Functional ambulation decline and factors associated in amyotrophic lateral sclerosis

Declínio da deambulação funcional e fatores associados na esclerose lateral amiotrófica

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Date of first submission: November 29, 2021
Last received: May 27, 2022
Accepted: June 24, 2022
Associate editor: Clynton Lourenço Correa

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Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a disabling neurodegenerative disease, which compromises locomotion and functional independence. As the goal of physical therapy is to maintain the individual's locomotion capacity and independence as long as possible, it is necessary to gain a better understanding of the possible factors associated with the loss of this capacity. **Objective:** To evaluate functional ambulation in patients with ALS and possible factors associated with its decline. **Methods:** A cross-sectional study was conducted with sporadic ALS patients. Demographic and clinical/functional aspects were evaluated. ALS Functional Rating Scale-Revised (ALSFRS-R), Functional Ambulation Category, Medical Research Council scale and Fatigue Severity Scale were used. Descriptive and comparative analyses were conducted of the groups capable and incapable of functional ambulation. Binary logistic regression (stepwise forward method) was performed to determine potential factors associated with the loss of functional ambulation. **Results:** Among the 55 patients (mean age: 56.9 ± 11.2 years), 74.5% were able to walk functionally. Differences were found between groups regarding time of diagnosis, number of falls, pain, use of noninvasive ventilation, gastrostomy, ability to turn in bed, mobility aids, home adaptations, functional performance, muscle strength and fatigue. The possible predictors of walking disability were overall muscle strength (OR = 0.837; p = 0.003) and fatigue (OR =1.653; p = 0.034). **Conclusion:** Muscle strength and fatigue are associated with the decline in ambulation capacity in patients with ALS. In view of the complexity of elements involved in walking, further studies are needed to investigate the influence of these aspects in this population.

Keywords: Amyotrophic lateral sclerosis. Fatigue. Functional status. Locomotion. Muscle strength.

Resumo

Introdução: *A esclerose lateral amiotrófica (ELA) é uma doença neurodegenerativa incapacitante, que compromete a locomoção e a independência funcional. Como o objetivo da fisioterapia é manter a capacidade de locomoção e independência do indivíduo pelo maior tempo possível, é necessário conhecer melhor os possíveis fatores associados à perda dessa capacidade.* ***Objetivo:*** *Avaliar a deambulação funcional em pacientes com ELA e possíveis fatores associados ao seu declínio.* ***Métodos:*** *Realizou-se um estudo transversal com ELA esporádica. Aspectos demográficos e clínicos/funcionais foram avaliados. A Escala Funcional de ELA (ALSFRS-R), a Escala de Categoria de Deambulação Funcional (FAC), a* Medical Research Council Scale *e a Escala de Severidade de Fadiga (FSS) foram usadas. Foram realizadas análises descritivas e comparativas dos grupos capazes e incapazes de deambulação funcional. A regressão logística binária (método* stepwise forward*) foi realizada para determinar os potenciais fatores associados à perda da deambulação funcional.* ***Resultados:*** *Entre os 55 pacientes (média de idade: 56,9 ± 11,2 anos), 74,5% eram capazes de deambular funcionalmente. Encontraram-se diferenças entre os grupos quanto ao tempo de diagnóstico, número de quedas, dor, uso de ventilação não invasiva, gastrostomia, capacidade de se virar no leito, auxiliares de locomoção, adaptações domiciliares, desempenho funcional, força muscular e fadiga. Os possíveis preditores de incapacidade de locomoção foram força muscular geral (OR = 0,837; p = 0,003) e fadiga (OR = 1,653; p = 0,034).* ***Conclusão:*** *A força muscular e a fadiga estão associadas ao declínio da capacidade de deambulação em pacientes com ELA. Diante da complexidade dos elementos envolvidos na caminhada, são necessários mais estudos que investiguem a influência desses aspectos nessa população.*

Palavras-chave: *Esclerose lateral amiotrófica. Fadiga. Estado funcional. Locomoção. Força muscular.*

