Factors Associated With Treatment-Related Changes in Voice Volume in People With Multiple Sclerosis

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ABSTRACT

BACKGROUND: Vocal disorders are frequent in people with multiple sclerosis (MS). Cognitive impairment, fatigue, depression, and other clinical characteristics can be associated with treatment effectiveness in rehabilitation. Finding baseline characteristics that identify those who are responding to treatment can help the clinical decision-making process, which can then help improve the effectiveness of voice treatment. We developed a model to identify factors associated with treatment-related improvement on voice intensity in people with MS.

METHODS: Data are from a randomized controlled trial of the effects of voice therapy. Forty-four people with MS were enrolled and randomized to receive Lee Silverman Voice Treatment LOUD, specifically addressing voice intensity, or conventional speech-therapy group. Voice intensity (dB) was measured during monologue before and after treatment and was used to differentiate those who responded (posttreatment voice intensity $>$ 60 dB) from those who did not. Possible associated factors were cognitive impairment, fatigue, depression, disability, and disease duration. Associations were assessed by univariate logistic regression and univariate and multivariate linear regressions.

RESULTS: Mean ± SD monologue voice intensity is improved in the whole sample (before rehabilitation: 51.8 ± 4.2 dB; and after rehabilitation 57.0 ± 6.5 dB; $P < .001$), and 11 people with MS (27.5%) responded to treatment. Specificity of treatment was associated with the return to normal voice intensity (OR, 14.28; 95% CI, 12.17-309.56) and we found a linear association between voice improvement and the specificity of treatment (6.65 [SE = 1.54] dB; $P < .05$). Moreover, the analysis revealed a nonlinear association between improvement and fatigue, suggesting increased benefits for people with MS with moderate fatigue. Other factors were not significantly associated with treatment effectiveness.

CONCLUSIONS: Moderate fatigue and the specificity of the intervention seem to be key factors associated with clinically relevant improvement in voice intensity even in people with MS with a high level of disability and long disease duration.

Int J MS Care. 2023;25(1):1-7. doi:10.7224/1537-2073.2021-056

Multiple sclerosis (MS) is a progressive, degenerative neurologic disease leading to demyelination and neurodegeneration involving different parts of the motor system,[1] including control systems for speech and voice.[2,3] Vocal disorders are common problems in people with MS.[2] The predominant voice impairments are harshness, breathiness, phonatory instability,[3] inability to maintain adequate adduction for phonation,[4] vocal fatigue,[5] and higher variability in fundamental frequency and sound pressure level (SPL). Consequently, the voice during conversation is unstable and hypophonic, leading to difficulties at work, participating in conversations with a wide range of people, using the telephone, and communicating in noisy environments.[6]

Although voice is a significant aspect of quality of life, only 2% of people with MS receive speech therapy.[2] Studies of vocal rehabilitation in people with MS are scarce with contradictory results,[7-10] low methodological quality, and small samples without instrumented assessment of voice. More consistent results may stem from randomized controlled trials that include individuals with specific baseline characteristics allowing for easier identification of those who respond to treatment. The rationale of the present study is that the identification of these factors will contribute to enhancing our understanding of how voice rehabilitation works in MS, thus allowing for more effective voice rehabilitation interventions to be developed and for better resource allocation. In addition, more information is necessary to identify the baseline characteristics associated with treatment-related changes to the voices of people with MS.

To date, no studies have investigated predictors of voice rehabilitation in people with MS. There is only 1 study on Parkinson disease[11] showing that age and cognitive status influence the magnitude of voice treatment-related changes. In the same study, a specific treatment, the Lee Silverman Voice Treatment (LSVT) LOUD, which aims to

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Note: Supplementary material for this article is available at IJMSC.org.

increase vocal fold adduction and respiratory support, was associated with better voice intensity after treatment.

