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What speech can tell us: a systematic review of dysarthria characteristics in Multiple Sclerosis

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ABSTRACT

IMPORTANCE: Multiple sclerosis produces neurological impairments that are variable in duration, severity and quality. Speech is frequently impaired, resulting in decreased communication skills and quality of life. Advancements in technology now makes it possible to use quantitative acoustic assessment of speech as biomarkers of disease progression.

OBSERVATIONS: Four domains of speech have been identified: articulation (slow articulation and imprecise consonants), voice (pitch and loudness instability), respiration (decreased phonatory time and expiratory pressure) and prosody (longer and frequent pauses, deficient loudness control). Studies also explored predictive models for diagnosis of MS and ataxia through speech assessment, the relationship of dysarthria with cognition

and very few studies correlated neuroimaging with dysarthria. We could not identify longitudinal studies of speech or dysarthria in Multiple Sclerosis.

CONCLUSION AND RELEVANCE: Refinement of objective measures of speech has enhanced our understanding of Multiple Sclerosis-related deficits in cross-sectional analysis while both integrative and longitudinal studies are identified as major gaps. This review highlights the potential for using quantitative acoustic assessments as clinical endpoints for diagnosing, monitoring progression and treatment in disease modifying trials.

Key words: Multiple Sclerosis, Dysarthria, Speech, Dysphonia, Voice, Cognition, Quality of Life, Deep Brain Stimulation, Acoustics

1. INTRODUCTION

Multiple sclerosis (MS) is the most common neurological disease to cause disability in young adults (1). Prevalence varies (<1 to 193 per 100 000) depending on ethnic and geographical variables (2). MS is caused by inflammatory damage to the myelin sheath of neurons occurring anywhere in the central nervous system (CNS). This damage can result in acute or chronic deficits across a variety of neurological domains (3).

Dysarthria (abnormal speech production) is the most common expressive communication deficit presenting in patients with MS (4) with prevalence around 45% (4-16). There are some reports of cognitive language disorders such as anomia and aphasia which share
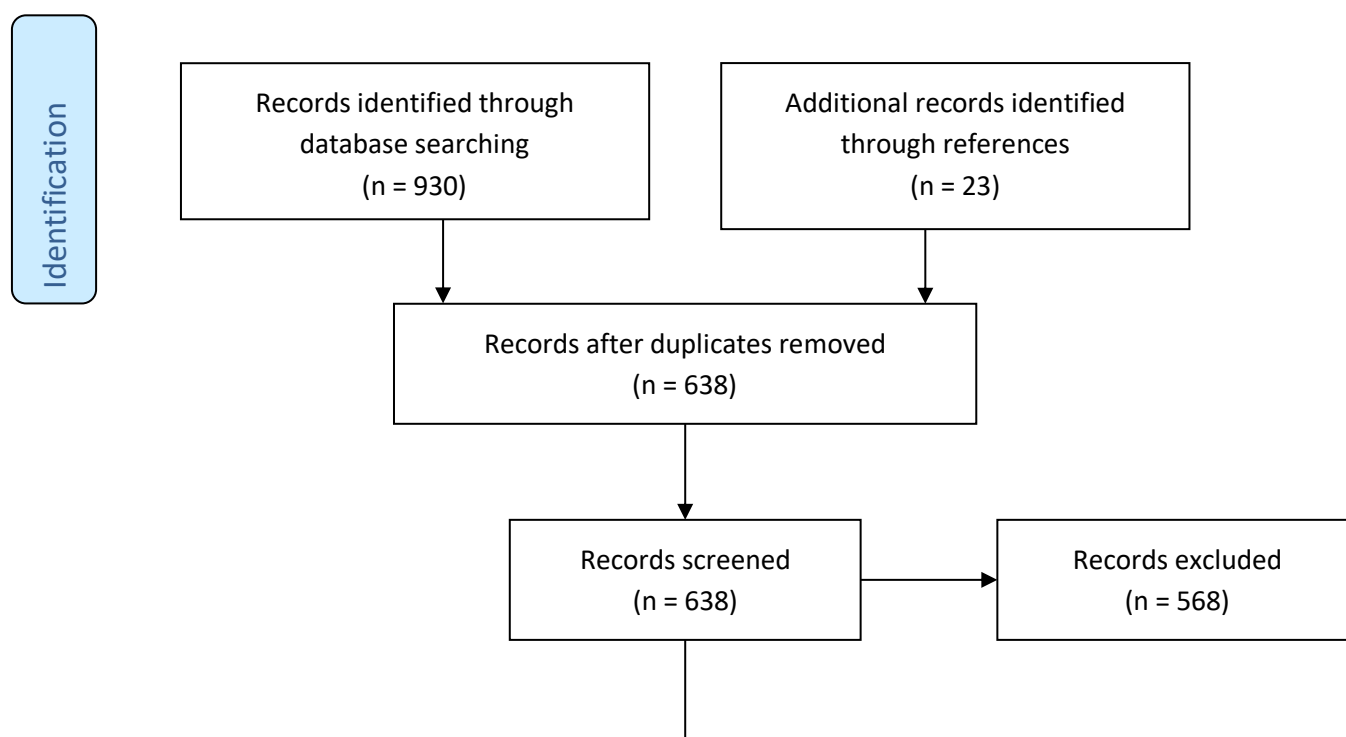
overlapping characteristics with other (non-language related) cognitive deficits and have an even less defined prevalence, however they are believed to be much less common than dysarthria itself (4, 8, 11) .

