinical change, but the EDSS score is not sensitive to minor change[29–31]. Thus, the observed difference in our study can be difficult to interpret; we did not expect a clinical state change as a modification of the EDSS score between SDV and PV, and the comparison of our results with the mentioned thresholds is not wholly adapted (median EDSS or condition to

realize the 10MWT differed from those of our study). Therefore, clinical interpretation of this PV improvement is subtle, and our data cannot lead to specific clinical recommendations.

There are many different perspectives from this study. First, a new study of the specific population within IwMS could improve the accuracy of results and clinical relevance. The role of detrusor overactivity was not shown, but there was likely a lack of power in secondary analysis, and owing to the study design, 27 of the 62 urodynamic data measurements available were older than 3 months. Also, all individuals did not have urodynamics data, and some measurements were prior to the inclusion date, which limits their interpretation. Further research is necessary to judge the influence on spasticity. Several conditions modify spasticity: urinary tract infections, ingrown nails, lithiasis, temperature[32]. Yet, the possibility of spasticity exacerbation during detrusor uninhibited contraction has never been considered. Moreover, considering the impact of the need to void as a dual task requires a comparison with cognitive tasks during gait evaluation, especially since an impact on attention skills has been demonstrated[9].

Finally, our study suggests that clinical walk tests are sensitive to changes in individual variations such as the need to void. The use of the tests in clinical practice and research must be standardized, to reduce bias in their interpretation and clinical significance.

Conclusion

This study suggests decreased walking speed at SDV in IwMS and urinary disorders, showing an increase in gait velocity after voiding with an SDV. Severity of disability and urodynamic parameters were not associated with greater difference in velocity at SDV than PV, but the heterogeneity of the MS population could suggest lack of power in our study to demonstrate the influence of a specific factor.

Funding. Dr. Hentzen reports grants from SIFUD-PP (the francophone society of urodynamics) and from LILIAL-GREEN GRC-01 UPMC (Group of clinical REsEarch in Neurourology), during the conduct of the study.

Conflict of interest. None declared.

Legend

Figure. Walking speed change between post-void and a strong desire to void.

