Clinical Nutrition 40 (2021) 4904–4911

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Oral function in amyotrophic lateral sclerosis patients: A matched case–control study

Martin Schimmel [a], Igor Leuchter [b], Anne-Chantal Héritier Barras [c], Claudio R. Leles [d], Samir Abou-Ayash [a], Valérie Viatte [e], Françoise Esteve [b], Jean-Paul Janssens [f], Frauke Mueller [g], Laurence Genton [e, *]

[a] Reconstructive Dentistry and Gerodontology, School of Dental Medicine, University of Bern, Bern, Switzerland
[b] Otorhinolaryngology, University Hospitals, Geneva, Switzerland
[c] Neurology, University Hospitals, Geneva, Switzerland
[d] Prevention and Oral Rehabilitation, School of Dentistry, Federal University of Goias, Goiania, Brazil
[e] Clinical Nutrition, University Hospitals, Geneva, Switzerland
[f] Pulmonology, University Hospitals, Geneva, Switzerland
[g] Gerodontology and Removable Prosthodontics, University Clinics of Dental Medicine, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 14 April 2021
Accepted 19 June 2021

Keywords:
Oral function
Chewing efficiency
Saliva
Tongue force
Lip force
Fat-free mass

SUMMARY

Background & aims: Patients with amyotrophic lateral sclerosis (ALS) develop swallowing difficulties with the progression of the disease. The present study aimed at comparing oral function and body composition between ALS patients and healthy controls, and at evaluating which parameters are the most discriminant between both groups.
Methods: We included ALS patients at the start of their multidisciplinary follow-up at the Geneva University Hospitals and healthy age-, gender-, and dental status-matched adults. We assessed the severity of the disease through the ALS Functional Rating Scale and the swallowing difficulties through the EAT-10 score. We performed an intraoral examination of the dental status, and measured chewing performance, bite, lip and tongue force, saliva weight, and body composition. Group comparisons were performed with t-tests or Mann–Whitney tests as appropriate. Linear discriminant analysis was used to determine the most discriminant parameters between groups.
Results: Twenty-six ALS patients (bulbar onset: $n = 7$, median (IQR) ALS Functional Rating Scale: 37 (11)) were included. The ALS patients had a significantly lower chewing performance ($p < 0.001$), lip force ($p < 0.001$), tongue force ($p = 0.002$), saliva weight ($p < 0.004$) and fat-free mass index ($p < 0.001$) as compared to the healthy individuals, and a higher EAT-10 score ($p < 0.001$). In ALS patients, a low chewing performance was correlated with a low bite ($r = -0.45$, $p < 0.05$)) and tongue force ($r = -0.59$, $p < 0.05$). The most discriminant parameters between both groups, by order of importance, were chewing performance, fat-free mass index and saliva weight and allowed the calculation of a discriminant function.
Conclusion: Compared to healthy controls, ALS patients have significant alterations of oral function and body composition. The most discriminant parameters between both groups were chewing performance, fat-free mass index and saliva volume. It remains to be demonstrated whether oral parameters predict outcome.
Clinical Trial registry: clinicaltrials.gov, identifier: NCT 01772888.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder, characterized by a loss of motor neurons in the cerebral cortex, brainstem, and spinal cord. The clinical onset can be bulbar, affecting swallowing and phonation, or spinal, presenting as

* Corresponding author. Geneva University Hospitals, Rue Gabrielle Perret-Gentil 4, 1205, Geneva, Switzerland. Fax: +41 22 372936.
E-mail address: laurence.genton@hcuge.ch (L. Genton).

https://doi.org/10.1016/j.clnu.2021.06.022

skeletal muscle atrophy. ALS leads eventually to paralysis and death within 3–5 years from the onset of symptoms [1].

Undernutrition is frequent in ALS patients. At their first visit, 16% of ALS patients have a body mass index below the 18.5 kg/m^2 defined as the threshold for undernutrition [2]. Furthermore, 55% show a weight loss of more than 15% of their usual body weight [3]. A low body mass index (BMI) (<21 kg/m^2 in patients <70 years and <18.5.5 kg/m^2 in patients ≥70 years) and a weight loss over 5% at the time of diagnosis have both been associated with a higher risk of death [4]. This suggests that undernutrition should be prevented and treated in ALS patients. Conversely, enteral nutrition may improve survival and nutritional state [5].

Numerous causes of insufficient oral intake have been described in ALS patients [6], but ultimately almost all patients develop difficulties in swallowing. Swallowing kinematics in ALS patients show a decreased bolus transport to the pharynx or an impaired holding of the bolus at the posterior part of the tongue. These abnormalities suggest a dysfunction of the oral phase of swallowing which normally encompasses chewing of the food to form a bolus and propulsion of the bolus to the caudal direction of the oral cavity [7–9]. The chewing capacity depends on the force and coordination of chewing muscles, cheek muscles, and the tongue, the production of saliva, and the dentition [10–13]. The gold standard test for determining chewing function are comminution tests ("sieving method"), where test foods (natural or artificial) are chewed during a given number of chewing cycles, spat out, dried, sieved through decreasing mesh apertures to separate them for size, and finally weighed to measure food grinding according to the achieved particle size distribution [13]. However, this method is expensive, time-consuming, and may result in the aspiration of the test-food. A reliable alternative to comminution tests represent color-mixing ability tests for masticatory performance [13]. For instance, the chewing function can be evaluated by the degree of mixing and kneading a two-colored chewing gum, using opto-electronic image analysis [14]. In stroke patients, the chewing function, measured by this method was about 50% lower than in age- and gender-matched controls [15]. Lip force, which is significantly correlated to the chewing performance, was also impaired [15].

