Clinical and epidemiological characteristics of patients with Amyotrophic Lateral Sclerosis (ALS) in central Brazil

Características clínicas e epidemiológicas de pacientes com Esclerose Lateral Amiotrófica (ELA) no Brasil Central

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Objective: This study aimed to evaluate the clinical-epidemiological characteristics of patients with Amyotrophic Lateral Sclerosis (ALS) in the State of Goiás, Brazil. Methods: We conducted a descriptive cross-sectional study to assess medical records of patients with ALS followed-up at the State Rehabilitation and Readaptation Medical Center Dr. Henrique Santillo, Goiânia, GO, Brazil, between 2005 and 2018. In addition, we registered and created a photographic panel with the main clinical findings of ALS cases. Results: From 224 investigated patients, 51.8% were male, and 67.4% manifested the classic form of the disease. Initial symptoms were more frequent in the lower limbs (37.9%), and complications resulted in 45.5% of tracheostomy, 60.3% of gastrostomy, and 49.1% of deaths. Most patients had a five-year survival from the onset of symptoms, and no significant association between the use of non-invasive ventilation and increased survival were found. The analysis of the clinical-epidemiological characteristics showed a more extended time between the first symptoms and the diagnosis of the disease was observed. Conclusion: In this study, the time between the first symptoms and diagnosis was longer than in the literature, resulting in late treatments. In addition, there was no satisfactory result regarding survival with the use of non-invasive ventilation. Therefore, clinical-epidemiological studies of the disease in Brazil, as well as public awareness and training of professionals in recognition of ALS clinical signs will assist in early and more efficient interventions.

Keywords: Amyotrophic lateral sclerosis, Brazil, Cross-sectional study, Epidemiology.

RESUMO

Objetivo: Este estudo teve como objetivo avaliar as características clínico-epidemiológicas de pacientes com Esclerose Lateral Amiotrófica (ELA) no Estado de Goiás, Brasil. Métodos: Foi realizado um estudo transversal descritivo para avaliação de prontuários de pacientes com ELA acompanhados no Centro Médico Estadual de Reabilitação e Readaptação Dr. Henrique Santillo, Goiânia, GO, Brasil, entre 2005 e 2018. Além disso, registramos e criamos um painel fotográfico com os principais achados clínicos dos casos de ELA. Resultados: Dos 224 pacientes investigados, 51,8% eram do sexo masculino e 67,4% manifestavam a forma clássica da doença. Os sintomas iniciais foram mais frequentes em membros inferiores (37,9%) e as complicações resultaram em 45,5% de traqueostomia, 60,3% de gastrostomia, e 49,1% de óbitos. A maioria dos pacientes teve sobrevida de cinco anos desde o início dos sintomas, e nenhuma associação significativa entre o uso de ventilação não-invasiva e aumento da sobrevida foi encontrada. A análise das características clínico-epidemiológicas mostrou um tempo mais prolongado entre os primeiros sintomas e o diagnóstico da doença. Conclusão: Neste estudo, o tempo entre os primeiros sintomas e o diagnóstico foi maior quando comparado à literatura, resultando em tratamentos tardios. Além disso, não houve resultado satisfatório em termos de sobrevida com o uso da ventilação não-invasiva. Portanto, estudos clínico-epidemiológicos sobre a doença no Brasil, bem como a conscientização pública e o treinamento de profissionais para o reconhecimento dos sinais clínicos de ELA, auxiliarão em intervenções precoces e mais eficazes.

Palavras-chave: Esclerose lateral amiotrófica, Brasil, Estudo transversal, Epidemiologia.

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INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that affects upper motor neurons (UMN) in the motor cortex and lower motor neurons (LMN) in the brainstem and spinal cord. Considered the most common form of motor neuron disease (MND), ALS is characterized by a rapid evolution of muscle weakness, and death occurs mainly due to respiratory failure within two to five years from the onset of symptoms.

The multifactorial etiology often allows classifying ALS as sporadic (sALS), while approximately 5 to 10% have an autosomal dominant inheritance, referred to as familial ALS (fALS). Both sporadic and familial ALS have similar clinical manifestations of neuromuscular degeneration. However, the wide variety of clinical characteristics among patients still classifies the disease according to the location of the onset of symptoms.

The classic form of ALS, characterized by initial degeneration of UMN, presents muscle weakness and atrophy, spasticity, and fasciculations. Bulb manifestations, such as dysphagia, dysarthria, dysphonia, and fasciculations of the tongue, are present in the bulbar form of the disease. This manifestation is defined by the degeneration of LMN in the brainstem that consequently impairs the practice of daily activities.

Some manifestations start before the age of 25, characterizing juvenile ALS, a rare form of the disease. Studies have also demonstrated that the development of ALS is related to Parkinson’s and frontotemporal dementia. It is estimated that 10-15% of cases will have a diagnosis of frontotemporal dementia, and an even greater percentage, 35-45% will have mild behavioral and/or cognitive alterations.

ALS is a rare and still incurable disease that mainly affects the elderly aged 50 to 75 years. The disease is 20 to 50% more frequent in men and affects more white individuals. The worldwide incidence is approximately two cases per 100,000 individuals per year, with the prospect of increasing to 40,000 new cases diagnosed in the year 2040.

