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The Prevalence and Management of Saliva Problems in Motor Neuron Disease: A 4-Year Analysis of the Scottish Motor Neuron Disease Register

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Abstract

Introduction—Saliva problems are common and distressing for people with motor neuron disease (pwMND). Despite clinical guidelines for assessment and treatment, management of saliva problems has received little research attention.

Objective—We aimed to investigate the prevalence of saliva problems in pwMND, their association with clinical factors, and their management practice using a highly curated population-based register for motor neuron disease (MND) with 99% case ascertainment.

Methods—We conducted an analysis of pwMND diagnosed between January 2015 and October 2019 using the Scottish MND Register (CARE-MND [Clinical, Audit, Research, and Evaluation of MND]). The association between clinical factors and saliva problems was investigated using

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Statement of Ethics
Ethical approval was granted for CARE-MND by the Scotland A Research Ethics Committee (15/SS/0126). Written informed consent was given prior to registration with CARE-MND.

Conflict of Interest Statement
The authors declare that they have no conflicts of interest.

Author Contributions
I.P. participated in the conception and design of the project, acquisition, analysis and interpretation of the data, and drafting of the manuscript. S.A.G. participated in analysis and interpretation of the data and drafting of the manuscript. J.N., A.R.M., E.B., R.D., and S.C. participated in data interpretation and critical revision of the manuscript for important intellectual content. S.P. participated in conception and design of the project, interpretation of the data, critical revision of the manuscript for important intellectual content, and supervision the project.

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univariate and multivariable logistic regression; results are reported as odds ratio (OR) and 95% confidence intervals. A survey of health-care professionals involved in the care of pwMND was performed to contextualize the findings.

Results—939 pwMND were included. Prevalence of saliva problems was 31.3% (294). Bulbar onset (OR 9.46 [4.7, 19.2]; $p < 0.001$) but not age, sex, time to diagnosis, or MND subtype were independently associated with the presence of saliva problems in multivariable regression, and 52.7% (155) of those with saliva problems received pharmacological management. The most commonly used medications were hyoscine, amitriptyline, carbocisteine, glycopyrrolate, and atropine. Evidence base (8, 72.7%) and local guidelines (10, 90.9%) were cited as the most important factors influencing treatment decision by survey respondents ($n = 11$).

Conclusion—Saliva problems are common and associated with bulbar onset MND. A substantial proportion of pwMND with saliva problems did not receive recommended treatments. Future research is required to determine the relative efficacy of individual pharmacological treatments.

Keywords

Motor neuron disease; Saliva problem; Hypersalivation

Introduction

Motor neuron disease (MND) is a rapidly progressive neurodegenerative disorder characterized by motor nerve degeneration. Disruption in normal saliva production and handling is common in people with MND (pwMND) and has a major impact on the quality of life [1]. Two broad categories of saliva problems occur: (1) thick, tenacious saliva, which can occur due to saliva evaporation during mouth breathing, and (2) sialorrhoea, excessive saliva accumulation due to dysphagia causing drooling [2]. Drooling is distressing, socially embarrassing, contributes to skin maceration, exacerbates dysarthria, and may precipitate complications such as aspiration pneumonia and respiratory failure [1].

Few studies have previously reported on the prevalence of saliva problems with estimates ranging from 50 to 70% with moderate to severe problems in 21–32% [3–5]. Heterogeneity in prevalence estimates may be attributable to variation in ascertainment method, which included retrospective analysis of trial populations and clinician surveys. To our knowledge, only one large population-based study, published in 2001, has reported on this area [5]. Evidence for treatment options for problematic saliva is limited, with most recommendations extrapolated from research undertaken in indirect patient populations [6]. As such, few drugs are specifically licenced for the management of saliva problems in MND in the UK [7, 8]. Research has been recommended to focus on gathering baseline information about current treatment choices to inform subsequent comparative studies [8].

Scotland benefits from a highly curated populationbased register for MND, CARE-MND (Clinical, Audit, Research, and Evaluation of MND) with a high level of case ascertainment (99%) and longitudinal clinical phenotypic data capture [9]. We used the CARE-MND database, supported by a survey to health-care professionals to (1) investigate the prevalence

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of saliva problems in pwMND living in Scotland, (2) examine whether the presence of saliva problems is related to clinical characteristics including age, sex, region of onset, and MND subtype (3) determine which pharmacological treatments are most commonly prescribed and which factors influence treatment choice.