Therefore, we hypothesized that patients diagnosed with ALS would show impaired oral function, due to decreased coordination ability of the lips and tongue, as well as decreased maximum voluntary bite force. This could negatively affect both the chewing function and consequently the nutritional intakes. The present study aimed to compare oral function and body composition of ALS patients to that of a sample, of age, gender, and intraoral status-matched healthy subjects and evaluate which parameters are the most discriminant between both study groups.

2. Subjects and methods

This cross-sectional controlled cohort study included adults diagnosed with ALS and participating in the clinical multidisciplinary follow-up of the Geneva University Hospitals (HUG) [16]. They were included at the start of their follow-up at the Geneva University Hospitals, while they had no enteral nutrition nor parenteral nutrition. We excluded ALS patients who did not foresee participating in the multidisciplinary follow-up of the HUG. As part of the clinical routine, the patients were evaluated at each visit with the functional rating scale (ALS-FRS-R) instrument and blood tests. The ALS-FRS-R estimates the degree of limitation of ALS patients and ranges from 0 (total limitation) to 48 points (no limitation) [17]. It is subdivided into scores evaluating the bulbar, fine motor, gross motor and respiratory impairments, each ranging from 12 (no limitation) to 0. The bulbar sub-score evaluates, besides speech and salivation, the swallowing function which ranges from 4 (normal swallowing) to 0 (need of exclusive enteral or parenteral nutrition). The blood tests included measurements of plasma urea and creatinine to evaluate the potential appearance of acute renal failure due to dehydration which would limit the interpretation of body composition measurements.

The control group consisted of healthy age- (±10 years), gender-, and dental status-matched adults recruited at the Department of Reconstructive Dentistry and Gerodontology, School of Dental Medicine, University of Bern, Switzerland. Since the number of potential study participants depended on the number of available ALS patients and no reference data were available, power analysis could not be performed prior to the study. The protocol was accepted by the Ethical Committee of Geneva and Bern (PB_2016-01916) and registered under clinicaltrials.gov (NCT 01772888).

The participants underwent the following clinical assessments, detailed thereafter: intraoral examination of the dental status, chewing performance, bite, lip and tongue force, saliva volume, swallowing disturbances and body composition.

2.1. Dental status

The number of remaining teeth, their occlusal relation in terms of the number of posterior teeth in contact (occlusal units in function; OU), and the Eichner classification [18], which classifies teeth based on the presence of four intraoral support zones (premolars and molars on the patient's right and left side), was recorded by a dentist. The main categories of the Eichner classification describe contact in all support zones (Eichner group A), in less than 4 support zones (Eichner group B), or lack of antagonistic contact (Eichner group C). The OUs are calculated from the number of antagonizing premolars and molars, where antagonizing premolars represent one OU, and molars represent two OUs. A premolar that has a molar as an antagonist or a molar that meets the antagonizing molar with only half its surface are also counted as one OU. Fixed dentures were equated with natural teeth for the calculation of OUs, but teeth replaced by removable dentures were not. The minimum number of OUs was therefore 0 and the maximum number 16, with the wisdom teeth included.

2.2. Chewing performance

Chewing performance was evaluated with a previously described two-color mixing ability test [14]. A commercially available chewing gum with two inseparable green and violet layers (Vivident Fruitswing® "Karpuz/Asai Üzümü"; Perfetti van Melle, Istanbul Turkey), which has been frequently used in previous studies, was applied as test food [19,20]. The participants were asked to chew the gum for 20 cycles. The time for performing the chewing cycles was recorded. Afterward, the chewing gums were removed from the mouth and placed in a transparent plastic bag. In this plastic bag, the chewing gums were flattened with the help of a plate to 1 mm thick test bodies, and then scanned on both sides with a flatbed scanner. The resulting images were analyzed using the freely available software (ViewGum®, www.dhal.com), which calculates the variance of the hue (VoH). A good mixing of the two colors of the gum, corresponding to a good chewing performance results in a low VoH, whereas a poor mixing of the phases leads to a high VoH value.

2.3. Bite force

The maximum voluntary bite force was measured with the Occlusal Force-Meter GM 10® (Nagano Keiki, Higashimagome, Ohta-ku, Tokyo, Japan). All participants were instructed to stabilize the bite plate in the region of the first molars, and then to bite down as hard as possible until a beep. A total of three measurements were taken on each side. The maximum values of the right and left side were averaged to obtain a single value per patient.

2.4. Lip force

The maximum voluntary lip force was measured using a 55 × 24mm curved plate (Dentaurum 'Oral screen Ulmer Modell' maxi/size 2, Dentaurum GmbH, Ispringen, Germany) whose curvature is based on the average curvature of a dental arch [21]. This plate contains a tab in the center of the curvature for attaching a digital force gauge (ZP50-N Imada digital force gauge; Imada Co., Toyohashi, Japan). Before inserting the plate into the oral vestibule of the participants, this force gauge was connected to the plate and only then inserted into the oral vestibule. The plate was positioned between the closed dentition and the lips of the patients. Subsequently, the patients were instructed to resist as much as possible with their lips against the removal of the plate by means of a horizontal pull on the force gauge. The operator then attempted to remove the plate using a horizontal pull, with the force gauge recording the peak force applied for removal. This procedure was repeated three times, with a one-minute pause between each measurement. An average value was then calculated for analysis.