Along with these factors, we hypothesized that treatment specificity, defined as "treatment directed at the cause of the functional disorders,"[12] could also predict voice improvements. The importance of specificity as an outcome predictor was supported by studies in other domains of MS rehabilitation, including walking and balance. Because voice and mobility rehabilitation share general motor control and learning principles,[13-15] we hypothesized that some prognostic factors identified in balance and gait rehabilitation in people with MS could also be effective for voice treatment. For example, Cattaneo et al[13] showed that individuals with more impaired balance benefit more from rehabilitation treatment and that MS type is not associated with improved mobility. Long disease duration and neurologic status measured by the Expanded Disability Status Scale (EDSS) are commonly considered predictors of the reduced benefit of balance rehabilitation, along with more severe pyramidal, cognitive, sensitive, verbal, and cerebellar impairments.[16] A randomized study by Coghe et al[14] showed that fatigue is a predictive factor for cognitive outcomes and that people with higher fatigue are more likely to have improved processing speed after exercises. Finally, depression is associated with fatigue[17] and with nonadherence to treatment[18] affecting the efficacy of treatment.

Thus, the potential impact of all the aforementioned factors—MS type, disease duration, neurological and cognitive status, fatigue, and depression—on treatments should be considered, and this study was designed to identify whether these factors were associated with a documented treatment-related improvement in voice intensity in functional communication in people with MS.

METHODS

Sample

In the present prospective study, we collected data from a randomized controlled trial.[19] Forty-four consecutive inpatients were recruited from January 2018 to July 2019 at IRCCS Fondazione Don Carlo Gnocchi (Milan, Italy). Details of the study are provided elsewhere.[19] In brief, people with MS were randomized after completion of a baseline assessment using a randomization list and the following inclusion criteria: (1) a diagnosis of MS according to Thompson and McDonald criteria[20]; (2) older than 18 years; (3) ability to understand the Italian language and the aims of the study; and 4) impairments in voice intensity during conversation (defined as a maximum voice intensity <60 dB SPL).[21]

The exclusion criteria were: (1) the presence of other neurological disorders; (2) visual/hearing impairments that would hinder participation in the rehabilitation program; (3) clinical history of laryngeal cancer, chemotherapy, radiotherapy, head and/or neck trauma, or endotracheal intubation; (4) relapse or sudden changes in MS symptoms within the previous 3 months; and (5) drug regimen changes during the intervention period.

The study was approved by the ethics committee of the IRCSS Fondazione Don Carlo Gnocchi and all participants signed informed consent paperwork before beginning the study.

Materials

The primary outcome measure was monologue intensity because it reflects a more natural, fluent speech output. Praat, software that is freely available online (www.praat.org), was used to record and analyze speech intensity at baseline and at the end of treatment. A specific task, identical for each participant, was given: *Please speak for at least a minute*. Recording setup followed published recommendations,[22] and mouth-to-microphone distance was kept equal at approximately 15 cm.

Of note, many studies[22] use sustained /a/ or reading voice intensity as the primary outcome measure in voice rehabilitation. However, we used monologue intensity to evaluate the effectiveness of treatment because it is more difficult than vocalization, requiring more dynamic laryngeal movements, attention, and concentration and it is closer to functional communication.[23,24] Monologue can be a less replicable measure compared with other more standardized voice measures. Thus, we adopted some strategies to increase reproducibility: first, we asked individuals to talk about their favorite subject, avoiding emotional topics and relying on a discussion of daily living activities to avoid prosodic shaping and lengthy pauses. Second, we suggested an alternative topic when the individual could not provide enough monologue for 60 seconds, and we used a stopwatch to inform individuals of the duration of their speech.

According to the literature,[5,11-14] we included the following factors as potential variables associated with improvement of voice intensity (**TABLE 1**).

1. Clinical characteristics: age, type of MS, time since diagnosis, and neurological status rated using the EDSS.[25]
2. Cognitive impairment: The Mini-Mental State Examination (MMSE) is the most common screening tool used to assess global cognitive functioning. The maximum score is 30 points; the most widely used and accepted cutoff score for the MMSE is 23 points or less.[26]
3. Depression: The Beck Depression Inventory-II (BDI-II) is one of the most widely used instruments to assess the severity of depression. The score ranges from 0 to 63 points, with a higher score suggesting a higher level of depressive symptoms and a score above the 14-point cutoff score revealing the presence of depressive symptoms.[27]
4. Fatigue: The Modified Fatigue Impact Scale (MFIS) is self-reported, is composed of 21 items, and is used to evaluate fatigue in a multimodal way. Scores range from 0 to 84, with higher scores indicating a greater impact of fatigue. A total score of 38 is used as a cutoff to differentiate fatigued from nonfatigued individuals.[28]
5. Intervention Type: People with MS were randomized into