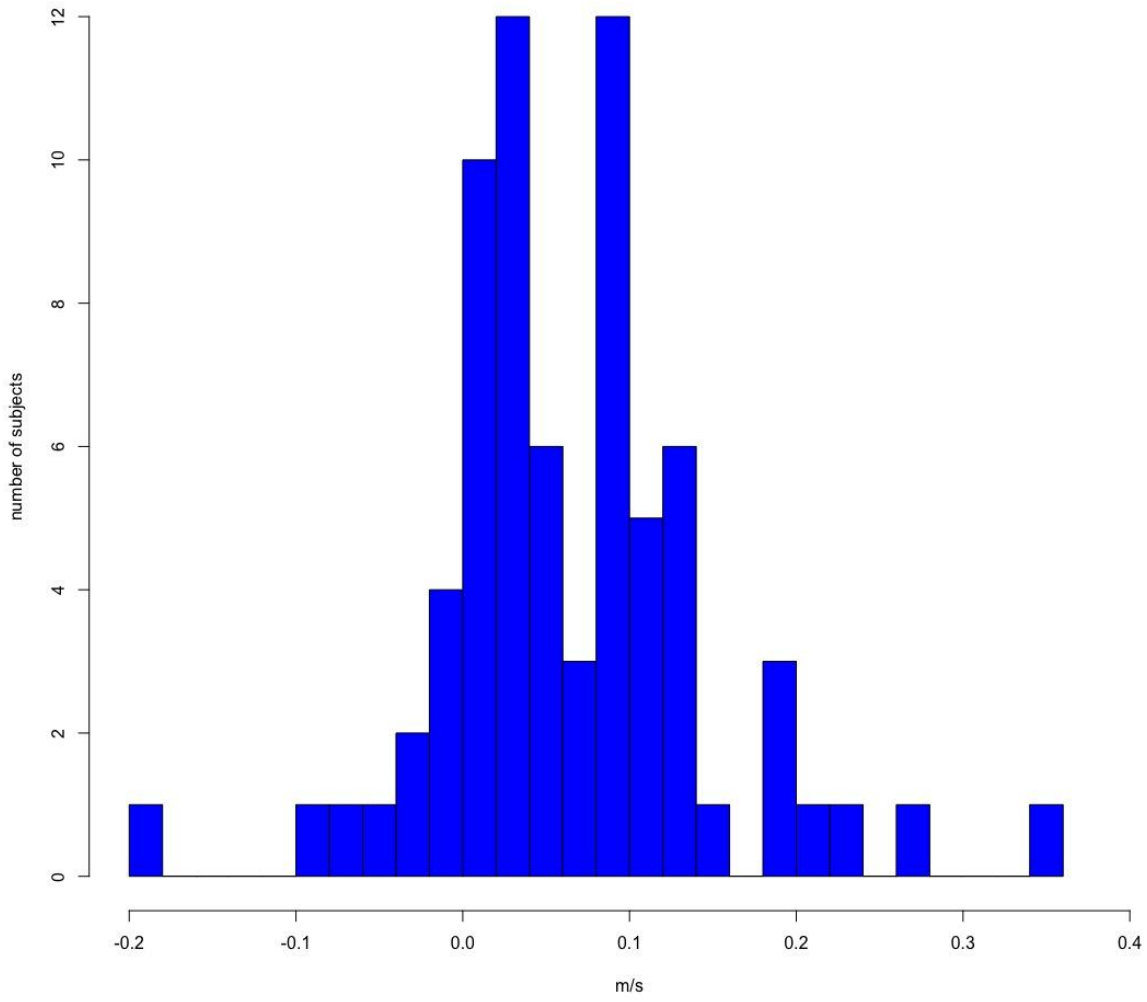

Table 1. Initial characteristics of individuals with multiple sclerosis (n=72).

		Median (Q1-Q3)
Age, years	50.6 (11.6)	51 (40.7-60.2)
Female	46 (64%)	
EDSS	4.8 (1.2)	5 (4-6)
MMSE (/30)	27 (2.8)	
BMI	23.4 (2.8)	23.1 (19.9-25.8)
USP stress score (/9)	1.2 (2.3)	0 (0-1)
USP OAB score (/21)	6.3 (3.7)	6.5 (4-9)
USP low stream score (/9)	4.9 (3.6)	4 (2-9)
Micturition status		
Spontaneous void	37 (52%)	
CISC	21 (29%)	
Mixed	14 (19%)	
Treatment for LUTS		
Anticholinergic	31 (43%)	
Alpha blocker	20 (28%)	
PTNS	6 (8%)	
Botulinum toxin in detrusor	21 (29%)	
Botulinum toxin in sphincter	4 (6%)	
None	22 (30%)	
Treatment for multiple sclerosis	52 (72%)	
Urodynamics data available	62 (86%)	
Detrusor overactivity	31 (50%)	

Data are mean (SD) or number (%).

EDSS, Expanded Disability Status Scale; MMSE, Mini Mental State Evaluation; BMI, body mass index; USP, Urinary Symptom Profile; OAB, overactive bladder; CISC: Clean Intermittent Self Catheterization; PTNS: Posterior Tibial Nerve Stimulation; LUTS, lower urinary tract symptoms

Table 2. Secondary analysis: predictive factors of higher impairment of walking speed at a strong desire to void (SDV) and post-void (qualitative variables).

	SDV	PV	t-test P-value
Detrusor overactivity			
Yes	1.02 (0.32)	1.1 (0.32)	0.91
No	0.97 (0.25)	1.03 (0.23)	
Way of voiding			0.95
Spontaneous void	1.01 (0.34)	1.07 (0.33)	
Self-catheterization	1.0 (0.27)	1.07 (0.27)	
Mixed	0.98 (0.28)	1.05 (0.29)	
Walking device			0.95
Yes	0.77 (0.24)	0.80 (0.23)	
No	1.07 (0.29)	1.15 (0.28)	

Data are mean (SD).

