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AMYOTROPHIC LATERAL SCLEROSIS

Combined nutritional, respiratory and functional assessment

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Abstract – Objective: To establish correlations between nutritional, functional and respiratory indices of patients with amyotrophic lateral sclerosis (ALS). **Method:** Twenty patients (13 appendicular – GA and 7 bulbar – GB) were included in the multidisciplinary study at the Neurological Clinic Ambulatory of the University of Campinas Hospital. **Results:** Among the GA type significant correlation was observed between maximal inspiratory (MIP) and expiratory (MEP) pressure (r= –0.76), MEP and pulse oxymetry (r=0.58), MIP and percent weight loss (%WL; r=0.59), and between MIP, total and subscale respiratory scores (ALSFRS-R) with %WL. With regard to the GB, correlation was found between MEP and body mass index (BMI) (r=0.97). In both GA and GB correlations were noticed between the BMI and the variables mass (kg), fat (%), arm and wrist circumference (cm), and tricipital, subscapular and supra-iliac skinfolds (mm), as well as the arm muscle circumference (cm) and fatty arm muscular area (mm^2). **Conclusion:** It is suggested that the application of simple anthropometric measurements could be useful in routine monitoring of patients with ALS.

KEY WORDS: amyotrophic lateral sclerosis, nutritional support, respiratory tests, ALSFRS scale.

Esclerose lateral amiotrófica: correlações dos indicadores da avaliação nutricional, funcional e respiratória

Resumo – Objetivo: Correlacionar os indicadores utilizados na avaliação nutricional, funcional e respiratória de indivíduos com esclerose lateral amiotrófica (ELA). **Método:** Vinte pacientes (13 apendiculares – GA e 7 bulbares – GB) foram incluídos no estudo usando parâmetros nutricionais, respiratórios e escala funcional (ALSFRS-R). **Resultados:** Entre os pacientes do GA, as correlações observadas foram: pressão inspiratória máxima (PI_{max}) e expiratória máxima (PE_{max}) (r= –0,76); PE_{max} e oximetria de pulso (r=0,58); PI_{max} e porcentagem de perda de peso (%PP) (r=0,59); e entre PI_{max}, escore ALSFRS-R com %PP. No GB, houve correlação entre MEP e índice de massa corporal (IMC) (r=0,97). Em GA e GB, observaram-se correlação entre IMC e as variáveis: massa, gordura (%), circunferência braquial e punho, pregas cutâneas tricipital, subescapular e supra-ilíaca, circunferência muscular do braço (cm), área muscular gordurosa do braço (mm^2). **Conclusão:** Sugere-se a aplicação deste conjunto de medidas durante a evolução clínica de indivíduos com ELA.

PALAVRAS-CHAVE: esclerose lateral amiotrófica, suporte nutricional, testes respiratórios, escala ALSFRS-R.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative condition characterized by progressive weakness and amyotrophy due to degeneration of motor neurons. ALS patients usually exhibit progressive disability that requires a multidisciplinary therapeutic approach. Bulbar dysfunction resulting from damage either to corticobulbar pathway or brainstem motor nuclei is one of the most important clinical problems encountered in ALS[1,2]. It is related to dysphagia and respiratory complications, which are major causes of morbidity and mortality in ALS. Decline in respiratory function occurs as disease progresses, due to diaphragmatic fatigue and weakness, atelectasis and broncoaspiration[3,4].

Malnutrition as a consequence of dysphagia may further worsen respiratory function and shorten survival. Abnormalities of the control and strength of the laryngeal

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and pharyngeal muscles may cause upper airway obstruction increasing resistance to airflow[4]. Although ALS patients with bulbar involvement suffer from more severe swallowing problems, "non-bulbar" ALS patients may also have dysphagia[3].

There are few data devoted to the combined assessment of nutritional and respiratory status of ALS patients. In this setting, we studied the nutritional, respiratory and functional profile of a cohort of ALS patients. We looked for correlations between these variables in order to identify determinant factors in the severity of the disease.