Existing evidence suggests that dysarthria in people with MS (PwMS) is typically mild in nature, with patients rarely becoming unintelligible (11, 17). Nevertheless, impaired speech is known to have a negative impact on employment status, social participation and overall quality of life in this population (9-11, 18-20). Furthermore, recent refinement of speech assessment methods suggest that discrete speech features might be used as an additional tool to monitor disease status.

This review aims to update and expand our current understanding of dysarthria in PwMS and the use of speech as marker of changes in disease state. We have included studies utilizing objective and subjective measures as well as the results from neuroimaging studies.

2. SEARCH METHODS

Figure 1. Flowchart of the reviewing process

Screening

Eligibility

Included

| Full-text articles assessed for eligibility (n = 70) | | Full-text articles excluded, with reasons (n = 12) |

| Studies included in qualitative synthesis (n = 58) |

Search and review processes are summarized in diagram 1 and a short glossary of common terminology is provided in Table 1.

A total of 626 publications were found. Reference lists from selected studies were also examined.

Screening inclusion criteria were 1) human subjects; 2) speech/dysarthria as being the primary outcome of investigation OR related to the primary outcome(s); 3) qualitative and/or quantitative data of dysarthria or speech in the MS population; and 4) definite or

probable diagnosis of MS. Studies were excluded after full-text analysis (eligibility) if they described: 1) speech perception by participants and auditory processing data only (i.e. hearing/comprehending by the participant as opposed to output production of speech); 2) animal studies; 3) books or book chapters; 4) non original data (e.g. consensus, professional opinion, letters); and 5) practical duplicates (same set of participants AND very similar hypothesis/findings as another study already included).

Table 1. Glossary of commonly used terms in the assessment of speech deficits.

Asthenia, voice	Perceptual measurement denoting low energy during phonation.
Articulatory rate	Quantitative measurement from both perceptual and acoustic assessments. Speech (syllables, words) produced per time, excluding silences (in contrast with 'speech rate' which includes silences).
Dysarthria	Impairment of motor control of speech production. The current definition goes beyond its etymological 'disturbed articulation' to also include deficits in respiratory support, phonation and prosody.(21)
F2 (second formant), from acoustic analysis	Formants are frequencies where there is high concentration of sound energy. Formants result from the resonance in the vocal tract (mostly pharynx, mouth and nasal cavities) of the sound produced in the vocal folds. Changes in F2 are associated with changes in the shape of the mouth cavity (e.g. during utterance of the word "you").
Fundamental frequency (f0)	Lowest frequency where sound energy concentrates. Produced by the vibration of the vocal folds in normal voicing. Acoustic analysis measurement frequently associated to perceptual pitch.

Imprecise consonants	Deviation from the expected perceptual sound of one or more consonants, impacting on intelligibility or requiring context to be understood.
Loudness	Perceptual quantification of sound volume in voice/speech.
Pitch	Perceived vocal tone, typically higher in children and women and lower in men.
Prosody	Collection of interrelated speech features (e.g. rhythm, variation in pitch and loudness) intentionally produced to add to or finely tune the meaning of phrases (frequently adding emotional/social cues).
Strain, voice	Perceived physical effort to phonate/speak, higher than expected for the resulting loudness.
Syllable repetition rate	Number of syllables per time produced during continuous and sequential fast repetition of one, two or three prescribed syllables without semantic meaning.