Table 3. Secondary analysis: predictive factors of higher impairment of walking speed at a strong desire to void (quantitative variables).

	rho (p)
EDSS	0.12 (0.32)
Age	0.09 (0.48)
USP OAB	0.06 (0.63)
MMSE	-0.11 (0.39)
PV residual volume	-0.07 (0.58)

EDSS, Expanded Disability Status Scale; MMSE, Mini Mental State Evaluation; USP, Urinary Symptom Profile; OAB, overactive bladder; PV, post-void

References

[1] Larocca NG. Impact of walking impairment in multiple sclerosis: perspectives of patients and care partners. The Patient 2011;4:189–201. doi:10.2165/11591150-000000000-00000.

[2] de Sèze M, Ruffion A, Denys P, Joseph P-A, Perrouin-Verbe B, GENULF. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. Mult Scler Houndmills Basingstoke Engl 2007;13:915–28. doi:10.1177/1352458506075651.

[3] Fragalà E, Russo GI, Di Rosa A, Giardina R, Privitera S, Favilla V, et al. Association Between the Neurogenic Bladder Symptom Score and Urodynamic Examination in Multiple Sclerosis Patients With Lower Urinary Tract Dysfunction. Int Neurourol J 2015;19:272–7. doi:10.5213/inj.2015.19.4.272.

[4] Koldewijn EL, Hommes OR, Lemmens WA, Debruyne FM, van Kerrebroeck PE. Relationship between lower urinary tract abnormalities and disease-related parameters in multiple sclerosis. J Urol 1995;154:169–73.

[5] Sung J, Shen S, Motl RW, Sosnoff JJ. Bladder function and falls in individuals with multiple sclerosis. Disabil Rehabil 2016;38:2193–7. doi:10.3109/09638288.2015.1123311.

[6] Giannantoni A, Scivoletto G, Di Stasi SM, Grasso MG, Finazzi Agrò E, Collura G, et al. Lower urinary tract dysfunction and disability status in patients with multiple sclerosis. Arch Phys Med Rehabil 1999;80:437–41.

[7] Athwal BS, Berkley KJ, Hussain I, Brennan A, Craggs M, Sakakibara R, et al. Brain responses to changes in bladder volume and urge to void in healthy men. Brain J Neurol 2001;124:369–77. doi:10.1093/brain/124.2.369.

[8] Khavari R, Karmonik C, Shy M, Fletcher S, Boone T. Functional Magnetic Resonance Imaging with Concurrent Urodynamic Testing Identifies Brain Structures Involved in Micturition Cycle in Patients with Multiple Sclerosis. J Urol 2017;197:438–44. doi:10.1016/j.juro.2016.09.077.

[9] Jousse M, Verollet D, Guinet-Lacoste A, Le Breton F, Auclair L, Sheikh Ismael S, et al. Need to void and attentional process interrelationships. BJU Int 2013;112:E351-357. doi:10.1111/bju.12224.

[10] Inghilleri M, Carbone A, Pedace F, Conte A, Frasca V, Berardelli A, et al. Bladder filling inhibits somatic spinal motoneurones. Clin Neurophysiol Off J Int Fed Clin Neurophysiol 2001;112:2255–60.

[11] Simonsen EB, Dyhre-Poulsen P. Amplitude of the human soleus H reflex during walking and running. J Physiol 1999;515 (Pt 3):929–39. doi:10.1111/j.1469-7793.1999.929ab.x.

[12] Hodapp M, Klisch C, Berger W, Mall V, Faist M. Modulation of soleus H-reflexes during gait in healthy children. Exp Brain Res 2007;178:252–60. doi:10.1007/s00221-006-0730-1.

[13] Voerman GE, Gregoric M, Hermens HJ. Neurophysiological methods for the assessment of spasticity: the Hoffmann reflex, the tendon reflex, and the stretch reflex. Disabil Rehabil 2005;27:33–68.

[14] Booth J, Paul L, Rafferty D, Macinnes C. The relationship between urinary bladder control

and gait in women. Neurourol Urodyn 2013;32:43–7. doi:10.1002/nau.22272.

[15] Smith MD, Coppieters MW, Hodges PW. Is balance different in women with and without stress urinary incontinence? Neurourol Urodyn 2008;27:71–8. doi:10.1002/nau.20476.

[16] Paltamaa J, West H, Sarasoja T, Wikström J, Mälkiä E. Reliability of physical functioning measures in ambulatory subjects with MS. Physiother Res Int J Res Clin Phys Ther 2005;10:93–109.