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, neurodegenerative disease of a multifactor etiology that affects upper and lower motor neurons and is ultimately fatal.[1] ALS is considered one of the most disabling chronic degenerative diseases and results in the complete loss of independence and autonomy. The progression of the disease leads to motor changes associated with the loss of strength, balance and coordination,[2] compromising activities that involve locomotion, transfers and self-care. ALS is characterized by a large variety of symptoms, such as muscle atrophy, weakness, spasticity, fatigue, dysarthria, dysphonia, dysphagia and dyspnea,[3,4] as well as non-motor symptoms related to cognitive and psychiatric impairment.[5,6] The evolution of the disease is generally fast, but quite heterogeneous. In most cases, the time between the onset of the first symptoms and dependence on ventilatory support is two to four years.[5,6]

Gait becomes altered throughout the course of the disease. The main changes described in the literature are a reduction in walking speed, increase in variability and longer stride time.[7,8] The loss of walking capacity is one of the most impacting aspects in the lives of affected individuals, as ambulation is essential to movements from one place to another in an independent, autonomous manner.[9] The decline in ambulation results in limitations regarding the functional activities necessary for the maintenance of self-care as well as restrictions to participation in work and social activities, creating a vicious cycle that contributes to even greater declines in functional capacity and quality of life.[10]

Ambulation is a complex process that requires sophisticated control of the neural system and muscles.[9,10] The potential mechanisms of altered gait in ALS are muscle weakness, the reduction in cardiorespiratory fitness and fatigability.[7] However, few studies have addressed the factors actually associated with impaired walking capacity in ALS. One of the central goals of physical therapy for affected individuals is to maintain locomotion capacity as long as possible.[11]

There is a lack of studies that investigate, in individuals with ALS, changes in locomotion, factors related to decline and the ability to maintain ambulation. Knowledge of locomotion characteristics and possible factors associated with changes provide data that can guide the implementation of more effective interventions. Understanding factors associated with changes in locomotion during the progression of the disease could assist in the maintenance of independence for a longer period of time. Therefore, the aim of the present study was to evaluate functional ambulation in patents with ALS and possible factors associated with the limitation of this ability.

Methods

This exploratory cross-sectional study involved the participation of individuals with a diagnosis of sporadic ALS according to the Awaji criteria[4] in care at the neuromuscular diseases outpatient clinic of the university hospital affiliated with Universidade Federal de Minas Gerais (UFMG).

Seventy patients under the care of the medical team between July 2019 and March 2020 with a diagnosis of sporadic ALS were invited to participated in the study, 55 of whom met the selection criteria. The following were the exclusion criteria: 1) diagnosis of familial ALS, flail arm and flail leg variants or other motor neuron disease (progressive muscular atrophy, primary lateral sclerosis) to ensure a more homogenous group; 2) signs and symptoms of dementia screened by the medical team at the neuromuscular disease outpatient clinic; 3) medical history of neurological disease, such as Parkinson's, stroke, acquired brain injury or spinal injury. All participants signed a statement of informed consent. The study received approval from the UFMG institutional review board (certificate number: 08661019.9.0000.5149). All assessments were performed by a trained researcher.

Sociodemographic and clinical characteristics

A questionnaire was used to collect data on sociodemographic and clinical characteristics: age, sex, comorbidities, pain in the previous week (presence and intensity measured using the numerical pain rating scale),[12] medication, ventilation, gastrostomy, hospitalization in the previous year, falls in the previous six months, muscle cramps, mobility (go from sitting to standing, change positions in bed, maintain standing position and walking capacity), use of mobility aids, home adaptations, personal assistance/caregiver and follow-up by a physiotherapist. Information on ALS was also collected: time in years since diagnosis, site of onset of symptoms and use of Riluzole.

Functional ambulation

The ability to walk functionally was assessed in all participants. The participants were divided into two groups based on the capacity for functional ambulation. The Functional Ambulation Category (FAC) was used to assist in the classification. The FAC classifies the ability to walk on a six-point scale according to the amount of physical support required: score zero (nonfunctional ambulator) – subject cannot ambulate or needs the assistance of two or more persons; score 1 (ambulator dependent on level II physical assistance) – subject requires manual contact from no more than one person during ambulation on level surfaces to prevent falling; manual contact is continuous and necessary to support body weight as well as maintain balance and/or assist in coordination; score 2 (ambulator dependent on level I physical assistance) – subject requires manual contact from no more than one person during ambulation on level surfaces to prevent falling; manual contact consists of continuous or intermittent light touch to assist in balance; score 3 (ambulator dependent on supervision) – subject can physically walk on level surfaces without manual contact of another person but, for safety purposes, requires no more than one person to stand guard due to poor judgment, questionable cardiac status or the need for verbal cuing to complete the task; score 4 (ambulator independent only on level surfaces) – subject can walk independently on level surfaces but requires supervision or physical assistance to negotiate stairs, inclines or non-level surfaces; score 5 (independent ambulator) – subject can walk independently on nonlevel and level surfaces, stairs and inclines.[13,14]