METHOD

This is a cross-sectional descriptive study of 20 ALS patients regularly followed at the Neuromuscular Outpatient Clinic of Campinas University Hospital (UNICAMP). The study was approved by the ethics committee of the School of Medical Sciences - UNICAMP and all patients accepted a written consent.

Patients meeting the El-Escorial criteria[5] for defined ALS, either with bulbar or appendicular predominance, regularly followed in the Clinic and without intervening neurological illnesses were included in the study. At the time of enrollment, none of the selected patients presented active heart or lung disease, including pneumonia. They were included regardless of gender or duration of disease. Patients with nasogastric tube or gastrostomy, or on assisted mechanical ventilation were excluded.

Nutritional assessment

We employed the following measures to assess body composition:

Body weight (kg) measured in a platform scale (Toledo do Brasil). Ideal body weight for each individual was defined according to tables of the Metropolitan Life Insurance Company[6].

Height (m) measured in meters. In bedridden or wheel-chair bound patients, it was estimated according to Chumlea et al.[7].

Body mass index[8] (BMI) defined as the ratio of body weight (kg) / squared height (m^2) and expressed as kg/m^2.

Midarm circumference (MAC) was expressed in cm and measured at the mid-point between the olecranon and the clavicular acromium[9].

Wrist circumference (WC) also expressed in cm was measured at the level of radial and ulnar styloid processes around the wrist[10].

Skinfolds (SF): triciptal (TSF), biciptal (BSF), supra-iliac (SISF) and subscapular (SESF) skinfolds were measured in mm in order to classify ALS patients according to estimates of relative body fat[11].

Midarm muscle circumference (MAMC), arm muscle area (AMA) and arm fat area (AFA) obtained from MAC and TSF[10].

Percentage of weight loss (%WL) was determined as follows:

$$\%WL = \frac{usual\ weight - measured\ weight \times 100}{usual\ weight}$$

Usual weight = regular weight reported by the patient before the disease onset; Measured weight = weight of the patient at the time of clinical evaluation.

Individuals with %WL ranging from 5 to 10% were considered to have malnutrition; those with %WL above 10% had severe malnutrition[12].

Classification of nutritional status: we employed the protein-caloric malnutrition score (PCMS)[13] to classify nutritional status of patients. PCMS is based on % ad (per-cent adequacy); IW (ideal weight); TSF (triceps skinfold); MAC (midarm circumference); MAMC (midarm muscle circumference) and calculated as follows:

$$PCMS = \frac{\%ad\ IW + \%ad\ TSF + \%ad\ MAC + \%ad\ MAMC + \%ad\ AMA}{Number\ of\ parameters}$$

Amyotrophic lateral sclerosis functional rating scale

Revised (ALSFRS-R)[14]. This is a questionnaire-based scale for activities of daily living. This scale contains 12 items grouped into three domains that encompass appendicular function (gross and motor tasks), bulbar and respiratory function. Each item has a 5-point scale (0 for unable. 4 for normal) and scores ranging from 0 to 48. Low scores denote a serious disease status.

Respiratory assessment

The strength of inspiratory and expiratory muscles was assessed through maximum inspiratory and expiratory pressures (MIP and MEP, respectively), obtained from residual volume and total lung capacity. A Marshall Town® device (Black and Hyatt)[15] was used to perform the measurements. While seated and using a nasal clamp, patients were instructed to breath as deep as possible in order to determine MIP e MEP. These procedures were consecutively repeated 3 times each. Thirty seconds apart, and the highest values were recorded for analysis. Individuals underwent spirometry in a seated position to quantify dynamic respiratory function. Forced vital capacity (FVC) expressed either as an absolute value or as percentage of the predicted value for age and sex, was recorded for all patients. Pulse oxymetry was accomplished with a Morvia 1001 device.

The patients were evaluated by an interdisciplinary group. The nutritional assessment was done by a nutritionist and the ALSFRS-R and respiratory assessment by physiotherapeutics.

