

Serum neurofilament light chains in MS

Association with the Timed Up and Go

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Abstract

Objective

This cross-sectional study aims to assess the association between neuroaxonal damage assessed by serum neurofilament light chain (sNfL) and the Timed Up and Go (TUG)—a reliable and rapid measure of global neurologic disability—in patients with MS.

Methods

A total of 41 consecutive patients with MS (38.0 ± 10.4 years; 57% women) with low level of disability (Expanded Disability Status Scale [EDSS] score 0–3) (EDSS score 1.0, interquartile range [IQR] 0.0–2.0) were included in this study. The TUG and sNfL were measured in a 6-month interval, together with a comprehensive neuropsychological and quantitative gait evaluation. The association of sNfL (dependant variable) with TUG, and other gait, cognitive, and behavioral measures (independent variables) were evaluated with multiple linear regressions adjusted for age, sex, and EDSS score.

Results

The sNfL concentration was 23.51 pg/mL (IQR 16.51–32.21 pg/mL), and the mean TUG was 9.27 ± 1.70 seconds. Only the TUG was associated with sNfL ($\beta = 0.021$; 95% CI 0.003–0.037; $p = 0.022$) (after adjusting for age, sex, and EDSS score), whereas this was not the case for gait and neuropsychological measures.

Conclusions

The TUG—an easy and unexpansive measure of disability—is associated with the degree of neuroaxonal damage, as measured by sNfL, in patients with MS with low level of disability. These findings confirm the validity of the TUG as a reliable bedside measure of global neurologic disability as a result of neuroaxonal damage.

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Glossary

EDSS = Expanded Disability Status Scale; IQR = interquartile range; NfL = neurofilament light chain; sNfL = serum NfL; TMT = Trail Making Test; TUG = Timed Up and Go.

The Timed Up and Go (TUG) is a rapidly operable and widely used test of mobility and risk of falls in neurologic settings and has been recently validated in MS as a measure of functional mobility.¹ The TUG is correlated with common measures of functional mobility in MS, such as the timed 25-foot walk or the Multiple Sclerosis Walking Scale-12 score. In comparison to other measures of functional mobility, the TUG captures elements of the everyday life, such as sitting, standing, and turning around,¹ and can be quickly performed by clinicians during the neurologic examination even in a limited office space. In a previous study, we have demonstrated that the TUG was correlated with gait parameters, as well as with cognitive performances, and is considered a sensitive marker for quantifying disability in early stage of MS.² The TUG has been associated with gray and white matter atrophy in patients with MS,³ but the relationship between the TUG and markers of neuroaxonal damage has not been evaluated.

Neurofilament light chain (NfL), a product of the scaffolding proteins of the neuronal cytoskeleton, represents a biomarker of axonal damage.⁴ Serum NfL (sNfL) has been validated as a reliable marker for present and potentially future disability in MS,⁵ including clinically isolated syndrome and early MS.⁶ However, the association between sNfL and a bedside clinical test of disability, such as the TUG, has never been tested in patients with MS with low disability.

This cross-sectional study aims to assess the association between a biological marker of neuroaxonal damage (assessed by sNfL) and disability (measured by the TUG) in patients with MS with low disability. As the TUG represents a good measure of gait and cognitive disability, and sNfL has been associated with fully established disability in MS, we aimed at evaluating whether the TUG will be associated with sNfL in early phases of disability. Establishing the association between sNfL and TUG in patients with MS with low level of disability will provide an important clue for clinicians to quickly evaluate the level of disability associated with axonal damage.

Methods

Participants

Forty-one consecutive outpatients with relapsing-remitting MS (38.0 ± 10.4 years; 57% female) were included in the protocol. Exclusion criteria were acute medical illness in the past month, neurologic and psychiatric diseases except MS, orthopedic or rheumatologic condition affecting walking, Expanded Disability Status Scale (EDSS) score >3, and an interval of >6 months between sNfL measurement and clinical assessment. All patients were stable under the same

treatment for at least 3 months before clinical assessment (table 1).

Serum sampling and sNfL measurements

Serum samples were centrifuged at 2,000g for 10 minutes at room temperature and stored at -80°C within 2 hours of collection. Serum NfL levels were determined by single molecule array assay as previously described.⁷

TUG test

The main outcome variable was the mean ± SD of the time (seconds) of the TUG described by Podsiadlo and Richardson. The TUG was performed at self-selected speed in a well-lit environment: the patients were asked to stand up, walk 3 m, turn around, walk back to the chair, and sit down.