2.5. Tongue force

The maximum voluntary tongue pressure was measured using the standard device for measuring tongue force, the IOPI (IOPI model 2.3, IOPI Medical LLC, Washington, USA) [22]. The device consists of an air-filled bulb connected to the actual digital measurement device via an elastic plastic tube. The bulb with the included approximately 2 mm wide bite block was placed between the central incisors of the maxilla and mandible. The participants were then asked to press the bulb with their tongue as hard as they could against the hard palate for 3 s. The digital measuring device calculates the maximum voluntary tongue force from the air displaced from the bulb. This procedure was repeated three times, with a pause of one minute between each measurement, and the average maximum tongue force was then calculated. This measurement was added as the study had already started.

2.6. Saliva weight

The unstimulated saliva production was measured applying sialometry. Three cotton wools (Roeko Luna #2; Coltène/Whaledent AG, Altstätten, Switzerland) were simultaneously placed in the participants' mouth, one each between the teeth and the cheek on the participants' right and left side, and one between the mandibular incisors and the tongue, to collect saliva from the parotid, submandibular, and sublingual glands [17,23]. The cotton wools were left in place for 6 min. All cotton wools were weighed before and after placing them into the patient's mouth. The weight-difference between the initial and the subsequent measurement was determined as the amount of produced saliva during 6 min.

2.7. Swallowing disturbances

Subjective swallowing complaints were described using the EAT 10 questionnaire, which was self-completed by the patients. The EAT-10 questionnaire was specifically designed to assess swallowing difficulties in terms of symptom severity, impact on quality of life, and treatment success [24]. The 10 questions of the questionnaire are each given a score from 0 (no problems) to 4 (maximum problems), resulting in a total score of 0–40 points. A total score of 3 or higher indicates the presence of dysphagia [25].

2.8. Body composition

The participants underwent measurement of weight, with light clothes but without shoes with a digital scale (Seca, Germany), and height with a height gauge. BMI was calculated as weight (kg)/height $(m)^2$.

The body composition was assessed by bioelectrical impedance analysis (Nutriguard ®, Data Input GmbH, Pöcking, Germany). The participants were lying in the supine position with, electrodes placed on the right hand, wrist, ankle and foot, as detailed elsewhere [26]. After connecting the generator to the electrodes, the measurement was performed at a current of 0.8 mA and a frequency of 50 kHz. Fat-free mass was calculated by the Geneva formula [27], and fat mass obtained by subtraction of fat-free mass from body weight. Fat-free mass and fat mass index were obtained by dividing fat-free mass and fat mass by height $(m)^2$.

2.9. Statistical analysis

Descriptive statistics were performed using frequency analysis for nominal, and mean values ± standard deviations (SD) or median (IQR) for numerical variables. The normality of data for ALS and control groups were verified using the Shapiro–Wilk tests. Bivariate comparison tests were performed to compare ALS and control groups using Chi-square tests, unpaired t-tests, and Mann–Whitney tests, as appropriate. The correlations between sets of variables was tested using Pearson correlation coefficient. A sub-analysis compared the oral function between ALS patients with and without swallowing impairment, according to the ALS-FRS-R, and healthy controls, by ANOVA or Kruskall–Wallis tests, as appropriate. We focused on a categorization according to swallowing function, instead of the more heterogeneous bulbar sub-score, because swallowing is obviously the main determinant of nutritional intakes and subsequent nutritional state.

Linear discriminant analysis was used to build predictive models that best discriminate the ALS from the control group. Parameters of oral function and body composition were used as independent quantitative predictors. Box's M tests were used to test the homogeneity of the variances between the variables. The variation inflation factor was calculated to exclude the presence of collinearity which is confirmed by a value below 10. We performed two models that included the independent variables that were significantly different between the groups in the bivariate comparison tests. Model 1 included all predictors together. Model 2 included the most relevant predictors obtained by stepwise selection performed automatically by the statistical software. A structure matrix was constructed with the canonical correlation coefficients for each predictor, which reflects the strength of the association between the independent predictors and the two dependent variables (ALS and control group). The standardized discriminant coefficients were used to construct a linear discriminant function for the selected independent variables to rank the contribution of each variable to the discrimination between groups. The significance of the models (Wilk's Lambda) and the predictive power of the models (canonical correlation, R^2) were calculated.

Finally, the discriminant scores were used to calculate the percent of correct classification of the predicted group membership compared to the actual groups of the study sample. The IBM-SPSS software was used for data analyses. Statistical significance was set at $p < 0.05$.

As this study has never been performed before and is limited by the number of ALS patients, we could not perform a calculation of the number of subjects needed. Based on the 33 patients with ALS included in the multidisciplinary follow-up between April 2010 and December 2011, we had planned on including 25 patients within 2 years.

3. Results

We included 26 ALS patients (11 women and 15 men) and 26 age-, gender- and dental-status matched healthy controls. Their mean (SD) age was 65.0 (15.7) and 59.5 (20.3) years ($p = 0.282$), respectively.

The ALS patients presented an ALS Functional Rating Scale ranging from 24 to 45 (median = 37; IQR = 11). The bulbar subscore was below 12 in 18 (69%) patients (Table 1), and swallowing was impaired in 11 patients (9 patients had early eating problems with occasional choking and 2 required a dietary texture modification). The EAT-10 score was below 3 in 14 (54%) ALS patients. The weight change at the time of the study assessment, as compared to usual body weight, ranged between −15.1 kg and 11.8 kg (median = −1.7 kg; IQR = 3.8 kg). All patients had normal plasma creatinine levels. Twenty-four patients had normal plasma urea (<7.5 mmol/l) and 2 patients had a slight increase (7.7 and 9.4 mmol/l), suggesting no major dehydration. Regarding drugs, 21 patients were taking Riluzole, 6 were taking anti-depressants, and 2 were taking anticholinergic drug to decrease salivation but none had undergone a botox injection.