Statistical analysis

We used Kolmogorov-Smirnov test to evaluate whether studied variables presented normal distribution. Pearson and Spearman correlation coefficients were employed to analyze normally and non-normally distributed variables, respectively. Significance level was set at 0.05. Spearman coefficients were considered as follows: 0 to 0.19 – weak correlations; 0.2 to 0.39 – mild correlations; 0.4 to 0.59 – moderate correlations; 0.6 to 0.79 – important correlations; 0.8 to 1 – almost perfect correla-

Table 1. Demographic data (n=20).

	Bulbar group (n=7)		Appendicular group (n=13)	
	Mean±SE	min–max	Mean±SE	min–max
Gender (Male/Female)	4/3		12/1	
Age	50.6±9.9	36–69	45.8±12.6	32–69
Total ALSFRS-R[1]	26.1±1.5	12–45	34.3±7.6	16–43
Bulbar	7.14±2.3	4–10	10.3±1.6	7–12
Appendicular (gross and fine tasks)	8.14±8.5	1–23	12.8±6.14	1–22
Respiratory	10.8±1.8	7–12	11.2±1.6	6–12
Oxymetry	0.94±0.03	0.86–0.97	0.94±0.03	0.87–0.99
MIP[2]	–24.1±17.7 (n=6)	–45; –5	–61. 6±33.6	–135; –25
MEP[3]	35±25.4 (n=5)	10–70	62.3±31.4	10–130
FVC%[4]	54 (n=1)	–	84 (n=9)	52–109

[1]ALSFRS-R, amyotrophic lateral sclerosis functional rating scale; [2]MEP, maximal expiratory pressure; [3]MIP, maximal inspiratory pressure; [4]FVC%, percentage of forced vital capacity.

Table 2. Correlations of nutritional, functional and respiratory indicators of bulbar and appendicular groups.

Correlations	Bulbar group (n=7)		Appendicular group (n=13)	
	r	p–value	r	p–value
Time onset ALS x bulbar score ALSFRS-R[1]	0.9	0.005*	–0.04	0.88
Time onset ALS x total ALSFRS-R	–0.82	0.023*	–0.37	0.206
Time onset ALS x Oximetry	–0.26	0.563	–0.75	0.003*
Time onset ALS x WL[2]	0.73	0.063	0.32	0.296
Respiratory score ALSFRS-R x %WL	–0.33	0.436	–0.59	0.042*
Total ALSFRS-R x %WL	–0.39	0.379	–0.59	0.042*
MIP[3] x Respiratory score ALSFRS-R	0.18	0.72	–0.65	0.016*
MIP x MEP[4]	–0.66	0.219	–0.76	0.002*
MEP x Oximetry	0.63	0.253	0.58	0.034*
MEP x BMI[5]	0.97	0.005*	0.49	0.09

*p<0.05; [1]ALSFRS-R, amyotrophic lateral sclerosis functional rating scale-revised; [2]%WL, % of weight loss; [3]MEP, maximal expiratory pressure; [4]MIP, maximal inspiratory pressure; [5]BMI, body mass index.

tions[16]. SPSS for Windows version 15.0 was employed in the statistical analysis[17].

RESULTS

Table 1 shows the demographic data of the patients enrolled in the study. In 13 patients, limbs were predominantly involved (appendicular ALS - GA), whereas in another 7, was predominantly bulbar (GB). We did not find significant differences regarding duration of disease or age between these groups (Table 1). Patients in the GB group had lower ALSFRS-R scores in comparison to patients in the GA group (54 vs 71% of maximum score).

Correlation coefficients of nutritional (%WL, BMI), functional (ALSRFS-R score) and respiratory (MIP, MEP, pulse oxymetry and FVC) parameters in groups GA and GB are displayed on Table 2. We did not find significant association between %FVC and MIP, MEP and oxymetry (p=0.158; 0.83; 0.246, respectively) in the GA group. In the GB group, however, only one patient was able to perform spirometry, thus precluding the analysis of correlations. In the GA group, there was a significant correlation between MIP and MEP (p=0.002), as well as MEP and pulse oxymetry (p=0.034). Similar findings were not identified in the GB group, since results of respiratory function were less reliable in that group due to the severe weakness of oropharyngeal muscles.