Gait and neuropsychological assessment

Patients were asked to walk on a 10-m walkway at their self-selected speed, as previously described.⁸ Spatiotemporal gait parameters were computed using Matlab 2015b (MathWorks, Natick, MA) based on the trajectories of heel reflective markers (14 mm) recorded at 100 Hz by an optoelectronic system (12 cameras, Vicon Mx3+; Vicon Peak) and reconstructed by Nexus 1.8.5 (Vicon Peak).

The neuropsychological assessment focused on the cognitive domains commonly disturbed in MS: memory (Selective Reminding Test), executive functions (verbal fluency task, Stroop, Trail Making Test (TMT) B, and divided attention and working memory subtests from Test of Attention Performance), attention (digit span and symbol digit modalities test from the Wechsler Adult Intelligence Scale-III, Stroop dot condition, and TMT A), fear of falling by the 16-item Falls Efficacy Scale-International, anxiety and depression assessed by the Hospital Anxiety and Depression scale, and were assessed by the same neuropsychologist.

Statistics

The participants' characteristics were summarized using mean values and SDs or frequencies and percentages, as appropriate. Multiple linear regressions were performed to examine the association between the sNfL (independent variable) and TUG, and other gait, cognitive, and behavioral parameters (dependent variables) adjusted for age, sex, and EDSS score. All statistics were performed using SPSS (version 22.0; SPSS, Inc., Chicago, IL).

Standard protocol approvals, registrations, and patient consents

The Geneva University Hospitals Committee on Human Research approved the research protocol, and informed consent was obtained from all participants.

Table 1 Clinical characteristics of patients with relapsing-remitting MS (n = 41)

Age, y, mean ± SD	38.0 ± 10.4
Female, n (%)	26 (57)
Education, ^a y, mean ± SD	15.2 ± 2.6
EDSS score (/10), mean ± SD (range)	1.13 ± 0.98 (0–3)
Disease duration, mo, mean ± SD	
Since diagnosis	33.2 ± 34.7
Since first symptoms	52.5 ± 44.1
Treatment, n (%)	
Fingolimod	17 (41)
Natalizumab	8 (20)
Dimethyl fumarate	6 (15)
Interferon β-1a	5 (12)
Glatiramer	1 (2)
None	5 (12)

Abbreviation: EDSS = Expanded Disability Status Scale.
^a Assessed with the number of years at school.

Data availability

Anonymized data that are not published in this article will be made available on request from any qualified investigator after the approval by the Institutional Review Board of the Geneva University Hospitals.

Results

Clinical characteristics of the 41 patients with MS are summarized in table 1. The median EDSS score was 1.0 (interquartile range [IQR] 0.0–2.0), with a mean disease duration of less than 3 years (time since diagnosis: 33.2 ± 34.7 months). The sNfL concentration was 23.51 pg/mL (IQR 16.51–32.21 pg/mL), without any difference between male and female ($p = 0.229$). Gait parameters were normal (gait speed: 1.30 ± 0.18 m/s; stride time variability: 1.75% ± 1.10%). The mean TUG was 9.27 ± 1.70 seconds. Cognitive and behavioral performances are reported in table e-1 (links.lww.com/NXI/A318).

Among spatiotemporal gait parameters, cognitive and behavioral performances, only the TUG was associated with sNfL in the univariable model; this association was sustained after adjusting for age, sex, and EDSS score ($\beta = 0.021$; 95% CI 0.003–0.037; $p = 0.022$) (table 2)—an increase of 1 pg/mL of NfL concentration was associated with a TUG increase of 0.02 seconds.

Discussion

We show that sNfL, a promising serum biomarker of neuroaxonal damage in MS, is associated with the TUG. We

observed this association in patients with MS with low disability.