3. RESULTS

Removal of duplicates, application of the selection criteria and additional search for cross-references yielded a total of 68 original studies and one review (see diagram 1). Eleven original studies were then excluded as their data were later updated (i.e. new cases added) or simply duplicated in more recent publications by same authors. The only review was also removed as it reported speech findings from only two original studies which are already included here. A critical summary of the remaining 58 articles is provided, organized by dysarthria domains and followed by a brief discussion.

3.1. Overall dysarthria characteristics

Dysarthria is considered the primary cause of communication deficit in MS, yet pwMS present with concurrent cognitive deficits that can interfere with effective communication. A series of recorded interviews with patients using open-ended questions (such as "What's communication like for you?") (22, 23) described naming deficits (expressive language), attentional problems (cognition) and fatigue as possible causes of communication difficulties in MS. Although one third of participants presented with dysarthria, there was little to no mention of dysarthria by patients. In contrast, self-reported prevalence of dysarthria ranges from 23% to 56% in structured questionnaires (5, 9-14). A few non-controlled variables may have interfered in the descriptive content of these studies, such as a failure to exclude individuals with cognitive impairment and the lack of standardized questions targeting speech features specifically.

Intelligibility is marginally reduced in MS, with the degree of impairment consistently reported between studies. In a rater blinded study of 78 PwMS, intelligibility for single words was 96±0.03% for PwMS and 97±0.01% for healthy controls. Other work reported similar results with either marginally decreased intelligibility in comparison to normal controls (97% vs 98%, F[1,71]=8.51; p=.005) (24) or a non-significant trend towards lower intelligibility (25).

Data derived from subjective listener-based scales have yielded different results. Subjective tests where blinded listeners used a visual analog scale for perceived naturalness demonstrated worse scores than intelligibility assessments for both healthy controls and MS groups (17, 26) with the MS group rated considerably worse than healthy

controls (3.07±1.32 vs 1.07±0.25, on a scale from 1=normal to 4=severely disturbed) (26). This would suggest that the ordinal scale approach either overestimates the magnitude of deficit or is more sensitive to pathology.

In general, the progression of dysarthria parallels progression in other neurological systems in MS. As such, severe dysarthria is usually only present in PwMS with advanced neurological disability. This observation is supported by the reports by Hartelius et al. where two comprehensive perceptual assessment protocols with multiple individual speech scores, were condensed into one composite "overall dysarthria score" for each participant. Both composite dysarthria protocols showed a strong relationship with Expanded Disability Status Scale (27) scores (EDSS, correlation coefficient of 0.6) (4).

Specific speech deficits are described below, and most prominent impairments are condensed in table 3. Only six studies reported both EDSS and the general degree of dysarthria, all of which used acoustic assessments (figure 1).

Figure 1. Overview of impaired speech characteristics in relation to overall disability (EDSS scores), severity of dysarthria and disease course. *p<0.05; **p<0.001.