Anthropometric data are shown in Table 3. Nutritional profiles of patients in both groups was similar. There were not significant differences between the GA and GB groups regarding nutritional profiles.

BMI was significantly associated with most nutritional markers both in patients of the GA and GB groups (Table 4).

Table 3. Anthropometric profile of patients with ALS according to the predominance symptoms.

	Bulbar group (n=7)		Appendicular group (n=13)		p*
	Mean	SE*	Mean	SE*	
Height (m)	1.684	0.007	1.71	0.004	0.156
Mass (kg)	63.99	1.38	68.51	1.12	0.356
Body mass index (kg/m^2)	21.97	0.35	23.26	0.36	0.097
Weight loss (%)	17.68	1.19	13.61	0.97	0.708
Fat mass (%)	25.66	0.60	23.72	0.40	0.188
Lean mass (%)	83.95	0.50	83.72	0.51	0.350
Initial arm circumference (cm)	25.94	0.41	26.12	0.36	0.273
Arm circumference (cm)	25.74	0.39	27.46	0.36	0.061
Initial wrist circumference (cm)	15.49	0.12	17.13	0.06	0.131
Wrist circumference (cm)	15.36	0.11	17.68	0.08	0.536
Tricipital skin fold (mm)	14.70	0.47	10.73	0.33	0.971
Bicipital skin fold (mm)	9.30	0.44	6.45	0.19	0.405
Supra-iliac skin fold (mm)	16.30	0.66	16.09	0.73	0.599
Subescapular skin fold (mm)	11.10	0.36	13.32	0.32	0.117
Sum of all skinfolds (mm)	51.40	1.46	46.59	1.37	0.935
Muscle circumference of the arm (cm)	22.22	1.77	24.13	0.28	0.438
Muscle area of the arm (cm)	41.36	2.97	59.75	1.65	0.340
Fat area of the arm (cm)	57.68	1.64	57.92	1.49	0.087

SE*, standard error; p*, Spearman correlation (α= 5%).

Table 4. Spearman correlation coefficients of BMI and other nutritional markers according to the predominance symptoms of the disease.

	Bulbar group (n=7)		Appendicular group (n=13)	
	r	p–value	r	p–value
Height (m)	0.148	0.684	1.38	0.695
Mass (kg)	0.661	0.038*	0.982	0.00*
Weight loss (%)	–0.164	0.651	–0.400	0.233
Fat mass (%)	0.127	0.726	0.834	0.001*
Lean mass (%)	–0.733	0.016	–0.955	0.00*
Arm circumference (cm)	0.912	0.00*	0.815	0.002*
Wrist circumference (cm)	0.215	0.551	0.332	0.319
Tricipital skin fold (mm)	0.209	0.562	0.701	0.016*
Bicipital skin fold (mm)	–0.038	0.918	0.424	0.194
Supra-iliac skin fold (mm)	0.535	0.111	0.748	0.009*
Subescapular skin fold (mm)	0.851	0.002*	0.814	0.002*
Muscle circumference of the arm (cm)	0.845	0.002*	0.811	0.002*
Muscle area of the arm (cm)	0.576	0.082	0.700	0.016*
Fat area of the arm (cm)	0.891	0.001*	0.719	0.004*

*p<0.05.

Among patients in the GA group, the variable that best correlated to BMI was mass (r=0.982), but in the GB group, arm circumference presented the best correlation (r=0.912).

DISCUSSION

Survival time is a major endpoint employed in clinical trials for ALS. Overall, mean survival ranges from 2 to 4 years, although there is great variability among patients[18]. Elderly individuals, women and those with predominance bulbar involvement have shorter survival odds after the onset of the disease[19].

Although FVC has been considered the most reliable

tool to monitor respiratory function in patients with ALS, it is not as useful to estimate strength of respiratory muscles[20,21]. FVC is not a sufficiently sensitive test to detect early respiratory involvement in ALS, and there is only a weak correlation between FVC and parameters such as MIP and MEP[22].