Functional assessment - ALS specific questionnaire

The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) was used for the functional assessment and to determine the stage of ALS of each patient. The ALSFRS-R questionnaire uses an ordinal scale to assess capacity and independence on twelve functional activities (speech, salivation, swallowing, handwriting, handling utensils and cutting food, dressing and personal hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea and breathing insufficiency). Each function is scored from zero to four points and the total ranges from zero (severe dysfunction) to 48 (normal).[15] The ALSFRS-R assesses the level of function in four domains: bulbar, gross motor, fine motor and respiratory function.[2,16,17]

Muscle strength

Muscle strength was measured bilaterally and scored on a scale from zero to 5 points using the Medical Research Council (MRC) scale. Four upper limb muscles (wrist extension, wrist flexion, elbow flexion and shoulder abduction) and four lower limb muscles (ankle dorsiflexion, plantar flexion, hip extension and flexion)

were considered. The score of the 16 muscle groups produced an overall strength score ranging from 0 to 80 points.[12,18,19]

Fatigue

Fatigue was assessed using the Fatigue Severity Scale (FSS), which is a nine-item self-report questionnaire to assess the severity of fatigue in the daily life of the respondent. Each statement on the scale is scored from 1 (strongly disagree) to 7 (strongly agree) points. The total is calculated by the average of all items and a score of ≥ 4 indicates the presence of fatigue.[20]

Statistical methods

Descriptive analysis was performed calculating frequency and measures of central tendency and dispersion according to the characteristics of each variable of interest. To identify demographic and clinical differences between the groups with and without functional ambulation, either the chi-square test or Fisher's exact test (if the expected number was less than 5) was used for the comparison of categorical variables, and either the Student's t-test or Mann-Whitney test was used for the comparison of continuous variables with normal or non-normal distribution, respectively. The normality of the data was determined using the Shapiro-Wilk test.

Binary logistic regression analysis was employed to determine potential factors associated with the loss of functional ambulation. The final model was created using the stepwise forward method. Variables that differed significantly between groups or had clinical relevance to the analysis were used as the independent variables (overall muscle strength, time since diagnosis, pain and fatigue). Multicollinearity was tested when selecting the independent variables. All analyses were performed with the aid of SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA) and the significance level was set at 5% ($p < 0.05$).

Results

Among the 55 individuals with sporadic ALS included in the present study (mean age: 56.9 ± 11.2 years), 74.5% (n = 41) were capable of functional ambulation. The clinical and functional characteristics of the participants are displayed in Tables 1 and 2.

Table 1 - Demographic and clinical characteristics of participants with amyotrophic lateral sclerosis

Characteristics#	All participants (n = 55)	Functional ambulator (n = 41)	Non-functional ambulator (n = 14)	p-value
Age (years)	56.9 ± 11.2	56.2 ± 10.8	59.1 ± 12.6	0.406
Male sex	31 (56.4)	26 (63.4)	5 (35.7)	0.071
Time since diagnosis (years)	0.9 (0-6)	0.6 (0-4)	2.5 (0.25-6.00)	0.014*
Site of onset				
Upper extremity	19 (34.5)	14 (34.1)	5 (35.7)	-
Lower extremity	28 (50.9)	19 (46.3)	9 (64.3)	
Bulbar	8 (18.8)	8 (19.4)	0 (0.0)	
Fall in previous six months				
Yes	33 (60.0)	27 (65.9)	6 (42.9)	0.129
Number	1 (0-20)	1 (0-20)	0 (0-4)	0.026*
Pain				
Yes	33 (60.0)	21 (51.2)	12 (85.7)	0.029*
Intensity	3 (0-10)	0 (0-9)	6 (0-10)	0.010*
Comorbidity	30 (54.5)	21 (51.2)	9 (64.3)	0.397
Medication use	49 (89.1)	35 (85.4)	14 (100.0)	0.320
Riluzole use	40 (72.7)	28 (68.3)	12 (85.7)	0.304
Noninvasive ventilation	11 (20.0)	4 (9.6)	7 (50.0)	0.003*
Tracheotomy/mechanical ventilation	0	0	0	-
Gastrostomy	7 (12.7)	2 (4.9)	5 (35.7)	0.009*
Hospitalization in previous year	18 (32.7)	12 (29.3)	6 (42.9)	0.349

Note: #Number (%) or mean ± standard deviation or median (minimum-maximum). *Statistical significance.