TABLE 1. Study Overview

Demographic characteristics	Sex, No. (%)	Men	25 (56.8)
		Women	19 (43.2)
	Barthel Index score (0 to 100 [favorable]), mean ± SD		40.8 ± 18.4
Predictors	Age, mean ± SD, y		56.5 ± 11.3
	MS type, No. (%)	Relapsing-remitting	10 (22.7)
		Progressive	34 (77.3)
	Disease duration, mean ± SD, y		26 ± 11.4
	EDSS score (0 [favorable] to 10), median (I-III quartile)		8.0 (6.5-8.0)
	MMSE score (0 to 30 [favorable]), mean ± SD		26.3 ± 4.3
	BDI-II score (0 [favorable] to 63), mean ± SD		8.25 ± 7.53
	MFIS score (0 [favorable] to 84), mean ± SD		33.8 ± 37.5
	Treatment group, No. (%)	LSVT LOUD	23 (52.3)
		Conventional	21 (47.7)
Primary outcome responders	Voice intensity › 60 dB after rehabilitation, No. (%)	Responders	11 (27.5)
		Not responders	29 (72.5)
Primary outcome	Voice intensity, mean ± SD, dB	Baseline	51.8 ± 4.2
		After rehabilitation	57.0 ± 6.5

BDI-II, Beck Depression Inventory-II; EDSS, Expanded Disability Status Scale; LSVT LOUD, Lee Silverman Voice Treatment LOUD; MMSE, Mini-Mental State Examination; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis

2 groups: the specific group received LSVT LOUD and the nonspecific group received conventional treatment. Both interventions are described later herein.

The Barthel Index for Activities of Daily Living was used to depict functional status at baseline. This tool evaluates a person's function in terms of their level of independence or dependence when performing certain activities required for daily living. Total scores range from 0 (complete dependence) to 100 (complete independence).[29]

The clinical assessments were performed by a speech therapist blinded to group allocation before the beginning of the rehabilitation program and monologue voice intensity was assessed before and after treatment.

Interventions

Both the LSVT LOUD and conventional treatments were intensive and focused on hypophonia, with 4 sessions per week for 4 weeks. In addition, participants in both groups were asked to complete 5 to 10 minutes of home practice on treatment days and up to 30 minutes of home practice on nontreatment days.[11,22]

The specific group performed LSVT LOUD, a specific, evidence-based, effective program[11,22] for hypophonia rehabilitation that is used for individuals with different neurological conditions, including MS.[10] This intervention facilitates phonation, enhances vocal quality, and reduces dysphonia by having participants practice "daily tasks" and by using a "speech hierarchy."[11] Daily tasks aim to increase vocal amplitude through multiple repetitions of sustained /*a*/, high/low pitch range exercises, and functional sentences. The speech hierarchy improves functional communication by training individuals to maintain enhanced vocal amplitude in more complex speaking situations (eg, reading, monologue).

The nonspecific group underwent conventional treatment consisting of tailored but less specific exercises,[6,8] including some or all of the following components.

- Respiratory and phonatory exercises to increase diaphragmatic and respiratory functions, ie, using natural or sibilant phonemes expiration, phonation time by pronouncing the vowel /*a*/, and exercises to reduce oral spasticity.
- Prosody exercises and articulation: repetition or reading aloud lists of possibly long and complex words, sentences, and texts without diminishing or increasing the rhythm of speech. If necessary, participants were asked to hyperarticulate, accelerate or slow down their rate of speech, or exaggerate intonation.

Statistical Analysis

Data are reported as number (percentage), mean ± SD, or median (first-third quartile). Improvement from before to after the intervention was assessed by paired *t* test.