Estimating the extent of neuroaxonal damage in very early disease stages represents a challenge. Here, we provide evidence that the duration of the TUG is associated with the severity of neuroaxonal injury quantified by sNfL.⁴ CSF NFL levels have been associated with attentional control in patients with MS.⁹ Also, attentional performances are associated with the duration of the TUG in older adults and in patients with

Table 2 Association between serum neurofilament light chain levels^a (independent variable) and Timed Up and Go, and other gait, cognitive, and behavioral variables (dependent variables) adjusted for age, sex, and EDSS score (n = 41)

	Multivariable			
	β	95% CI	p Value	R^2
Timed Up and Go	0.021	0.003 to 0.037	0.022	0.30
EDSS score	0.009	–0.002 to 0.019	0.112	—
Gait				
Gait speed	–0.001	–0.002 to 0.001	0.568	—
Stride time	0.000	–0.001 to 0.001	0.529	—
Stride time variability	0.012	–0.001 to 0.024	0.060	—
Stride length	0.000	–0.002 to 0.001	0.576	—
Step width	0.000	–0.000 to 0.000	0.587	—
Cognition				
Memory	–0.011	–0.027 to 0.005	0.168	—
Executive functions	–0.093	–0.210 to 0.023	0.112	—
Attention	0.080	–0.014 to 0.173	0.092	—
Behavior				
Fatigue	0.234	–0.189 to 0.657	0.267	—
Fear of falling	0.000	–0.043 to 0.042	0.993	—
Anxiety	–0.017	–0.060 to 0.025	0.413	—
Depression	0.007	–0.027 to 0.042	0.670	—

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; SRT = selective reminding test; TMT = Trail Making Test. Bold text indicates significant p values.

Memory domain includes SRT; we only present the regression with the SRT (delayed recall) because other tests assessing the memory domain were also not significant.

Executive functions include verbal fluency (semantic and phonemic), Stroop, and TMT part B; we only present the regression with the semantic verbal fluency because other tests assessing the executive function domain were also not significant.

Attention includes Wechsler Adult Intelligence Scale-III (digit span and symbol digit modalities test) and TMT part A (TMT-A); we only present the regression with the TMT-A because other tests assessing the attention domain were also not significant.

Fatigue was assessed by the modified fatigue impact scale.

Fear of falling was assessed by 16-item Falls Efficacy Scale-International. Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale.

^a Serum neurofilament light chain (median): 23.51 pg/mL (IQR 16.51–32.21 pg/mL).

MS,² in addition to its strong association with the EDSS score and gait disability.¹ The multimodality of the TUG that integrates several components of both gait and cognitive parameters may explain why the TUG is the only one measure (among spatio-temporal gait parameters and cognitive performances) that was associated with sNfL in our study. Key phases of the TUG, such as the turn-to-walk and turn-to-sit phases, are associated with specific cognitive domains, such as executive function and visuospatial performance.¹⁰ The TUG, which can be performed in the doctor office without any expansive equipment other than a stopwatch, provides important insight to the clinician to the extent of axonal damage in their patients with MS.

Our study has some limitations. We only include patients with MS with low disability (EDSS score ≤ 3), preventing the generalization of the study findings to the entire MS population. Although the association between sNfL and TUG has been adjusted on age, sex, and EDSS score, the small number of participants prevents to adjust our association on other variables, such as falls or fear of falling. Future studies should verify whether this association between sNfL and TUG remains significant for patients with MS with increased levels of disability (EDSS score >3).

In conclusion, we demonstrated an association between a biological marker of neuroaxonal damage—measured by sNfL—and the TUG in patients with MS with low disability. These findings may help the clinicians to estimate and monitor the progression of the disease.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Gilles Allali, MD, PhD	Geneva University Hospitals, Switzerland	Designed and conceptualized the study; analyzed the data; major role in the acquisition of data; and drafted the manuscript for intellectual content
Jens Kuhle, MD, PhD	University Hospital Basel, Switzerland	Interpreted the data and revised the manuscript for intellectual content
Gautier Breuille, MD	Geneva University Hospitals, Switzerland	Interpreted the data and revised the manuscript for intellectual content
David Leppert, MD	University Hospital Basel, Switzerland	Interpreted the data and revised the manuscript for intellectual content
Stephane Armand, PhD	Geneva University Hospitals, Switzerland	Major role in the acquisition of data; interpreted the data; and revised the manuscript for intellectual content
Patrice H. Lalive, MD	Geneva University Hospitals, Switzerland	Designed and conceptualized the study; interpreted the data; and revised the manuscript for intellectual content

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