Methods

We retrospectively extracted clinical and demographic data for pwMND from the CARE-MND register. We included people diagnosed with amyotrophic lateral sclerosis, primary lateral sclerosis, progressive bulbar palsy, and progressive muscular atrophy between January 01, 2015 and October 21, 2019. We defined saliva problems as sialorrhoea or thick, tenacious saliva. PwMND with saliva problems were identified using the saliva domain (scores 0–2) of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) [10]. For those with missing data on the ALSFRS-R, we extracted data on direct questioning about problematic saliva. The ALSFRS-R saliva domain screens for sialorrhoea, whereas direct questioning about saliva problems identifies both sialorrhoea and thick, tenacious saliva. Unfortunately, differential data for each problem were not available.

Survey of Clinicians

To contextualize data obtained from analysis of the CARE-MND register, a range of health-care professionals ($n = 15$) involved in the care of pwMND in Scotland were invited to complete an anonymous online survey (Appendix 1). Respondents were presented with the list of guideline-recommended treatment options for saliva problems and asked about their treatment preferences.

Statistical Analysis

Summary statistics are reported as median and interquartile range (IQR). Associations between saliva problems and clinical characteristics were analysed using univariate and multivariable logistic regression and results are reported as odds ratio with 95% confidence intervals. Missing data were handled using multiple imputation with a predictive mean matching ($m = 5$) in regression analysis. All p values are 2-tailed and a p value of <0.05 was defined as statistically significant.

Results

939 pwMND were diagnosed in the 4-year period studied, of whom 785 (83.6%) had data available regarding saliva problems derived from either ALSFRS-R or direct questioning. PwMND with data missing regarding saliva problems were slightly older than those for whom there were data available (mean age 68.0 vs. 65.2 years; $p = 0.032$), but there were no significant differences in sex, site of onset, and MND subtype.

Overall, the median age at diagnosis was 67 years (IQR 16) and 60.2% (565) were male. Amyotrophic lateral sclerosis was seen in 75.0% (704), 8.5% (80) had progressive bulbar palsy, 2.9% (27) had primary lateral sclerosis, and 2.7% (25) had progressive muscular atrophy; for the remainder, the subtype was not specified.

Of the people diagnosed, 31.3% (294) pwMND were classified as having saliva problems based on the above definition. Of those with available ALSFRS-R data (690, 73.5%), 13.3% had marked excess of saliva with drooling (92, score 0 or 1), 12.9% had moderate excess saliva with minimal drooling (89, score 2), 28.3% had slight but definite excess of saliva (195, score 3), and 45.5% had no excess saliva (314, score 4). The ALSFRS-R was administered within a median of 6 months from diagnosis (IQR 1–15).

In univariate logistic regression, age at symptom onset, female sex, bulbar onset, progressive bulbar palsy, and progressive muscular atrophy subtypes were all associated with higher odds of saliva problems. In multivariable analysis, only bulbar onset remained independently associated with saliva problems (odds ratio 9.46 [4.7, 19.2]; $p < 0.001$) (Table 1).

Management of Saliva Problems

Of those with saliva problems, 52.7% (155) received pharmacological treatment: 32.0% (94) received one medication, 17.7% (52) received two medications, and 3.1% (9) received three or more medications during their disease course. Hyoscine was the most frequently prescribed drug (85, 28.9%), followed by amitriptyline (44, 15.0%), carbocisteine (41, 13.9%), glycopyrrolate (24, 8.2%), atropine eye drops administered sublingually (19, 6.5%), and botulinum toxin (14, 4.8%).

Survey Results

Responses to the questionnaire were received from 11 clinicians (five clinical nurse specialists, four consultants, and two trainee doctors), giving a response rate of 73.3%. Nine respondents (81.8%) indicated they ask directly about problematic saliva either “every time” or “usually” in consultations with pwMND. Ten respondents (90.9%) reported using supportive measures in management of problematic saliva, with postural advice, the most frequently reported technique. Postural advice revolves around ensuring upright posture with good head support. Three respondents (27.3%) identified botulinum toxin as a treatment option; they were interested in using but were unable to due to limitations such as lack of availability or expertise. Destruction of salivary glands by radiotherapy or surgery was identified as a treatment option, which most respondents (8, 72.7%) were reluctant to consider given its irreversibility. Similarly, respondents reported they did not routinely prescribe benztropine, bromelaine, clonidine, or beta-blockers for saliva problems. Local guidelines (10, 90.9%) and evidence base (8, 72.7%) [8] were cited as the most important factors influencing choice of medication, whereas drug expense and patient request were the least important factors.