Participants were "responders" if they had posttreatment voice intensity greater than 60 dB.[21] The association between predictors and probability to return within the normal range of voice volume in monologue was assessed via univariate logistic regression models. The variables listed in **TABLE 2** are predictors and responding/nonresponding

TABLE 2. (A) Univariate Logistic Analysis of Factors Associated With a Clinically Meaningful Improvement in Voice Intensity (B) Univariate Linear Analyses of Factors Associated With Improvement in Voice Intensity

(A) Logistic Regression					
	Estimate	Standard error	Pseudo R^2	OR (95% CI)	*P* value
Disease duration	0.04	0.03	0.03	1.07 (0.89-1.02)	.23
Age	0.04	0.04	0.03	1.05 (0.89-1.03)	.26
EDSS	-0.16	0.35	0.04	0.85 (0.41-1.72)	.64
MMSE	0.25	0.26	0.03	1.28 (0.79-2.33)	.35
BDI-II	-0.01	0.09	0.01	0.99 (0.78-1.63)	.92
MFIS	-0.01	0.03	0.01	1.00 (0.93-1.06)	.92
Group (REF - SPEC)	2.65	1.14	0.20	14.28 (2.17-309.56)	.03[a]

(B) Linear regression				
	Estimate	Standard error	R^2	*P* value
Disease duration	0.08	0.08	0.02	.32
Age	0.01	0.09	<0.01	.93
EDSS	0.21	0.92	<0.01	.82
MMSE	0.70	0.61	0.04	.26
BDI-II	0.05	0.12	0.01	.62
Group (REF - SPEC)	6.65	1.54	0.32	<.01[a]
Prescore voice intensity	-0.29	0.22	0.04	.21
MFIS	-2.04	2.84	0.01	.33

BDI-II, Beck Depression Inventory-II; EDSS, Expanded Disability Status Scale; MFIS, Modified Fatigue Impact Scale; MMSE, Mini-Mental State Examination; REF - SPEC, reference group - specific group.
N = 44, reference level: "responded".
[a]Statistically significant ($P < .05$)

is the dichotomous dependent variable. Treatment type was the only predictor showing a clinically and statistically significant association with responders in both univariate and multivariate logistic models. Thus, in the present study, we present only univariate logistic models.

Univariate linear regression models assessed the association between predictors and magnitude of pretreatment and posttreatment improvement in voice intensity, with voice intensity as a continuous dependent variable and the same variables reported previously herein as predictors (Table 2). A squared and cubic polynomial transformation of MFIS was included to account for nonlinear associations between MFIS and voice intensity.

A multivariate linear regression model that included variables showing univariate statistically significant association between predictors and response was used to assess the multiple contributions of collected variables in predicting improvement in voice intensity.

Variance explained by the models was provided by adjusted R^2 values or pseudo R^2 values for logistic models. We also checked for collinearity among predictors by using pairwise correlation plots among different predictors and calculating the variance inflation factor. A variance inflation factor less than 4 was considered good for the model. R (2008) (R Foundation for Statistical Computing) was used for analysis.

RESULTS

The study included 44 people with MS; the demographic and clinical characteristics are reported in Table 1. The specific group had 23 participants (52.3%) and the nonspecific group had 21 participants (47.7%).

After treatment, individuals showed a statistically significant improvement in mean ± SD monologue voice intensity (before rehabilitation: 51.8 ± 4.2 dB; after rehabilitation 57.0 ± 6.5 dB; $t = -5.88$; $P < .001$).

Overall, 10 individuals (43.5%) from the specific group and 1 person from the nonspecific group (4.8%) crossed the threshold (60 dB SPL) discriminating between normal and abnormal voice intensity and were considered responders. Univariate logistic analyses showed that the posttreatment likelihood of crossing the 60 dB threshold was 14.28 times greater for the specific group than for the nonspecific group (Table 2).

Univariate linear analyses comparing pretreatment and posttreatment changes are shown in Table 2. We found an association between change in voice intensity and type of treatment. Participants in the specific group showed a significant 6.65 dB improvement compared with participants in the nonspecific group. In addition, we found a statistically significant nonlinear association between change in voice intensity and the MFIS.

In the multivariate model (**TABLE S1**, which is published online at IJMSC.org), improvement in monologue voice intensity was associated with treatment type and fatigue.