Table 2 - Clinical characteristics of participants with amyotrophic lateral sclerosis

Characteristics[#]	All participants (n = 55)	Functional ambulator (n = 41)	Non-functional ambulator (n = 14)	p-value
Mobility aspects				
Sit to stand				
Able without external help	16 (39.0)	16 (39.0)	0 (0.0)	
Unable without external help	28 (50.9)	25 (61.0)	3 (21.4)	-
Unable	11 (20.0)	0 (0.0)	11 (78.6)	
Turn in bed				
Able without external help	30 (54.5)	29 (70.7)	1 (7.1)	< 0.001*
Unable without external help	25 (45.5)	12 (29.3)	13 (92.9)	
Standing position				
Able without external help	25 (45.5)	25 (61.0)	0 (0.0)	
Unable without external help	21 (38.1)	16 (39.0)	5 (35.7)	-
Unable	9 (16.4)	0 (0.0)	9 (64.3)	
Mobility aids	34 (61.8)	20 (48.8)	14 (100.0)	-
Type of mobility aids				
None	21 (38.2)	21 (51.2)	0 (0.0)	
Cane	3 (5.5)	3 (7.3)	0 (0.0)	
Lofstrand crutches	2 (3.6)	2 (4.9)	0 (0.0)	
Axillary crutches	5 (9.1)	1 (2.4)	0 (0.0)	-
Walker	20 (36.4)	5 (12.2)	0 (0.0)	
Manual wheelchair	3 (5.5)	8 (19.5)	12 (85.7)	
Electrically powered wheelchair	1 (1.8)	1 (2.4)	2 (14.3)	
Professional prescription for mobility aid	15 (27.3)	9 (22.0)	6 (42.9)	0.003*
Training for mobility aid	14 (25.5)	8 (19.5)	6 (42.9)	0.003*
Adequacy of mobility aid	21 (38.2)	13 (31.7)	8 (57.1)	0.003*
Time of mobility aid use (months)	3 (0-84)	0 (0-84)	21 (3-60)	< 0.001*
Home adaptation	25 (45.5)	15 (36.6)	10 (71.4)	0.024*
ALSFRS-R total	29.5 ± 10.8	34.0 ± 8.1	16.4 ± 5.9	< 0.001*
ALSFRS-R				
Bulbar	8.6 ± 3.5	9.2 ± 3.1	7.0 ± 3.5	0.035*
Fine motor	5.5 ± 4.2	7.0 ± 7.8	1.1 ± 1.5	< 0.001*
Gross motor	5.3 ± 3.9	7.0 ± 3.0	0.36 ± 0.7	< 0.001*
Respiratory function	10.2 ± 2.4	10.9 ± 1.6	7.93 ± 2.9	< 0.001*
Muscle strength				
MRC global score	39.2 ± 16.2	45.3 ± 12.5	21.3 ± 12.1	< 0.001*
MRC upper limb	18.2 ± 8.6	20.8 ± 7.6	10.6 ± 6.8	< 0.001*
MRC lower limb	20.9 ± 9.7	24.5 ± 7.9	10.7 ± 6.9	< 0.001*
Cramp	39 (70.0)	30 (73.2)	9 (64.3)	0.527
Fatigue				
Yes	25 (45.5)	16 (39.0)	9 (64.3)	0.039*
Total score	3.4 ± 2.2	3.02 ± 2.5	4.6 ± 2.3	0.026*
Physiotherapeutic approach	27 (49.1)	21 (51.2)	6 (42.9)	0.589

Note: [#]Number (%) or mean ± standard deviation or median (minimum-maximum). ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; MRC = Medical Research Council Scale. *Statistical significance.