The main characteristics of the ALS and control groups are shown in Table 1. The ALS patients had a significantly lower chewing performance, lip force, tongue force, and saliva weight as compared to the healthy individuals, and a higher EAT-10 score. In terms of the physical parameters, ALS patients had significantly lower BMI and fat-free mass index, but not fat-mass index. An example of the two-color mixing ability tests in an ALS patient and his matched control is shown in the Supplemental figure. Table 2 shows the correlations between the oral function and anthropometric variables in both groups. In ALS patients, a low chewing performance was correlated with a low bite and tongue force, and the EAT-10 score was positively correlated with saliva weight and negatively with lip force. No correlations were found between oral function and anthropometric variables. As expected, the ALS patients with swallowing impairment had lower chewing capacity, tongue force, and higher EAT-10 score and saliva weight than those without swallowing impairment (Supplemental Table 1).

In the linear discriminant analysis, we used chewing performance, lip force, saliva weight, body mass index and fat-free mass index since they differed between groups in bivariate comparisons (Table 3). We excluded the EAT-10 score because it was normal in all healthy controls as expected and the tongue force due to the high number of missing values. The remaining variables did not show any collinearity (maximum VIF value = 1.04). In order to satisfy the assumption of equal covariances between groups required for linear discriminant analyses (Box's M tests), we had to normalize the data, which was best obtained through a square root transformation for all data except VoH (Table 3). After the stepwise selection (model 2), only the chewing performance, the fat-free mass index, and the saliva weight remained in the final discriminant function (D) according to the following equation:

$$(D) = 0.816*(1/VoH) + 0.542*(sqrt\ (fat\text{-}free\text{-}mass\ index)) + 0.465\ (sqrt\ (saliva\text{-}weight))$$

The higher standardized discriminant function coefficient for VoH (0.816) than for the two other variables indicated that the chewing function (VoH) had the highest ability to discriminate ALS patients from healthy controls. Of interest, when keeping the tongue in the analysis and thus including only 15 ALS patients, the

Table 1
Characteristics of the ALS patients and control patients.

		ALS patients (n = 26)	Controls (n = 26)	p-value[d]
ALS-FRS score revised				
Total score	Median (IQR)	37 (11)	–	–
Bulbar score	Median (IQR)	10 (3)	–	–
Fine motor score	Median (IQR)	5 (3)	–	–
Gross motor score	Median (IQR)	7 (5)	–	–
Respiratory	Median (IQR)	12 (1)	–	–
Dental status				
Number of occlusal units	Median (IQR)	9 (7)	10 (5)	0.901
Number of remaining teeth	Median (IQR)	27.0 (8)	26.5 (4)	0.920
Eichner group (%)				
A	n (%)	15 (57.7)	20 (76.9)	0.284
B	n (%)	1 (3.8)	4 (15.4)	
C	n (%)	0 (0%)	2 (7.7)	
Edentulous	n (%)	1 (3.8)	0 (0%)	
Oral function				
Variation of hue	Mean (SD)	0.43 (0.17)	0.12 (0.05)	<0.001
Time for mastication (seconds)	Mean (SD)	18.3 (4.3)	17.4 (4.8)[a]	0.471
Bite force (Newton)	Mean (SD)	373.6 (139.6)[b]	369.9 (174.3)	0.936
Lip force (Newton)	Mean (SD)	11.49 (6.98)	21.20 (6.49)	<0.001
Tongue force (Newton)	Mean (SD)	27.82 (14.59)[c]	42.62 (12.78)	0.002
EAT-10 score	Mean (SD)	5.20 (8.84)[a]	0.35 (0.89)	0.001
Saliva weight (g)	Mean (SD)	4.88 (2.58)	2.86 (1.80)	0.004
Anthropometry				
Body Mass Index (kg/m^2)	Mean (SD)	24.3 (4.3)	27.4 (5.4)	0.024
Fat-free mass index (kg/m^2)	Mean (SD)	15.9 (2.18)	19.3 (3.1)	<0.001
Fat mass index (kg/m^2)	Mean (SD)	8.5 (3.4)	8.1 (3.0)	0.725

[a] n = 25.
[b] n = 23.
[c] n = 15.
[d] Comparisons were performed with unpaired t-test for continuous normally distributed data, Chi-square test for proportions, and Mann–Whitney tests for continuous non-normally distributed data.

Table 2
Correlation matrix of the oral function and anthropometric variables.

	Chewing performance	Time of mastication	EAT-10 score	Bite force	Lip force	Tongue force	Saliva weight	BMI
Controls								
Time of mastication	−0.250							
EAT-10 score	−0.135	0.102						
Bite force	−0.117	−0.158	−0.240					
Lip force	−0.259	−0.349	−0.099	0.196				
Tongue force	−0.170	−0.111	0.003	0.176	−0.101			
Saliva weight	0.018	−0.175	0.001	−0.096	0.041	−0.124		
BMI	0.097	−0.380	−0.062	0.275	0.225	−0.023	−0.316	
Fat-free mass index	0.032	−0.307	−0.179	0.363	0.316	−0.196	−0.281	0.884***
ALS patients								
Time of mastication	0.048							
EAT-10 score	0.159	0.086						
Bite force	−0.450*	−0.274	−0.117					
Lip force	−0.149	−0.113	−0.562**	0.260				
Tongue force	−0.592*	0.176	−0.528	0.341	0.701**			
Saliva weight	0.179	−0.158	0.508*	−0.032	−0.268	−0.275		
BMI	0.036	−0.096	−0.280	0.161	0.066	0.244	0.098	
Fat-free mass index	0.279	0.121	−0.103	−0.093	−0.049	0.184	0.013	0.630**

*p < 0.05; **p < 0.01; ***p < 0.001.