We found a nonlinear relationship between the MFIS and the probability of a good outcome (**FIGURE S1**): improvement is more relevant for individuals in the specific group with MFIS scores ranging from 40 to 60 points. Considering that 38 points is the cutoff score between fatigued and nonfatigued individuals,[28] a hypothetical person with MS not reporting fatigue (MFIS score = 28 points) treated with the specific treatment is expected to improve 5.74 dB (95% CI 3.19-8.29 dB), and a person with higher fatigue (MFIS score = 48 points) treated with the specific treatment is expected to improve 9.25 dB (95% CI, 5.80-12.69 dB). According to the multivariate model, a smaller improvement (8.06 dB; 95% CI, 4.38-11.74) is expected for a person with MS with severe fatigue (MFIS score = 58 points). Likewise, 2 hypothetical individuals with the same baseline MFIS score of 48 points and receiving specific and nonspecific treatment are expected to improve 9.25 dB (95% CI, 5.80-12.69 dB) and 5.68 dB (95% CI, 2.76-8.63 dB), respectively.

PRACTICE POINTS

Voice intensity in monologue improved after rehabilitation in the whole sample and almost one-third demonstrated normal-range voice intensity in monologue.

Tailored interventions specifically aimed at improving voice intensity are needed to increase the probability of obtaining clinically meaningful improvement.

Patients with multiple sclerosis with mild to moderate levels of fatigue (Modified Fatigue Impact Scale score: 40-60) showed posttreatment improvement in voice volume on monologue.

Severe neurologic impairment, disease duration, mild cognitive disorders, and depression were factors that did not impede improvement in voice intensity. ■

DISCUSSION

This study aimed to assess factors associated with treatment-related changes in voice intensity in people with MS. Overall, the data showed higher percentages of people with MS with voice intensity greater than 60 dB in monologue discourse in the specific group after treatment compared with the nonspecific group and highlighted that specificity of treatment and fatigue were predictors of improvement.

Data analyses revealed that the type of intervention was the most important predictor of a clinically meaningful improvement, highlighting the importance of a specific treatment. Participants treated with LSVT LOUD for hypophonia showed larger improvement than participants treated with the conventional approach, and almost half of the people with MS in the specific group obtained normal values of monologue voice volume compared with 4.8% in the nonspecific group. Both treatments were intensive and directed toward increasing vocal loudness, but the LSVT LOUD treatment is specific to hypophonia. LSVT LOUD focuses on the load of the larynx and the expiratory muscles enhancing glottal closure[9] and incorporates some of the recognized principles of motor learning and neuroplasticity, such as intensity of practice with high repetition.[30] In addition, LSVT LOUD addresses deconditioning and learned nonuse[22] because it is intensive, including significant repetition and an increase in task complexity over time. Tackling deconditioning is a key feature in the treatment of MS because disability often leads to inactivity, resulting in muscle disuse atrophy.[31] Deconditioning prevents people with MS from efficiently using their residual capacities,[32] also affecting speech.[32,33] Conversely, conventional treatment is more tailored to a person's needs, but is less systematic and focuses on other voice aspects (such as prosody, articulation, posture, etc).

The importance of intervention specificity in predicting treatment-related changes was also reported in another study of factors associated with improvement after balance rehabilitation in people with MS.[13]

Fatigue was the second most important predictor. The present results (Figure S1) suggest a nonlinear relationship between fatigue and voice improvement. Participants who reported moderate fatigue (MFIS score = 40-60) benefited more from the voice treatment than participants with lower or higher fatigue. Of note, our results cannot be generalized to severely fatigued people with MS since our sample did not include MFIS scores higher than 60 points. Mixed results on the association between fatigue and motor improvements are reported in the literature. Petajan et al[34] suggested that intensive training can improve function in those parts of the body that are prone to fatigue. Coghe et al[14] found a linear association between fatigue (measured by the MFIS) and balance rehabilitation outcome in people with MS. Conversely, Liberatore et al[15] found no evidence of fatigue impacting balance rehabilitation, and a preceding study found that the short version of the MFIS had no predictive capacity on outcomes from a respiratory exercise intervention in a similar cohort of people with MS and an EDSS score greater than 7.5.[35]

To the best of our knowledge, no studies have investigated the impact of vocal fatigue and lack of endurance on voice in patients with MS. Clearer results could be obtained by using a specific scale to measure vocal fatigue as well as laryngoscopy or specialized manometry to assesses strength and endurance. Also, it may be important to verify if persons with MS would benefit more from voice treatments adapted to their level of disability and when the exercise difficulty follows their improvements.