In the comparison of clinical and functional characteristics between the two groups, differences were found with regards to the time since diagnosis, number of falls, pain, use of noninvasive ventilation, gastrostomy, ability to turn in bed, mobility aids (prescription, training, adjustment and time), home adaptations, functional performance (ALSFRS-R), muscle strength and fatigue (Tables 1 and 2). The group with functional ambulation had a significantly shorter time since diagnosis (median: 0.6 vs. 2.5 years; p = 0.014), lower frequency of pain (51.2% vs. 85.7%; p = 0.029), less use of noninvasive ventilation (9.6% vs 50%; p = 0.003) and lower frequency of gastrostomy (4.9% vs. 35.7%; p = 0.009). The same group also had greater functional capacity, with statistically significant differences regarding the ability to turn in bed (70.7% vs. 7.1%; p < 0.001) and greater overall muscle strength (45.3 ± 12.5 vs 21.3 ± 12.1; p < 0.001). The group with functional ambulation had a higher mean ALSFRS-R score (34.0 ± 8.1 vs. 16.4 ± 5.9; p < 0.001) and this difference was found in all domains (bulbar, fine motor, gross motor and respiratory function). With regards to fatigue, the group with functional ambulation had both a lower frequency (39% vs. 64.3%; p = 0.039) and lower score (3.0 ± 2.5 vs. 4.6 ± 2.3; p = 0.026). The number of falls was higher among the participants with functional ambulation (median: 1 fall vs. 0 falls; p = 0.026).

The degree of walking capacity differed among the individuals with functional ambulation (Table 3). Approximately 39% were capable of walking independently anywhere; 12.2% needed assistance to climb stairs and walk on unlevel surfaces; 24.4% needed verbal supervision; 12.2% required intermittent support from another person; and 12.2% required continuous support from another person for balance and supporting their body weight.

The potential factors associated with the incapacity for functional ambulation were overall muscle strength and fatigue. The binary logistic regression analysis revealed that overall muscle strength (OR = 0.837; p = 0.003) and the fatigue score (OR = 1.653; p = 0.034) were associated with the incapacity for functional ambulation in ALS (Table 4). Greater muscle strength reduced the likelihood of walking disability by 18% and an increase in the fatigue score led to a 1.7-fold increase in the likelihood of walking disability. The other variables (time since diagnosis and pain) were not significantly associated with the outcome and therefore did not remain in the final model.

Table 3 - Functional Ambulation Category (FAC) of functional ambulators in patients with amyotrophic lateral sclerosis

FAC	n (%)
Score 1	5 (12.2)
Score 2	5 (12.2)
Score 3	10 (24.4)
Score 4	5 (12.2)
Score 5	16 (39.0)

Note: Score 1 - ambulator dependent on level II physical assistance; Score 2 - ambulator dependent on level I physical assistance; Score 3 - ambulator dependent on supervision; Score 4 - independent ambulator only on level surfaces; Score 5 - independent ambulator.

Table 4 - Potential factors associated with inability to walk in patients with amyotrophic lateral sclerosis

IV	B (SE)	Wald#	p-value	OR	95%CI
Muscle strength*	-0.178 (0.059)	9.097	0.003	0.837	0.720-0.924
Fatigue score	0.502 (0.238)	4.472	0.034	1.653	1.037-2.633

Note: IV = independent variables; B = estimated coefficient; SE = standard error; #Wald test; OR = odds ratio; CI = confidence interval. *Global score.

Discussion

The decline in walking capacity in individuals with ALS occurs throughout the course of the disease, resulting in the loss of independence, with a considerable impact on participation in society. It is therefore extremely important to understand the possible factors associated with this limitation so that measures can be implemented for the maintenance of ambulation for as long as possible. In the present study, the potential clinical factors related to the incapacity for functional ambulation in the regression model were overall muscle strength and fatigue.

The groups with and without functional ambulation also differed with regards to some clinical and functional aspects, such as the time since diagnosis, use of noninvasive ventilation, gastrostomy, number of falls, use of a mobility aid (prescription, training, adaptation and time), home adaptations, ability to turn in bed, functional performance (ALSFRS-R), pain, muscle strength and fatigue. Declines in functional ambulation, respiratory function and swallowing capacity occur with

the progression of the disease, as the progressive loss of upper and lower motor neuron leads to incapacity regarding responses and muscle control, resulting in the loss of functioning.[21] It was therefore expected that the groups would differ in terms of time since diagnosis, the need for ventilatory support, feeding via gastrostomy and the ALSFRS-R score.