Discussion

The prevalence of saliva problems in this populationbased study of 939 pwMND was 31.3%. We defined saliva problems using the ALSFRS-R saliva sub-score and direct questioning to ensure standardised reporting. The CARE-MND register achieves 99% case ascertainment with detailed phenotypic capture of people with all subtypes of MND. Our findings are, therefore, generalizable to routine clinical care, in comparison to results of previous studies relying on trial populations or clinician surveys [3–5].

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We identified that bulbar onset was independently associated with the presence of saliva problems. There was no association between saliva problems and age, sex, time between onset and diagnosis, or MND subtype in multivariable analysis. This finding highlights the importance of screening all pwMND regardless of clinical or demographic characteristics. Without adequate assessment, many pwMND will be unable to access treatment for this distressing symptom. Saliva problems may develop after first presentation of the disease, so regular, repeated screening for the symptom is necessary [11].

Of those with saliva problems, 52.7% received pharmacological treatment, despite clinical guidelines recommending treatment in all affected individuals [8, 12]. Previous observational studies reported even lower figures of 46-54% [3, 5]. Reasons for this apparent under-treatment are likely to be varied and warrant further investigation. Side effects of pharmacological treatments, including the impact on cognition of anticholinergics, might limit their use in this vulnerable patient group. Additionally, therapeutic nihilism may relate to the treatment of a life-limiting illness, perhaps compounded by the limited evidence regarding the efficacy of frequently used pharmacological agents. Indeed, 23.7% of affected individuals received two or more drugs highlighting difficulties in controlling symptoms with existing treatments. Our survey confirmed that availability of research evidence for treatment was one of the most important factors influencing decision-making in the management of problematic saliva. There is a comparatively large evidence base for botulinum toxin and radiotherapy in the management of saliva problems [10, 13–15]; however, survey respondents reported difficulties accessing botulinum toxin treatment and were reluctant to consider radiotherapy given irreversibility. Lastly, for a minority of pwMND with saliva problems, supportive treatments alone may have been sufficient to achieve symptomatic control. Encouragingly, the vast majority of survey respondents reported the use of such measures to manage saliva problems.

Limitations

Our study is retrospective in nature, with attendant limitations. We are unable to report on the respective prevalence of sialorrhoea and thick tenacious saliva as the ALSFRS-R only screens for sialorrhoea, whereas direct questioning encompasses both problems, but does not yet yield differential data for each problem. This means that the prevalence of thick, tenacious saliva may have been underestimated. More sensitive scales, such as the Oral Secretion Scale [16], are available and validated for use in pwMND but are not routinely used in our cohort.

Furthermore, as our assessment of saliva problems occurred cross-sectionally, we are unable to comment on the rate of progression of saliva problems. Although the majority of the drugs we identified will have been primarily indicated for managing saliva problems, we were unable to establish with certainty whether some medications may have been prescribed for other indications. Previous research has reported a high rate of side effects and discontinuation of drugs used in the management of saliva problems; investigation of the efficacy of individual treatments and side-effect profiles were beyond the scope of this study.

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Conclusions

This large population-based study has demonstrated a prevalence of saliva problems in pwMND of 31.3%, of whom 52.7% received pharmacological management. The most commonly used medications were hyoscine, amitriptyline, carbocisteine, glycopyrrolate, and atropine. Bulbar onset was independently associated with the presence of saliva problems but not age, sex, time between onset and diagnosis, or MND subtype. Current practice could be improved by encouraging frequent and repeated assessment for saliva problems, promoting the use of supportive and medical treatments, and strengthening the evidence base for medical treatments used to inform clinician decision-making. Future research should ascertain patient preferences regarding treatments, efficacy of individual treatments, and rates of discontinuation due to adverse effects.