Table 3
Parameters of the discriminant function models.

Predictors	Normalization	Model 1		Model 2	
		Structure matrix	Standardized Discriminant Function Coeff.	Structure matrix	Standardized Discriminant Function Coeff.
Chewing performance (VoH)	1/VoH	0.715	0.699	0.761	0.816
Lip force (Newton)	square root	0.435	0.284		
Fat-free mass index (kg/m^2)	square root	0.404	0.730	0.430	0.542
Saliva weight (g)	square root	0.297	0.471	0.315	0.465
Body mass index (kg/m^2)	square root	0.185	0.313		
Box's test		p = 0.127		p = 0.126	
Significance of the model (Wilks' Lambda)		0.274; p < 0.001		0.299; p < 0.001	
Canonical correlation (R^2)		0.852 (0.73)		0.837 (0.70)	
% of overall cases correctly classified		98.10%		94.2%	

Model 1: All variables together.
Model 2: Stepwise selection of variables (entry: p < 0.05; removal: p > 0.10.

chewing performance remained a discriminant parameter but the model did not improve (Supplemental Table 2).

When plotting the selected predictors and the scores obtained from the final discriminant function, the individuals from the study groups were well separated (Fig. 1). The overall percent of correct classification of the original groups, based on the predicted group membership from the discriminant function was 94.2% (92.3% of the ALS group, and 96.2% for the control group).

4. Discussion

This study showed that patients with ALS had a significantly lower chewing performance, lip force, tongue force, saliva volume, BMI and fat-free mass index, and higher swallowing difficulties as compared to healthy individuals matched for age, gender and dental status. The most discriminant parameters between both groups, by order of importance, were chewing performance, fat-free mass index and saliva volume, and they allowed the calculation of a discriminant function. The latter predicted a correct group membership in 92% of the ALS patients and in 96% of the healthy volunteers.

Several studies evaluated the oral function of ALS patients either subjectively or with other methods than in our study. The largest one used the 8-item Jaw Functional Limitation Scale to compare 153 ALS patients and 23 controls [28]. This scale requires each participant to rate his capacity to chew soft food, chew chicken, eat soft food not requiring chewing, open the mouth, swallow, talk, yawn and smile. The 106 patients with bulbar dysfunctions had higher difficulties in chewing, opening their mouth, swallowing and talking than the ALS patients without bulbar dysfunction and healthy controls. Another study included 14 newly diagnosed ALS patients who underwent the Nordic Orofacial Test-Screening which encompasses a standardized interview evaluating the sensory function, breathing habits, chewing, swallowing, drooling and dryness of the mouth, as well as a clinical examination of the oropharyngeal region by a dental team [29]. The maximum score was 12 points. The tests were performed every 3 months, until the score reached 6 points twice indicating severe orofacial dysfunction. The most prevalent findings were chewing and swallowing disturbances associated with drooling. The patients with bulbar onset had more severe oral dysfunction at inclusion and follow-up, as compared to the patients with spinal onset. The authors suggested that these patients would benefit from early monitoring of oral health conditions.

Two studies measured directly the chewing capacity in ALS patients, with sophisticated methods, such as electromyography [30] or jaw kinematics using a 3-dimensional motion capture technology [31]. Both methods confirmed a decreased chewing capacity in ALS patients but they cannot be used as bedside methods in clinical routine. Our results confirmed the impairment of chewing ability in ALS patients described in the previously mentioned studies. We could assess it objectively with a fast, easy, readily available and low-cost bedside method. Furthermore, our statistical analyses highlighted that it was the most discriminant

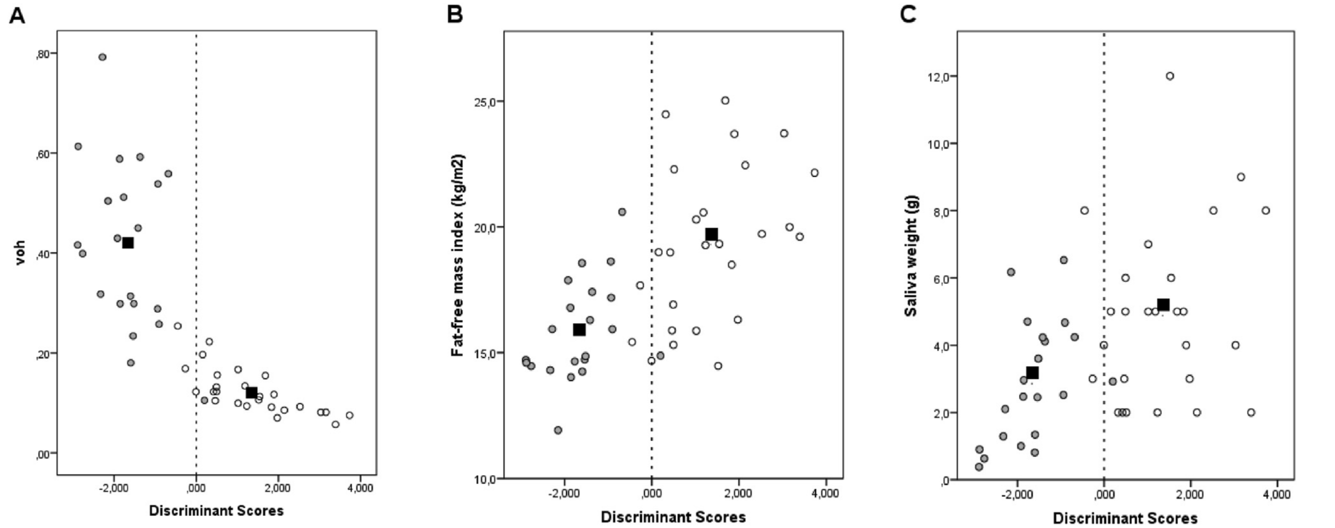

Fig. 1. Scatterplot of the study showing the discriminant scores in the patients with ALS and healthy controls, for the variables selected in the discriminant model (VoH, fat-free mass index, and saliva weight). The discriminant scores of ALS patients are shown as filled circles and the discriminant scores of the healthy controls as empty circles. The black squares are the group centroids plotted against the mean values for the control and ALS groups.