DEGREE OF DYSARTHRIA
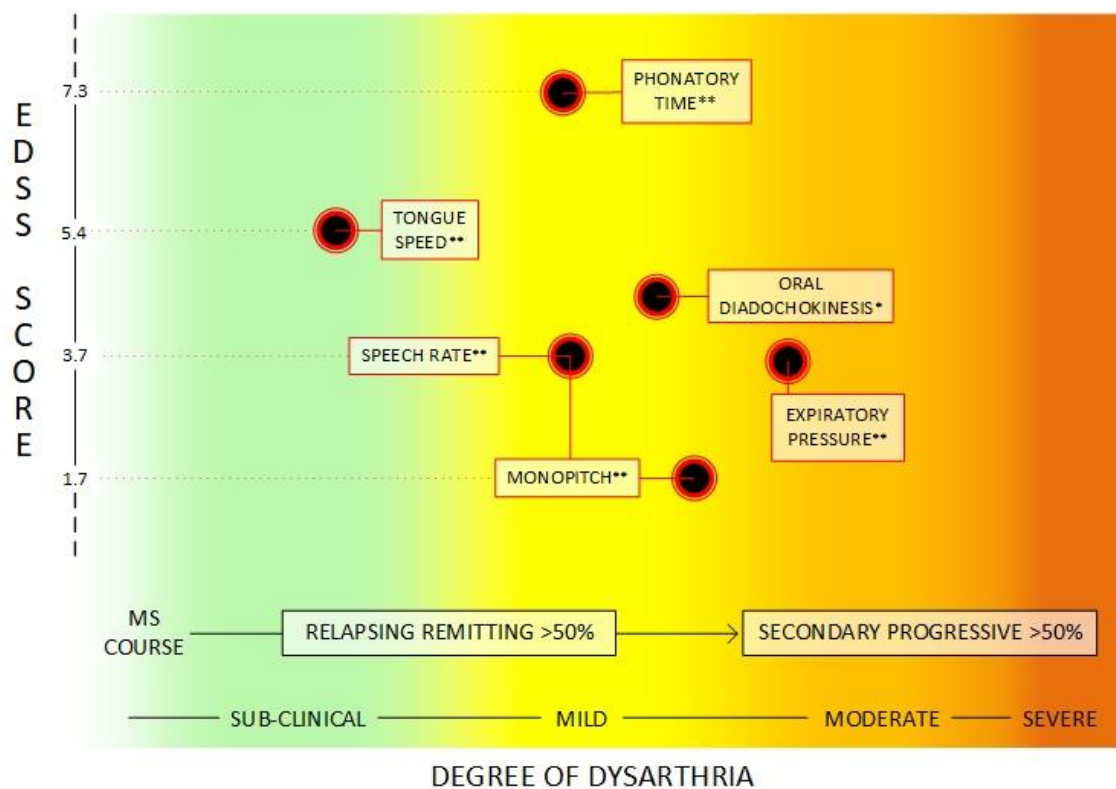
3.2. Articulation

Articulation of speech was analysed in 576 PwMS across 14 studies. Articulation in MS is characterized by consonant imprecision, decreased word output rate and slow vowel transitions likely due to slow tongue movements. Listener rated scores reported that consonants were mispronounced by 26- 40% of PwMS (4, 8, 26, 28) accounting for 90% of intelligibility variance in one study (8).

Articulatory rate was consistently reduced in both subjective and objective studies and correlates with non-speech disabilities. Longer duration of syllables was observed in different tasks including spontaneous speech, reading and syllable repetition (7, 8, 24, 29-31). Additionally, results from acoustic analysis showed an inverse moderate correlation

between articulation rate and overall disability (EDSS, r=0.5, p<0.001), hand dexterity (9 peg hole test, r=0.54, p<0.001), and walking speed (timed 25-foot walk, r=0.41, p<0.001)(31).

Tongue movements are particularly affected in PwMS and can be detected even before overt dysarthria manifests. Studies that utilized acoustic analysis showed, through investigation of the maximum slope of the second formant (F2), that phoneme transitions requiring fast tongue or fast pharyngeal movements were slower in dysarthric PwMS (32, 33). When studied in isolation, tongue speed, strength and endurance were lower not only in dysarthric but also in non-dysarthric PwMS (34, 35) whereas lip and velopharyngeal movements were abnormal in dysarthric but spared in non-dysarthric PwMS (26, 34, 35).

3.3. Voice

Voice function in pwMS is characterized by glottal inefficiency (i.e. the sound energy produced in relation to the amount of air passing between the vocal folds), decreased loudness control and both short and long-term (tremor-like) vocal instability.

Voice quality was studied in a total of 484 persons from 14 studies. Perceptual studies were mostly non-blind, without a matched control group and largely descriptive where speech-language pathologists rated PwMS as vocally impaired in 45% to 91% of the cases (5, 7, 8, 15).

A number of studies support the hypothesis that loss of glottal efficiency is a contributor to decreased voice quality in PwMS. Phonatory asthenia and strain were found to be

different between MS and healthy control groups in two studies, present in up to a third of PwMS. Additionally, asthenia was strongly correlated with disease duration (r=0.53) and Voice Handicap Index scores (r=0.44)(36, 37). No correlation with EDSS scores were found except for reported voice fatigue(5). A quarter of PwMS had frequent voice breaks (5, 8, 15) which inversely correlated with Closed Quotients in an electroglotographic study (i.e. the proportion of time that the vocal folds sustain full contact during vocalization) (38). The same electroglottographic variables were also used to create a discriminant regression model (equation) resulting in perfect classificatory for the diagnosis of MS, achieving perfect classificatory accuracy (sensitivity and specificity of 100%) for the experiments cohort of 64 PwMS and 64 matched controls (39). Some less commonly reported findings concerned glottal inefficiency manifesting in reduced mean loudness (30) and increased breathiness as measured by the soft phonation index (37).