Neurological symptoms related to ALS, such as muscle weakness, imbalance, a reduction in endurance and altered muscle tone, contribute to postural instability and predispose affected individuals to a greater risk of falls.[11] In the present study, no difference in the occurrence of falls was found between the two groups. However, the group with functional ambulation had a higher number of falls than the group without functional ambulation. Individual with ALS who are able to walk are exposed to a greater risk of falling. Moreover, an increase in episodes of falling is found as the disease progresses prior to the loss of ambulation.[22] Falls can lead to negative health outcomes and increase the need for care.[11,22,23] Therefore, it is important for fall prevention measures, such as educational programs, environmental modifications and the prescription of mobility aids adequate to the needs of the individual, to be adopted independently of ambulation capacity.[11,22,23]

The aim of mobility aids is to enhance safety, promote independence and facilitate activities and participation for the longest possible time.[24] However, the use and prescription of mobility aids in ALS has been investigated little. In the present study, less than half of the group with functional ambulation (48.8%) used a mobility aid and the types of devices varied greatly. In the group without functional ambulation, all used a wheelchair for locomotion. The frequency of an aid prescribed by a healthcare provider and training for its use was lower in the group with functional ambulation. Moreover, the device was more likely to be inadequate for the patient's functional status in the group with functional ambulation compared to the group without functional ambulation. These findings demonstrate that, despite the importance of mobility aids for maintaining gait, these resources have not received due attention in clinical practice prior to the accentuated decline in locomotion capacity. Future studies should investigate the association between the adequate prescription of a mobility device and the maintenance of ambulation in ALS.

Pain was another clinical aspect that differed between the groups. The group without functional ambulation had a greater frequency and intensity of pain. The occurrence of pain has been associated with greater disease severity, longer duration of the disease, immobility and muscle dysfunction.[25] However, this is a frequently overlooked symptom that is treated little, especially in more advanced phases of the disease.[25] Pain can lead to a process of immobilization, which can result in more accentuated functional decline. Therefore, the prevention and treatment of pain should be a priority in ALS.

In the group with functional ambulation were found individuals with different degrees of walking capacity. Gait typically becomes altered during the course of the disease, with considerable variability in the gait pattern and different degrees of dependence.[7,8] It is therefore important for future studies to investigate the changes the occur throughout the disease in individuals who are still capable of walking.

Overall muscle strength was associated with walking disability, as greater muscle strength reduced the likelihood of walking disability by 18%. The association between lower limb muscle strength and the decline in gait capacity has been described previously.[26] Jette et al.[26] found that a 46% reduction in predicted lower limb strength independently led to the loss of walking capacity and an 81% reduction led to walking disability. The degree of muscle strength may also be directly influenced by the reduction in muscle mass due to the diminished diameter of muscle fibers, especially type II fibers, which are responsible for fast contractions and the generation of the power necessary for the execution of functional activities.[27]

Studies with different populations have demonstrated that muscle strength is a protective factor against dysfunction, and it has been hypothesized that there is a minimum quantity of muscle strength necessary for gait capacity.[26,27] These findings underscore the importance of maintaining muscle strength in order to prolong functional ambulation in patients with ALS. Studies addressing muscle strengthening in individuals with ALS have demonstrated gains in strength, especially in the early phases of the disease, with less positive results achieved as atrophy progresses.[14,28] Thus, the early implementation of strength training is essential to the maintenance of strength, which can exert an influence on walking capacity. Studies have demonstrated that moderate-intensity muscle strengthening does not have harmful effect and can be used safely.[14,28] However, due to the nature of ALS, the decline in muscle strength will undoubtedly occur even with interventions.

As described above, fatigue was also associated with walking disability in the present sample. The increase in

the fatigue score led to a 1.7-fold increase in the risk of walking disability. Fatigue is considered an important symptom that limits the performance of activities of daily living as well as labor and leisure activities in individuals with ALS.[29,30] This condition is manifested as overall weariness and is reported to be a sensation of exhaustion, excessive tiredness and a lack of energy that tends to worsen throughout the day.[21,29,30] The etiology of fatigue seems to be multifactorial, but is not yet fully understood. Muscle activation dysfunction, deconditioning and psychological factors are among the mechanisms described.[21,29,30] Despite the negative impact of fatigue on ambulation, the investigation of the presence of fatigue and the implementation of interventions directed at this condition are scarce in clinical settings. Relatively simple interventions, such as counseling on energy conservation techniques, rest periods and the use of adaptation equipment and mobility aids, could contribute to the maintenance of functioning in ALS.[11]

The mechanisms behind altered gait in ALS are complex and go beyond the interaction between muscle weakness and fatigue. Other aspects, such as cardiorespiratory fitness, balance, altered muscle tone, inadequate mobility aid, and depression need to be considered and investigated better.