oral function compared to healthy subjects. Interestingly, chewing deficit was shown to predict the onset of dysphagia within 12 months [32]. As dysphagia has been associated with low quality of life in ALS patients [33], it is likely that chewing impairment also affects quality of life of ALS patients, as such relationship has been shown in older people [34].

We demonstrated that the spontaneous saliva volume was another oral function discriminating ALS patients, which is in line with one other study. Easterling et al. followed 23 ALS patients, among which 9 had bulbar onset, over 6 months [35]. They found that spontaneous and stimulated salivary flow decreased with time, suggesting that the progression of the disease affected the salivary volume.

Weight loss is reported in approximately two-thirds of the ALS patients at the time of diagnosis, irrespective of the presence of bulbar symptoms, and the severity of weight loss is a relevant predictor of mortality [4,36]. Body weight consists of fat mass and fat-free mass. It has been acknowledged that the fat-free mass component decreases with the progression of the disease, which is logical due to the loss of motor neurons, and is associated with increased mortality [37,38]. It is therefore not surprising to find fat-free mass as discriminant parameter. The fact that fat mass index was not different between the ALS patients and controls could be due to the fact that we have included the patients at the start of their follow-up at the University Hospitals of Geneva, which was generally relatively early in the course of the disease. They likely had not yet experienced an oral dysfunction that was severe enough to lead to an energy deficit. Of note, most patients reported in the ALS-FRS-R that they had no problem with eating ($n = 15$), early eating problems with occasion choking ($n = 9$) and only 2 had undergone a change in the dietary texture.

4.1. Strengths and limitations

The greatest strength of the present study is the direct comparison of age-, gender- and dental-status matched participants, as these parameters all have a significant impact on oral function [39–41] and physical parameters [42,43]. Because of this matching, the differences shown in this study can be attributed with a higher probability to ALS than if simply a healthy cohort had been used as a control. We used only instruments that are readily available, easily transportable and can thus be applied in the ambulatory setting. We performed linear discriminant analyses instead of logistic regressions because the set of continuous predictor variables and well-separated groups in the matched-pair design may result in highly unstable parameter estimates for logistic regression.

The major limitation is the rather small study sample of 26 participants per group, which was limited by the number of available ALS patients and did not allow us to perform separate analyses according to the type of onset (bulbar vs. spinal). We had few measurements of tongue force and thus preferred not to include them in the final linear discriminant analysis. Even though tongue force was shown to decrease with the progression of the disease [35,44], the measurement of chewing performance likely integrates partly the tongue force, as tongue mobility is essential for chewing ability. Finally, although the discriminant function was highly relevant in our study population, it needs to be validated in a larger and different population of ALS patients in the initial stages of the disease. Furthermore, it has to be demonstrated whether providing nutritional support as soon as the discriminant function is pathologic improves the survival of ALS patients.

5. Conclusion

Compared to healthy controls, ALS patients had a significantly lower chewing performance, lip force, tongue force, saliva volume, BMI and fat-free mass index, and higher swallowing disturbances. The most discriminant parameters between both groups were chewing performance, fat-free mass index and saliva volume. Longitudinal studies are needed to provide more insight on the role of oral parameters in the outcome of ALS.

Funding statement

Research Fellowship of the European Society for Clinical Nutrition and Metabolism (ESPEN).

Author contributions

Martin Schimmel: Conceptualization, methodology, software development for analysis of chewing performance, investigation, resources, data curation, review and editing, visualization, supervision, project administration.

Igor Leuchter: methodology, investigation, resources, review and editing.

Anne-Chantal Héritier Barras: Conceptualization, resources, review and editing.

Claudio R. Leles: formal analysis, data curation, writing original draft.

Samir Abou-Ayash: formal analysis, investigation, writing original draft.

Valérie Viatte: methodology, validation, investigation, review and editing.

François Esteve: investigation, resources, review and editing.

Jean-Paul Janssens: Conceptualization, resources, review and editing.

Frauke Müller: Conceptualization, methodology, software development for analysis of chewing performance, resources, review and editing.

Laurence Genton: Conceptualization, methodology, validation, investigation, resources, data curation, writing original draft, visualization, supervision, project administration, funding acquisition.

Conflict of interest

The authors had no conflict of interest pertaining to the presented data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.06.022.

References

[1] Chiò A, Logroscino G, Hardiman O, Swingler R, Mitchell D, Beghi E, et al. Prognostic factors in ALS: a critical review. Amyotroph Lateral Scler 2009;10:310–23. https://doi.org/10.3109/17482960802566824.

[2] Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional status is a prognostic factor for survival in ALS patients. Neurology 1999;53:1059–63. https://doi.org/10.1212/wnl.53.5.1059.