A second contributor to poor voice quality is related to phonatory instability. Pitch (4, 8, 15) and loudness (4, 7, 8, 15) control were rated as impaired in approximately one third of PwMS in perceptual (subjective) studies. However, only loudness control remained statistically different from healthy controls in a protocol where raters were blinded to the diagnosis (4). Data from acoustic analysis suggest that instability of intensity (acoustic equivalent of loudness) and frequency (acoustic equivalent of pitch) are common in PwMS (14, 40). Both jitter and shimmer (which reflect short term variation of frequency and intensity respectively, between two consecutive vocal pulses) were higher in PwMS than in healthy control speakers, most markedly for males (5, 14, 37, 40). Longer term "tremor-like" instability (taking into consideration several consecutive pulses, i.e. a few

seconds of continuous vocalization) was also reported as a predictor differentiating PwMS from healthy individuals with sensitivity of 80-85% and specificity of 90-100% (41).

Data on fundamental frequency (acoustic measure related to perceived pitch) appeared inconsistent across studies with some reporting either lower (14, 37, 38) or higher (40) when compared to matched controls.

3.4. Respiration

Respiratory support was described in a total of 415 PwMS from six studies. Respiration (also cited as ventilation) was impaired in one third of PwMS in early studies (7, 8) and expiratory and phonatory times were inversely correlated with EDSS scores in a high disabled cohort of 50 PwMS (average EDSS of 7.3) in the only study to test for non-speech correlations (42). Respiration (rather than either articulation, phonation, oral motor performance, prosody and intelligibility) was found to be the speech-related domain that best differentiated MS from healthy participants in one study (4). Accordingly, maximum phonatory time, maximum expiratory time and maximum expiratory pressure were significantly reduced (5, 20, 37, 42) or showed a trend towards reduction in PwMS (15) when compared to healthy controls.

3.5. Prosody

Prosody was described in at least 470 subjects from ten studies. Speech rate was perceived as reduced (slower) in 39% to 47% of individuals with MS (7, 8, 15) and confirmed in

objective measurements – means of 11% and 24% less syllables per second (32, 43) and around 14% less words per minute (20, 31) were produced by PwMS in comparison to matched controls.

Acoustic analysis showed that longer and more frequent pauses were observed both in reading and spontaneous speech tasks (4, 8, 15, 29, 30, 44). Particularly in ataxic PwMS, deficient "on-the-flight" timing-adjustments were apparent. For this people, data showed lack of variation in syllable length within a single utterance – named intra-sentence syllable isochrony – but higher than normal variation between sentences, which could be argued to be a delayed overcorrection resulting in decomposition of rhythm, similar to what occurs for limb movements in ataxia. PwMS with the ataxic type of dysarthria were found to sacrifice the rhythmic pattern of stressing words in order to keep syllable length fixed while normal speakers kept the rhythm constant by varying syllable length (29, 30).

While overall speech intonation (i.e. stressing the wrong part of a word or phrase) was found to be impaired in 34 to 43% of PwMS (7, 8, 15), supporting data suggest that pitch and loudness control may reflect different neuro-networks, thus should be treated separately. Excessive loudness variation was found only in ataxic participants and correlated with hand dexterity whereas monotonic reading (monopitch) strongly differentiated healthy control and no-disability MS groups (EDSS<2)(14, 31) but was not associated with hand dexterity or ataxia (31). Recently, acoustic analysis of pitch variation was included in two prediction models to classify speakers as healthy control or PwMS without disability, reaching accuracies of 78% and 100% (31, 45).

Table 3. Summary of main speech deficits found in MS. Types of assessment: AA= acoustic analysis; BM= biomechanical assessments; EP= electrophysiology; PA= perceptual assessments.

Deficit	Findings	Type	Studies
Flaccidity of oropharyngeal muscles, particularly the tongue	Long phonemes	PA	(7, 8, 29)
		AA	(7, 24, 30, 31)
	Reduced F2 slope	AA	(32, 33)
	Slow, weak tongue, lips and velopharyngeal	PA	(26, 34)
		BM	(26, 35)
Glottal insufficiency and instability	Vocal asthenia	PA	(36, 37)
	Voice breaks	PA	(5, 8, 15, 38)
	Reduced closed quotient	EP	(38, 39)
	Phonatory instability	PA	(4, 7, 8, 15)
		AA	(5, 14, 37, 40, 41)
	Breathiness, reduced loudness	AA	(30, 37)
Decreased strength of expiratory muscles and/or control over voluntary respiratory movements	Respiratory support	PA	(4, 7, 8)
	Expiratory pressure	BM	(20)
	Max. expiratory time	BM	(42)