[17] Sebastião E, Sandroff BM, Learmonth YC, Motl RW. Validity of the Timed Up and Go Test as a Measure of Functional Mobility in Persons With Multiple Sclerosis. Arch Phys Med Rehabil 2016;97:1072–7. doi:10.1016/j.apmr.2015.12.031.

[18] Valet M, Lejeune T, Devis M, van Pesch V, El Sankari S, Stoquart G. Timed up-and-go and 2-minute walk test in patients with multiple sclerosis with mild disability: reliability, responsiveness and link with perceived fatigue. Eur J Phys Rehabil Med 2018. doi:10.23736/S1973-9087.18.05366-2.

[19] Haab F, Richard F, Amarenco G, Coloby P, Arnould B, Benmedjahed K, et al. Comprehensive evaluation of bladder and urethral dysfunction symptoms: development and psychometric validation of the Urinary Symptom Profile (USP) questionnaire. Urology 2008;71:646–56. doi:10.1016/j.urology.2007.11.100.

[20] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–52.

[21] Postigo-Alonso B, Galvao-Carmona A, Benítez I, Conde-Gavilán C, Jover A, Molina S, et al. Cognitive-motor interference during gait in patients with Multiple Sclerosis: a mixed methods Systematic Review. Neurosci Biobehav Rev 2018;94:126–48. doi:10.1016/j.neubiorev.2018.08.016.

[22] Lee J, Park S. Effects of a priority-based dual task on gait velocity and variability in older adults with mild cognitive impairment. J Exerc Rehabil 2018;14:993–7. doi:10.12965/jer.1836402.201.

[23] Griffiths D, Tadic SD. Bladder control, urgency, and urge incontinence: Evidence from functional brain imaging. Neurourol Urodyn 2008;27:466–74. doi:10.1002/nau.20549.

[24] Kang GE, Gross MM. The effect of emotion on movement smoothness during gait in healthy young adults. J Biomech 2016;49:4022–7. doi:10.1016/j.jbiomech.2016.10.044.

[25] Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zych G, Green BA. Involuntary stepping after chronic spinal cord injury. Evidence for a central rhythm generator for locomotion in man. Brain J Neurol 1994;117 (Pt 5):1143–59. doi:10.1093/brain/117.5.1143.

[26] Bussel B, Roby-Brami A, Néris OR, Yakovleff A. Evidence for a spinal stepping generator in man. Paraplegia 1996;34:91–2.

[27] Petersen N, Christensen LO, Nielsen J. The effect of transcranial magnetic stimulation on the soleus H reflex during human walking. J Physiol 1998;513 (Pt 2):599–610. doi:10.1111/j.1469-7793.1998.599bb.x.

[28] Meyer C, Killeen T, Lörincz L, Curt A, Bolliger M, Linnebank M, et al. Repeated assessment of key clinical walking measures can induce confounding practice effects. Mult Scler Houndmills Basingstoke Engl 2019:1352458519845839. doi:10.1177/1352458519845839.

391 [29] de Groot V, Beckerman H, Uitdehaag BMJ, de Vet HCW, Lankhorst GJ, Polman CH, et al.
392 The usefulness of evaluative outcome measures in patients with multiple sclerosis. Brain J Neurol
393 2006;129:2648–59. doi:10.1093/brain/awl223.

394 [30] Vaney C, Blaurock H, Gattlen B, Meisels C. Assessing mobility in multiple sclerosis using the
395 Rivermead Mobility Index and gait speed. Clin Rehabil 1996;10:216–26.
396 doi:10.1177/026921559601000306.

397 [31] Learmonth YC, Paul L, McFadyen AK, Mattison P, Miller L. Reliability and clinical
398 significance of mobility and balance assessments in multiple sclerosis. Int J Rehabil Res Int Z Rehabil
399 Rev Int Rech Readaptation 2012;35:69–74. doi:10.1097/MRR.0b013e328350b65f.

400 [32] Chiara T, Carlos J, Martin D, Miller R, Nadeau S. Cold effect on oxygen uptake, perceived
401 exertion, and spasticity in patients with multiple sclerosis. Arch Phys Med Rehabil 1998;79:523–8.

402