Although respiratory complaints are frequent in ALS, studies on the relationship of dyspnea and objective measurements of respiratory function in the disease are scanty. Melo et al.[23] reported that severity of dyspnea was related to respiratory muscle weakness expressed as abnormal MIP and MEP. Similarly, Dugan et al.[24] found reduced values of MIP and MEP in dyspneic ALS patients. Our data are in accordance with those findings since MIP and respiratory scores of ALSFRS-R, which is a reliable marker for dyspnea in ALS, were significantly correlated (p=0.016). These findings suggest that clinical evaluation and MIP may be useful to monitor the loss of respiratory quality in ALS.

Cedarbaum et al.[14] found that FVC and respiratory scores of ALSFRS-R were related in ALS (r=0.53 e p=0.0001) but this was not replicated in our patients. These authors emphasized that the items dyspnea and orthopnea of ALSFRS-R may be altered in patients with normal FVC. Four patients in the GB group showed respiratory scores below maximum. However, mean FVC was 84% for patients in the GB group. Therefore, dyspnea in some patients with preserved respiratory reserve may be more closely related to factors such as fatigue and bad conditioning.

Malnutrition in ALS is closely associated to dysphagia and thus an early finding in patients with progressive bulbar palsy occurrance[25]. Due to oro-pharyngeal muscle weakness, measurements such as MIP and MEP are less reliable in those patients. Despite this, MEP and BMI were strongly correlated in patients of the GB group (p=0.005).

Both dysphagia and neurogenic muscle atrophy may contribute to the percent weight loss in ALS[26], MIP, ALSFRS-R total score and respiratory sub-score correlated independently with %WL ($p<0.05$) in patients of the GA, but not GB group. This may be explained by the more severe muscular atrophy identified in the GA group (FFM%=79.6 and 84.9, respectively).

There were no significant differences between the GA and GB groups regarding nutritional profiles. BMI was slightly lower among patients in the GB group, but difference did not reach statistical significance. Our data on body mass, BMI, fat%, TSF, MAMC, AMA and AFA were also similar to those found by Stanich et al.[27], in a cohort of patients with ALS from São Paulo (Brazil), suggesting they accurately characterize the disease.

In this series, patients would be classified as eutrophic according to BMI; however, if we take into account the PCMS score, patients would be classified as moderately malnourished (mean PCMS scores of 76.66 and 79.76 in groups GB and GA, respectively). Overall, PCMS is more appropriate than BMI to characterize nutritional status of patients because it includes separately muscle and adipose mass rather than total body mass. We found high %WL values, indicating significant differences between the usual weight and the actually measured weight of the patient at clinical evaluation. Percent WL is a parameter readily determined and useful to assess nutritional status in ALS. BMI should not be the unique marker to assess nutritional status because of the lack of sensitivity to low weight losses, adipose accumulation, lean mass reduction and dehydration, all of which may make it difficult to interpret the results[28-30].

MAC and WC are frequently used in population studies[31]. In our patients, they were tightly related to BMI. Among patients of the GA group, MAC and WC were parameters smaller at the side initially affected by the disease process (mean difference=1.34 and 0.55, p=0.003 and 0.037, respectively). Such an asymmetry may be clinically relevant since it may either overestimate or underestimate the actual nutritional needs of the patients (measurements are usually performed on one side). PCMS also helped to accurately perform nutritional classification of patients with ALS, since parameters employed to calculate this score were correlated with BMI.

There was significant correlation between respiratory parameters, namely MIP and MEP, and ALSFRS-R in both groups, GA and GB. As shown in Table 2, BMI and %WL were also related to the respiratory parameters. In addition, we found significant correlations between BMI and other measures of nutritional status, thus suggesting that these tools might help to prevent morbidity in the disease.

In conclusion, nutritional, functional and respiratory profiles were similar in patients with ALS of either bulbar or appendicular predominance. Nutritional status was tightly related to functional and respiratory disability. Although preliminary, our data indicate that these tools might help to prevent morbidity in the disease.

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