Nonspecific. Might be related impairment of cognition (attention, language), respiratory support, or might reflect motor hesitancy	Frequent, longer and inappropriate pauses	PA AA	(4, 8, 15) (29, 30, 44)
Nonspecific. Early sign. Might be related to depressive mood	Monopitch	PA AA	(7, 8, 28, 29) (14, 31, 39)
Pneumo-phonatory incoordination, related to ataxia	Excessive loudness variation	PA AA	(7, 8, 28, 29) (31)

3.6. Dysarthria and MS disease course

Clinically evident dysarthria often presents in more advanced stages of the disease thus being significantly correlated with overall disease severity as rated in EDSS (27). Accordingly, overt dysarthria is more frequently described in primary and secondary progressive subtypes of MS (4, 5, 7, 11) (Figure 2). However, it should be noted that MS-related disability is inconsistently reported in the published literature.

There are also several less common speech presentations reported within the literature. At least forty-nine patients with paroxysmal episodes of dysarthria have been described. The case reports describe acute onset of frank dysarthria lasting only for a few seconds per episode, and recurring often and daily, frequently associated with other

cerebellar/brain-stem symptoms (e.g. generalized ataxia). They occurred approximately 6-10 weeks after a classic relapsing episode. Six (more recent) cases were investigated at the time of the primary relapse with magnetic resonance imaging (MRI), reporting new enhancing lesions including one or more at or below the red nucleus. Repeat imaging at the time of onset of the paroxysmal dysarthria, however, did not show new demyelinating lesions. Most of these patients were treated with carbamazepine and the symptoms resolved within few weeks or months, leaving no permanent functional deficit (46-53). Demographic data was reported for 24 of these patients with 14 being male and an overall mean age of 37.5 years.

Additional data describing the relationship between dysarthria and anatomical lesion location in PwMS are very limited. Beside the reports already mentioned, three cases of acute-onset persistent dysarthria were associated with lesions within the brain stem, cerebellum and motor cortex (54-56) and two reports of worsening dysarthria following thalamotomy and deep brain stimulation of the thalamus (57, 58) for MS-associated upper limb tremor.

3.7. Dysarthria and cognition

PwMS are often tested for cognitive deficits, thus some studies have explored the relationship between dysarthria and abstract mental processes. PwMS with dysarthria were shown to have poorer performance in neuropsychological tests (NPT) where speech was required to gauge performance (59, 60) (e.g. Paced Auditory Serial Addition Test – PASAT(61); oral version of the Symbol Digit Modality Test – SDMT (62)). This

correlation was found in MS but not in healthy controls (24) and was corroborated by similar findings between NPT and speech intelligibility (19), speech rate (total output per time) (24, 43) and articulatory rate (i.e. length of phonemes) (24, 31). Time and frequency of pauses may have a stronger correlation than articulatory rate (24, 63). Pause time accounted for most of the difference between PwMS and control participants in NPT in one study (63) where articulation speed had no influence.

Despite those findings, most investigations have a clear confounding bias where speech rate is used at the same time as predictor (in dysarthria scores) and response (in timed oral NPT). Clinicians and researchers must be aware when interpreting oral cognitive tests in dysarthric people and choose an alternative assessment whenever where possible.

3.8. Treatment for dysarthria in MS

Resistive respiratory training showed better results than non-resistive exercises. One study tested an integrated protocol of respiratory, phonatory and articulatory exercises in supervised sessions of 45 minutes, four times per week also for eight weeks in 30 PwMS. No effect was observed over maximum phonation time, maximum expiratory time and dysarthria scores during the experiment (42). Another intervention used an intensive protocol similar to limb strength training. Seventeen PwMS and fourteen healthy controls were instructed to blow through a modified simple pressure-controlling device (modified Threshold®PEP, Healthscan Products Inc, Marietta, USA) for five seconds, six consecutive times, resting for 30-60 seconds between sets and completing four sets per day, five days per week (under supervision once per week), for eight weeks. Maximal

expiratory pressure increased 40% from baseline in PwMS and 29% in healthy controls. Small but significant improvement in measured reading rate and in self-reported dysarthria were also observed (reported only for the MS group). Results were more evident in the moderate versus mild subgroup (as per EDSS scores) and remained relevant four weeks after the end of the training period. Maximum phonation time was not significantly affected by training (20). The lack of a non-training control group prevents exclusion of practicing-effect bias and the effects of respiratory training on quality of life and other speech measures need further exploration.