Survey Questions

1. What is your job title? (free text).
2. Which NHS board do you work for? (free text).
3. In consultations with people with MND, how often do you directly ask the person about saliva problems? (multiple choice: never, occasionally, around half of the time, usually, every time).
4. In consultations with people with MND, how often do you use the ALSFRS-R to assess saliva problems? (multiple choice: never, occasionally, around half of the time, usually, every time).
5. Which (if any) of the following NICE-recommended drugs/treatments have you used/recommended for use for your patients with saliva problems? (multiple choice: atropine sublingual drops, benzatropine, hyoscine, glycopyrrolate, amitriptyline, clonidine, botulinum toxin, propranolol, metoprolol, carbocisteine, bromelaine, bioxtra, radiotherapy, surgery).
6. Do you use any other drugs/treatments for saliva management in MND, which are not mentioned above? (yes/no).
7. If you answered “yes” to question 6, please specify which other drugs/treatments you use for saliva management in people with MND? (free text).
8. Which (if any) of the following NICE-recommended drugs would you be reluctant to use/recommend for use for your patients with saliva problems? (multiple choice: atropine sublingual drops, benzatropine, hyoscine, glycopyrrolate, amitriptyline, clonidine, botulinum toxin, propranolol, metoprolol, carbocisteine, bromelaine, bioxtra, radiotherapy, surgery).
9. If you ticked any boxes in question 8, please explain why you would be reluctant to use this/these medication(s)? (free text).
10. Which of the following factors contribute to your decision-making, when deciding which drug(s) to use/ recommend? (multiple choice: local guidelines,

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national guidelines, drug availability, drug effectiveness, evidence base for drug, expense of drug, previous experience with the drug, patient request, other).

11. Which (if any) of the following drugs would you be interested in using/ recommending for use, but cannot due to availability within your Health Board, or due to lack of training/expertise? (multiple choice: atropine sublingual drops, benzatropine, hyoscine, glycopyrrolate, amitriptyline, clonidine, botulinum toxin, propranolol, metoprolol, carbocisteine, bromelaine, bioxtra, radiotherapy, and surgery).

12. Which (if any) of the following NICE-recommended supportive measures have you used/recommended for use for your patients with saliva problems? (suction, humidification and nebulizer, postural advice, behavioural approaches, oral care, dietary modification).

13. Do you use any other supportive measures for saliva management, which are not mentioned above? (yes/ no).

14. If you answered “yes” for question 13, please specify which other supportive measures you use for management of saliva problems in people with MND? (free text).

15. Which (if any) of the following NICE-recommended supportive measures would you be reluctant to use/ recommend for use for your patients with saliva problems? (suction, humidification and nebulizer, postural advice, behavioural approaches, oral care, dietary modification).

16. If you ticked any boxes in question 15, please explain why you would be reluctant to use this/these supportive measure(s)? (free text).

17. Have you ever received specific training for dealing with saliva problems in MND? (yes/no).

18. If you answered “yes” to question 17, please specify what was this training and who provided this training? (free text).

19. Do you have resources available to you and your patients, which are specific for saliva problems? (yes/no).

20. If you answered “yes” to question 19, please specify what resources you have? (free text).

21. Can you think of any resources which you would find helpful for managing saliva problems in your patients? (free text).

22. If you have any other comments about saliva management in MND, please share them here (free text).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of Data and Material

Upon request from the authors.

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Table 1

Demographic and clinical factors associated with saliva problems

Characteristic	Category	Univariable OR (95% CIs; p value)	Multivariable OR (95% CIs; p value)
Age at symptom onset (years)		1.02 (1.01, 1.03); <0.001	1.01 (0.99, 1.03); 0.05
Male sex		0.60 (0.44, 0.81); <0.001	0.72 (0.53, 1.03); 0.22
Time between onset and diagnosis (months)		0.99 (0.98, 1.00); 0.01	0.99 (0.98, 1.00); 0.05
Region of onset	Spinal (reference)	1	1
	Bulbar	12.46 (7.09, 21.92); <0.001	9.46 (4.7, 19.2); <0.001
	Mixed	3.40 (1.39, 8.47); 0.01	2.63 (1.2, 5.7); 0.63
	Pure respiratory	1.47 (0.2, 14.79); 0.59	1.53 (0.25, 9.26); 0.06
MND subtype	Amyotrophic lateral sclerosis (reference)	1	1
	Progressive bulbar palsy	2.70 (1.63, 4.49); <0.001	0.85 (0.43, 1.67); 0.63
	Primary lateral sclerosis	1.31 (0.57, 3.02); 0.52	2.76 (0.70, 10.9); 0.14
	Progressive muscular atrophy	0.23 (0.05, 0.96); 0.04	0.239 (0.06, 1.43); 0.13

OR, odds ratio.