[3] Mazzini L, Corrà T, Zaccala M, Mora G, Del Piano M, Galante M. Percutaneous endoscopic gastrostomy and enteral nutrition in amyotrophic lateral sclerosis. J Neurol 1995;242:695–8. https://doi.org/10.1007/BF00866922.

[4] Marin B, Desport JC, Kajeu P, Jesus P, Nicolaud B, Nicol M, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. J Neurol Neurosurg Psychiat 2011;82:628–34. https://doi.org/10.1136/jnnp.2010.211474.

[5] Katzberg HD, Benatar M. Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2011;2011. https://doi.org/10.1002/14651858.cd004030.pub3.

[6] Cameron A, Rosenfeld J. Nutritional issues and supplements in amyotrophic lateral sclerosis and other neurodegenerative disorders. Curr Opin Clin Nutr Metab Care 2002;5:631–43. https://doi.org/10.1097/00075197-200211000-00005.

[7] Kawai S, Tsukuda M, Mochimatsu I, Enomoto H, Kagesato Y, Hirose H, et al. A study of the early stage of dysphagia in amyotrophic lateral sclerosis. Dysphagia 2003;18:1–8. https://doi.org/10.1007/s00455-002-0074-3.

[8] Ertekin C, Aydogdu I, Yüceyar N, Kiylioglu N, Tarlaci S, Uludag B. Pathophysiological mechanisms of oropharyngeal dysphagia in amyotrophic lateral sclerosis. Brain 2000;123:125–40. https://doi.org/10.1093/brain/123.1.125.

[9] Fattori B, Grosso M, Bongioanni P, Nacci A, Cristofani R, AlSharif A, et al. Assessment of swallowing by oropharyngoesophageal scintigraphy in patients with amyotrophic lateral sclerosis. Dysphagia 2006;21:280–6. https://doi.org/10.1007/s00455-006-9052-5.

[10] Morita K, Tsuka H, Kato K, Mori T, Nishimura R, Yoshida M, et al. Factors related to masticatory performance in healthy elderly individuals. J Prosthodont Res 2018;62:432–5. https://doi.org/10.1016/j.jpor.2018.03.007.

[11] Takahashi M, Koide K, Arakawa I, Mizuhashi F. Association between perioral muscle pressure and masticatory performance. J Oral Rehabil 2013;40:909–15. https://doi.org/10.1111/joor.12105.

[12] van der Bilt A. Assessment of mastication with implications for oral rehabilitation: a review. J Oral Rehabil 2011;38:754–80. https://doi.org/10.1111/j.1365-2842.2010.02197.x.

[13] Gonçalves TMSV, Schimmel M, van der Bilt A, Chen J, van der Glas HW, Kohyama K, et al. Consensus on the terminologies and methodologies for masticatory assessment. J Oral Rehabil 2021. https://doi.org/10.1111/joor.13161. joor.13161.

[14] Schimmel M, Christou P, Herrmann F, Müller F. A two-colour chewing gum test for masticatory efficiency: development of different assessment methods. J Oral Rehabil 2007;34:671–8. https://doi.org/10.1111/j.1365-2842.2007.01773.x.

[15] Schimmel M, Leemann B, Herrmann FR, Kiliaridis S, Schnider A, Müller F. Masticatory function and bite force in stroke patients. J Dent Res 2011;90:230–4. https://doi.org/10.1177/0022034510383860.

[16] Sukockiene E, Iancu FR, Truffert A, Héritier BAC, Genton L, Viatte V, et al. Multidisciplinary care in amyotrophic lateral sclerosis: a 4-year longitudinal observational study. Swiss Med Wkly 2020;150. https://doi.org/10.4414/smw.2020.20258.

[17] Ahlner BH, Lind MG. A swab technique for sialometry. Acta Otolaryngol 1983;95:173–82. https://doi.org/10.3109/00016488309130932.

[18] Eichner K. Renewed examination of the group classification of partially edentulous arches by Eichner and application advices for studies on morbidity statistics. Stomatol DDR 1990;40:321–5.

[19] Schimmel M, Christou P, Miyazaki H, Halazonetis D, Herrmann FR, Müller F. A novel colourimetric technique to assess chewing function using two-coloured specimens: validation and application. J Dent 2015;43:955–64. https://doi.org/10.1016/j.jdent.2015.06.003.

[20] Kaya MS, Güçlü B, Schimmel M, Akyüz S. Two-colour chewing gum mixing ability test for evaluating masticatory performance in children with mixed dentition: validity and reliability study. J Oral Rehabil 2017;44:827–34. https://doi.org/10.1111/joor.12548.

[21] Hägg M, Olgarsson M, Anniko M. Reliable lip force measurement in healthy controls and in patients with stroke: a methodologic study. Dysphagia 2008;23:291–6. https://doi.org/10.1007/s00455-007-9143-y.

[22] Adams V, Mathisen B, Baines S, Lazarus C, Callister R. A systematic review and meta-analysis of measurements of tongue and hand strength and endurance using the Iowa Oral Performance Instrument (IOPI). Dysphagia 2013;28:350–69. https://doi.org/10.1007/s00455-013-9451-3.

[23] Dawes C. Physiological factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. J Dent Res 1987;66:648–53. https://doi.org/10.1177/00220345870660S107.

[24] Bartlett RS, Moore JE, Thibeault SL. Temporal analysis of factors associated with EAT-10 in outpatients with oropharyngeal dysphagia from a tertiary care clinic. Dysphagia 2018;33:457–67. https://doi.org/10.1007/s00455-018-9874-y.

[25] Hansen T, Kjaersgaard A. Item analysis of the Eating Assessment Tool (EAT-10) by the Rasch model: a secondary analysis of cross-sectional survey data obtained among community-dwelling elders. Health Qual Life Outcome 2020;18. https://doi.org/10.1186/s12955-020-01384-2.