Disease duration and age did not correlate with improvement in voice intensity. There was also no correlation with the EDSS, meaning that individuals with a higher level of disability could also benefit from voice interventions; this expands the range of individuals who could benefit from treatment. It should be noted that most of the individuals in our sample were severely affected (median EDSS = 8; mean disease duration = 26 years). This is important since individuals with high levels of disability usually have a progressive form of MS and disease-modifying therapies are less effective in preventing functional loss: rehabilitation is the only viable solution to improve function.[15]

The present results are in contrast to those reported by Grasso et al[36] in a large sample of people with MS showing that disease duration and neurologic status measured by EDSS are important factors related to posttreatment improvement in activities of daily living and mobility. They hypothesized that the presence of severe impairment and long disease duration could be responsible for the lack of the neurophysiopathologic compensation mechanism that is likely required for any rehabilitation. Differences between the present results and those reported by Grasso et al[36] might be due to use of the EDSS to assess the presence of severe impairments. The EDSS mainly measures walking impairment in severely impaired individuals[37] without assessing speech and voice characteristics. However, further research is needed to examine less severely impaired and recently diagnosed people to verify the generalizability of treatment effects across all stages of MS.

In the present study, depression did not influence treatment effects; a similar result was reported by Ramig et al[11] in individuals with Parkinson disease. However, our participants did not report a high level of depressive symptoms (mean ± SD BDI-II score = 8.25 ± 7.53), and it is thus possible that higher levels of depression could hinder the effects of the treatment. Similarly, cognitive impairments did not correlate with treatment-related changes. However, most of the people in this study were in the mild to moderate cognitive disorder range (mean ± SD MMSE score = 26 ± 4.3). Moreover, use of the MMSE to identify cognitive impairment in people with MS has been questioned because many people who score higher than the suggested cutoff of 24 exhibit severe focal or global cognitive deficits.[38] Further research should be conducted using a more specific and extensive battery of neuropsychological tests or newer cognitive screening tools, such as the Symbol Digit Modalities Test or the Montreal Cognitive Assessment.[39]

This study contains a variety of biases. First, the small number of participants prevented the use of more robust statistical methods to assess the real predictor power of fatigue and the specificity of the intervention. Moreover, this is a monocentric study that engaged very neurologically compromised (median EDSS score = 8) people with MS. Therefore, we must be very careful in the generalization of results. Second, the evaluation of voice intensity does not exhaust all the expected benefits of voice rehabilitation, and so future studies are needed, including a multidimensional assessment. Voice intensity in conversation reflects more natural outcomes and increased ecological validity; however, its assessment results in less consistent and less controlled data collection compared with more standardized measures. Third, the participants were instructed to perform at-home exercises after treatment. However, we did not formally assess adherence; it is impossible to say how compliance to the home program affected results. Finally, increasing voice intensity to within the normal range may not necessarily be a meaningful improvement for the individual. For example, higher voice intensity could come at the cost of added vocal effort and fatigue. To verify this hypothesis, future studies should assess vocal fatigue before and after treatment.

CONCLUSIONS

Overall, these results show that speech therapy has a significant beneficial effect on voice intensity in people with MS. Neurologic status was not associated with improved voice intensity, suggesting that even people with MS with severe neurological impairments and a long disease duration can benefit from voice treatment. Moreover, we observed an association between the specificity of the intervention and improvements in monologue voice intensity in people with a moderate level of fatigue. ■

ACKNOWLEDGMENTS: We would like to thank Kevin Russell Bateman and Dr Elisa Gervasoni for helping revise the manuscript. Thanks also to Ilaria Giavarini for supporting the study.

FINANCIAL DISCLOSURES: The authors declare no conflicts of interest.

FUNDING/SUPPORT: None.

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