The present study has some limitations. One is the large difference between groups in terms of the number of individuals. The fact that the sample was composed of individuals recruited from an outpatient clinic may have exerted an influence on the greater number of individuals with functional ambulation (n = 41) compared to those without functional ambulation (n = 14). Moreover, the cross-sectional design does not enable identifying changes in walking capacity over time, which limits the findings of the present study. Another point to be considered is the fact that the generic instruments, FAC and FSS, despite being widely used in research, have not yet had their validity and reliability tested for this population.

Conclusion

Muscle strength and fatigue are associated with the decline in ambulation in patients with amyotrophic lateral sclerosis. Considering the complexity of elements involved in walking, further studies are needed to investigate the influence of these aspects in this population, enabling more adequate therapeutic interventions for the maintenance of overall muscle strength, the prevention of fatigue and the prolongation of both walking capacity and independence in these patients.

Acknowledgments

We thank all participants with ALS who agreed to participate in this study, as well to their families; Hospital das Clínicas da UFMG, for the support in the realization of this work; and Pró-Reitoria de Extensão (PROEX/UFMG) and Pró-Reitoria de Pesquisa (PRPq/UFMG) for the financial support.

Authors' contribution

MAA and LCS were involved with the study concept and design, acquisition, analysis and interpretation of data; MCBG and TALP, with study concept and design, analysis and interpretation of data; MFAR and JSA, with the recruitment of subjects and data collection. All authors were involved in the preparation of the manuscript and approved the final version.

References

1. Sandstedt P, Littorin S, Johansson S, Gottberg K, Ytterberg C, Kierkegaard M. Disability and contextual factors in patients with amyotrophic lateral sclerosis - A three-year observational study. J Neuromuscul Dis. 2018;5(4):439-49. DOI

2. Sanjak M, Langford V, Holsten S, Rozario N, Patterson CGM, Bravver E, Bockenek WL, Brooks BR. Six-Minute Walk Test as a measure of walking capacity in ambulatory individuals with amyotrophic lateral sclerosis. Arch Phys Med Rehabil. 2017;98(11):2301-7. DOI

3. Longinetti E, Fang F. Epidemiology of amyotrophic lateral sclerosis: an update of recent literature. Curr Opin Neurol. 2019;32(5):771-6. DOI

4. Castro-Rodríguez E, Azagra R, Gómez-Batiste X, Povedano M. La esclerosis lateral amiotrófica (ELA) desde la Atención Primaria. Epidemiología y características clínico-asistenciales. Aten Primaria. 2021;53(10):102158. DOI

5. Su WM, Cheng YF, Jiang Z, Duan QQ, Yang TM, Shang HF, et al. Predictors of survival in patients with amyotrophic lateral sclerosis: A large meta-analysis. EBioMedicine. 2021;74:103732. DOI

6. Oskarsson B, Gendron TF, Staff NP. Amyotrophic lateral sclerosis: an update for 2018. Mayo Clin Proc. 2018;93(11):1617-28. DOI

7. Hausdorff JM, Lertratanakul A, Cudkowicz ME, Peterson AL, Kaliton D, Goldberger AL. Dynamic markers of altered gait rhythm in amyotrophic lateral sclerosis. J Appl Physiol (1985). 2000;88(6):2045-53. DOI

8. Radovanović S, Milićev M, Perić S, Basta I, Kostić V, Stević Z. Gait in amyotrophic lateral sclerosis: Is gait pattern differently affected in spinal and bulbar onset of the disease during dual task walking? Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(7-8):488-93. DOI

9. Xia Y, Gao Q, Lu Y, Ye Q. A novel approach for analysis of altered gait variability in amyotrophic lateral sclerosis. Med Biol Eng Comput. 2016;54(9):1399-408. DOI

10. Gor-García-Fogeda MD, Cano de la Cuerda R, Carratalá-Tejada MC, Alguacil-Diego IM, Molina-Rueda F. Observational gait assessments in people with neurological disorders: a systematic review. Arch Phys Med Rehabil. 2016;97(1):131-40. DOI