[26] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis - Part I: review of principles and methods. Clin Nutr 2004;23:1226–43. https://doi.org/10.1016/j.clnu.2004.06.004.

[27] Kyle UG, Genton L, Karsegard L, Slosman DO, Pichard C. Single prediction equation for bioelectrical impedance analysis in adults aged 20-94 years. Nutrition 2001;17:248–53. https://doi.org/10.1016/S0899-9007(00)00553-0.

[28] Riera-Punet N, Martinez-Gomis J, Willaert E, Povedano M, Peraire M. Functional limitation of the masticatory system in patients with bulbar involvement in amyotrophic lateral sclerosis. J Oral Rehabil 2018;45:204–10. https://doi.org/10.1111/joor.12597.

[29] Bergendal B, McAllister A. Orofacial function and monitoring of oral care in amyotrophic lateral sclerosis. Acta Odontol Scand 2017;75:179–85. https://doi.org/10.1080/00016357.2016.1276212.

[30] Gonçalves LMN, Palinkas M, Hallak JEC, Marques Júnior W, de Vasconcelos PB, Frota NPR, et al. Alterations in the stomatognathic system due to amyotrophic lateral sclerosis. J Appl Oral Sci 2018;26:e20170408. https://doi.org/10.1590/1678-7757-2017-0408.

[31] Wilson EM, Kulkarni M, Simione M, Rong P, Green JR, Yunusova Y. Detecting bulbar motor involvement in ALS: comparing speech and chewing tasks. Int J Speech Lang Pathol 2019;21:564–71. https://doi.org/10.1080/17549507.2018.1557254.

[32] Ruoppolo G, Schettino I, Frasca V, Giacomelli E, Prosperini L, Cambieri C, et al. Dysphagia in amyotrophic lateral sclerosis: prevalence and clinical findings. Acta Neurol Scand 2013;128:397–401. https://doi.org/10.1111/ane.12136.

[33] Paris G, Martinaud O, Petit A, Cuvelier A, Hannequin D, Roppeneck P, et al. Oropharyngeal dysphagia in amyotrophic lateral sclerosis alters quality of life. J Oral Rehabil 2013;40:199–204. https://doi.org/10.1111/joor.12019.

[34] Kim HY, Jang MS, Chung CP, Paik D Il, Park YD, Patton LL, et al. Chewing function impacts oral health-related quality of life among institutionalized and community-dwelling Korean elders. Community Dent Oral Epidemiol 2009;37:468–76. https://doi.org/10.1111/j.1600-0528.2009.00489.x.

[35] Easterling C, Antinoja J, Cashin S, Barkhaus PE. Changes in tongue pressure, pulmonary function, and salivary flow in patients with amyotrophic lateral sclerosis. Dysphagia 2013;28:217–25. https://doi.org/10.1007/s00455-012-9436-7.

[36] Janse Van Mantgem MR, Van Eijk RPA, Van Der Burgh HK, Tan HHG, Westeneng HJ, Van Es MA, et al. Prognostic value of weight loss in patients with amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry 2020;91:867–75. https://doi.org/10.1136/jnnp-2020-322909.

[37] Burgos R, Bretón I, Cereda E, Desport JC, Dziewas R, Genton L, et al. ESPEN guideline clinical nutrition in neurology. Clin Nutr 2018;37:354–96. https://doi.org/10.1016/j.clnu.2017.09.003.
[38] Roubeau V, Blasco H, Maillot F, Corcia P, Praline J. Nutritional assessment of amyotrophic lateral sclerosis in routine practice: value of weighing and bioelectrical impedance analysis. Muscle Nerve 2015;51:479–84. https://doi.org/10.1002/mus.24419.
[39] Arakawa I, Abou-Ayash S, Genton L, Tsuga K, Leles CR, Schimmel M. Reliability and comparability of methods for assessing oral function: chewing, tongue pressure and lip force. J Oral Rehabil 2020;47:862–71. https://doi.org/10.1111/joor.12976.
[40] Arakawa I, Igarashi K, Imamura Y, Müller F, Abou-Ayash S, Schimmel M. Variability in tongue pressure among elderly and young healthy cohorts: a systematic review and meta-analysis. J Oral Rehabil 2020:1–19. https://doi.org/10.1111/joor.13076.
[41] Schimmel M, Memedi K, Parga T, Katsoulis J, Müller F. Masticatory performance and maximum bite and lip force depend on the type of prosthesis. Int J Prosthodont (IJP) 2017;30:565–72. https://doi.org/10.11607/ijp.5289.
[42] Makizako H, Shimada H, Doi T, Tsutsumimoto K, Lee S, Lee SC, et al. Age-dependent changes in physical performance and body composition in community-dwelling Japanese older adults. J Cachexia Sarcopenia Muscle 2017;8:607–14. https://doi.org/10.1002/jcsm.12197.
[43] Lee JS, Weyant RJ, Corby P, Kritchevsky SB, Harris TB, Rooks R, et al. Edentulism and nutritional status in a biracial sample of well-functioning, community-dwelling elderly: the Health, Aging, and Body Composition Study. Am J Clin Nutr 2004;79:295–302. https://doi.org/10.1093/ajcn/79.2.295.
[44] Weikamp JG, Schelhaas HJ, Hendriks JCM, De Swart BJM, Geurts ACH. Prognostic value of decreased tongue strength on survival time in patients with amyotrophic lateral sclerosis. J Neurol 2012;259:2360–5. https://doi.org/10.1007/s00415-012-6503-9.