Behavioural interventions have also been trialled to improve dysarthria in MS. In a study involving 30 PwMS and 32 healthy individuals, participants had their voices individually recorded while reading a standardized passage and then were intensively instructed to speak (in turns) louder, clearer or slower. Improvements in both acoustic characteristics and intelligibility (40, 58-61) were observed. The "loud version" brought the largest increment of consonant distinctiveness and intelligibility. Additionally, a variable enhancement of F2 slopes was very apparent in half PwMS. None of the behavioural interventions results were reported to last longer than the study session itself.

Successful treatment of phonatory dystonia by injection of botulinum toxin A in the thyroaritenoid muscle has been reported for three PwMS. Unilateral and very low doses(1-3 units) were sufficient to achieve the desired effect of fluid phonation without vocal spasms (64). Little detail of speech, clinical and neuroimaging characteristics of those patients was reported.

Finally, a single case of acute relapse-related dysarthria (among other symptoms) was successfully treated with plasma exchange after failure to improve with corticosteroids (65). Schmidt and colleagues (66) reported good results using the potassium channel agonist, Fampridine, in three cases of severe dysarthria. These results were only reported in a brief letter to the editor, with non-blinded assessment, no objective measures of speech, and with declared conflicts of interest.

4. CONSIDERATIONS

Different assessment methods influenced the magnitude and generalizability of results. For example, where a speech characteristic was investigated through more than one type of assessment, the frequency and severity of abnormalities were most pronounced when recorded using instrumental measures (e.g. acoustic analysis), followed by professional perceptual ratings (speech pathologists > neurologists) and, lastly, patient self-scoring.

It is clear that greater use of objective tests (i.e. acoustic analysis, electrophysiology and imaging) along with the usual clinical assessments has the potential to address much of the discordance in naming and definitions, as well as the inherent dependency on training and influence from professional background observed in subjective investigations (67).

The relationship between dysarthria and cognitive impairment in PwMS requires further exploration. It is reasonable to assume that any condition that slows speech rate would affect cognitive scores derived from verbal output. Similarly, where individuals present with concomitant cognitive and motor deficits, the competing demands of each process can place stress on each domain, potentially leading to exacerbation of the perceived

deficit in a formal testing setting(68, 69). This is not unique to MS – people with Myasthenia Gravis (a disease of the neuro-muscular junction) scored below controls in all NPT requiring a verbal response (and in one test that required rapid hand response) but normally in other NPT (70). Furthermore, mean scores in the standard version of the written SDMT (rather than oral) in a large cohort of 811 PwMS, did not report lower than expected scores (71).

5. CONCLUSION

Speech production (as a mean of transmitting information) is impaired in PwMS but is usually only clinically evident in more advanced stages of the disease. Although intelligible, speech in PwMS is often perceived as deficient by both the general population and specialists, having a negative impact on communicative participation and quality of life. The main dysarthric features in PwMS are slowness, increase of pauses (frequency, duration and inappropriate onset), deficient loudness control, monopitch, imprecise consonants, asthenic/strained voice and decreased respiratory capacity (table 3). Most speech variables were studied in isolation from one another, from other disease characteristics (i.e. ambulation, cerebellar dysfunction, disease phenotype), and from progression and neuroimaging correlates.

Objective speech assessments offer greater accuracy, replicability and feasibility in comparison to perceptual analysis. If coupled with additional meaningful outcomes such as measures of speech-related quality of life, objective assessments have the potential to assist decision making when tracking disease progression and treatment response in MS.

Longitudinal studies are needed to define whether dysarthria and its measurement provides additional and unique insights into MS disease progression or as a subclinical surrogate marker of cerebellar network involvement.

6. TAKE-HOME MESSAGES

- Mild dysarthria is highly prevalent in MS and significantly impacts quality of life.

- Slow, imprecise and monotonic speech are common findings in PwMS and can be associated with other neurological deficits. ·

- Objective speech assessments show high classification accuracy for early-MS against no-MS in experimental cohorts.

- The potential to monitor disease progression has been demonstrated through correlation of objective speech measurements with clinical scores of accrued disabilities. Longitudinal studies are warranted.

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