11. Majmudar S, Wu J, Paganoni S. Rehabilitation in amyotrophic lateral sclerosis: why it matters. Muscle Nerve. 2014;50(1):4-13. DOI

12. Hanisch F, Skudlarek A, Berndt J, Kornhuber ME. Characteristics of pain in amyotrophic lateral sclerosis. Brain Behav. 2015;5(3):e00296. DOI

13. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther. 1984;64(1):35-40. DOI

14. Kato N, Hashida G, Konaka K. Effect of muscle strengthening exercise and time since onset in patients with amyotrophic lateral sclerosis: A 2-patient case series study. Medicine (Baltimore). 2018;97(25):e11145. DOI

15. Guedes K, Pereira C, Pavan K, Valério BCO. Cross-cultural adaptation and validation of ALS Functional Rating Scale-Revised in Portuguese language. Arq Neuropsiquiatr. 2010;68(1):44-7. DOI

16. Rooney J, Burke T, Vajda A, Heverin M, Hardiman O. What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2017;88(5):381-5. DOI

17. Franchignoni F, Mora G, Giordano A, Volanti P, Chiò A. Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis. J Neurol Neurosurg Psychiatry. 2013;84(12):1340-5. DOI

18. Shamshiri H, Fatehi F, Abolfazli R, Harirchian MH, Sedighi B, Zamani B, et al. Trends of quality of life changes in amyotrophic lateral sclerosis patients. J Neurol Sci. 2016;368:35-40. DOI

19. Paternostro-Sluga T, Grim-Stieger M, Posch M, Schuhfried O, Vacariu G, Mittermaier C, et al. Reliability and validity of the Medical Research Council (MRC) scale and a modified scale for testing muscle strength in patients with radial palsy. J Rehabil Med. 2008;40(8):665-71. DOI

20. Toledo FO, Junior WM, Speciali JG, Sobreira CFDR. Cross-cultural adaptation and validation of the Brazilian version of the fatigue Severity Scale (FSS). Value Health. 2011;14(7):A329-30. DOI

21. Ramirez C, Piemonte MEP, Callegaro D, Silva HCA. Fatigue in amyotrophic lateral sclerosis: frequency and associated factors. Amyotroph Lateral Scler. 2008;9(2):75-80. DOI

22. Schell WE, Mar VS, Silva CP. Correlation of falls in patients with Amyotrophic Lateral Sclerosis with objective measures of balance, strength, and spasticity. NeuroRehabilitation. 2019;44(1):85-93. DOI

23. Rice LA, Ousley C, Sosnoff JJ. A systematic review of risk factors associated with accidental falls, outcome measures and interventions to manage fall risk in non-ambulatory adults. Disabil Rehabil. 2015;37(19):1697-705. DOI

24. Bertrand K, Raymond MH, Miller WC, Ginis KAM, Demers L. Walking aids for enabling activity and participation: a systematic review. Am J Phys Med Rehabil. 2017;96(12):894-903. DOI

25. Kaido M, Kawashima M, Ishida R, Tsubota K. Relationship of corneal pain sensitivity with dry eye symptoms in dry eye with short tear break-up time. Invest Ophthalmol Vis Sci. 2016;57(3):914-9. DOI

26. Jette DU, Slavin MD, Andres PL, Munsat TL. The relationship of lower-limb muscle force to walking ability in patients with amyotrophic lateral sclerosis. Phys Ther. 1999;79(7):672-81. DOI

27. Wang DXM, Yao J, Zirek Y, Reijnierse EM, Maier AB. Muscle mass, strength, and physical performance predicting activities of daily living: a meta-analysis. J Cachexia Sarcopenia Muscle. 2020;11(1):3-25. DOI

28. Tsitkanou S, Gatta PD, Foletta V, Russell A. The role of exercise as a non-pharmacological therapeutic approach for amyotrophic lateral sclerosis: beneficial or detrimental? Front Neurol. 2019;10:783. DOI

29. Gibbons C, Pagnini F, Friede T, Young CA. Treatment of fatigue in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2018;1(1):CD011005. DOI

30. Lo Coco D, La Bella V. Fatigue, sleep, and nocturnal complaints in patients with amyotrophic lateral sclerosis. Eur J Neurol. 2012;19(5):760-3. DOI