Population aging contributes to this perspective and culminates in a high socioeconomic burden on global health systems. Approximately £ 1,889 (≈ US 2,482) is spent quarterly on assistance to ALS patients in the United Kingdom, demonstrating that ALS causes significant financial costs to both patients and the healthcare system.

The treatment of the disease is still palliative and limited to the use of Riluzole, approved by the Food and Drug Administration (FDA) in 1995, which increases patient survival by approximately three months. Interventions, such as non-invasive ventilation (NIV), are also used to mitigate the progression of symptoms in cases of day or night hypoventilation.

Tracheostomy, used as ventilatory support and airway management, is also a therapeutic option. However, despite respiratory failure being responsible for more than 80% of deaths among ALS patients, tracheostomy is used less frequently, especially in European and North American countries. Weight loss due to severe dysphagia is also a common manifestation of ALS patients that affects all bulbar patients and approximately 60% of those with the classic disease. In these cases, a gastrostomy is chosen to assist the patient’s quality of life, survival, and nutritional maintenance.

Few studies investigate the clinical and epidemiological profile of ALS patients in Brazil; however, in the State of Goiás, no study was found describing this profile and the evolution of the disease in this population. Thus, this is the first study to evaluate the clinical-epidemiological characteristics of patients diagnosed with ALS in the State of Goiás.

METHODS

A descriptive, cross-sectional study was performed to assess medical records of patients diagnosed with ALS at the neuromuscular disease outpatient clinic at the State Rehabilitation and Readaptation Medical Center Dr. Henrique Santillo (CRER), Goiânia - Goiás, in the Central region of Brazil. Medical records from March 2005 to December 2018 were assessed. The patients included in the study were diagnosed with definitive or probable ALS, following the revised criteria of El Escorial based on symptoms of impairment of UMN and LMN and assisted by electroneuromyography and cranial and spinal magnetic resonance imaging.

Familial ALS was determined when at least one family member (first or second degree) had a confirmed diagnosis of the disease. Participation in the study was voluntary, and all recruited individuals signed informed consent. This project was approved by the Research Ethics Committee of the Federal University of Goiás (No. 2.496.856/2018; CAAE: 79593117.7.0000.5083).
Data on sociodemographic variables, age at onset of symptoms, disease classification, initial symptoms, use of interventions, and death were collected from medical records. All participants were over 18 years old.

In addition, from 2018 to 2019, photographic documentation of patients with ALS was carried out to monitor and record the main clinical signs and interventions characteristic of the disease. The registration was performed by a professional from the health institution, and all participants who agreed to participate signed an Authorization Term for Image Use.

Statistical analysis

The analyses were performed using SPSS software v24.0. Categorical variables were analyzed using descriptive statistics, with a determination of absolute (n) and relative (%) frequency. The time from symptom onset to death, symptom onset to diagnosis, and diagnosis to death were calculated by linear regression analysis, considering the significance level of 5% in all analyses.

RESULTS

Of 224 selected patients, 51.8% were male, and a higher percentage of individuals (45.1%) belonged to the age group between 50-65 years. Sporadic ALS was predominant in the sample evaluated (96.9%), and fALS was diagnosed in 3.1% of the cases. The classic and bulbar forms of the disease were diagnosed in 67.4% and 29.5% of patients, respectively, thus being the most frequent within the classifications under study (Table 1).

We observed that the initial symptoms described in 37.9% of the patients were present in the lower limbs, followed by the involvement of the upper limbs (33.5%). Bulbar symptoms such as dysarthria and dysphagia occurred in 11.6% of cases. The use of interventions, such as tracheostomy and gastrostomy, occurred in 45.5% and 60.3% of cases, respectively, with 49.1% of deaths reported (Table 1). Corroborating the results, the photo panel (Figure 1) shows the main clinical signs found in ALS cases, such as spasticity and atrophy of the upper and lower limbs (Figure 1A and 1B), atrophy of muscles in the anterior trunk (Figure 1D and 1E) and substantial wear of the tongue muscles (Figure 1C), as well as the use of interventions such as gastrostomy and tracheostomy (Figure 1F and 1G).

Concerning the form of the disease to the age of the patients, the distribution revealed classic ALS and bulbar ALS as the most frequent in individuals aged 50 to 65 years (45.7% and 45.5%, respectively). Death was also homogeneously distributed in both forms of classic and bulbar ALS (Table 2).

The time from symptom onset to death was between three and five years for most patients. Lower values were found when analyzing the time from onset of symptoms to diagnosis of the disease (one to two years), as well as from diagnosis to death (two years) (Figure 2).

Additionally, we assessed whether the use of NIV would influence survival, reporting a more significant number of deaths in the first years of using the intervention (Table 3). It was not possible to estimate the association between the time of symptom onset and the age of death (p = 0.62).
### Table 2. Distribution of ALS form according to age and death.

<table>
<thead>
<tr>
<th>Age range</th>
<th>Classic (N: %)</th>
<th>Bulbar (N: %)</th>
<th>Youth ALS (N: %)</th>
<th>Parkinson ALS (N: %)</th>
<th>Dementia ALS (N: %)</th>
<th>Generalized (N: %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>16 (10.6)</td>
<td>3 (3.0)</td>
<td>1 (100.0)</td>
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<td>0 (0.0)</td>
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</tr>
<tr>
<td>40 to &lt; 50 years</td>
<td>20 (13.2)</td>
<td>8 (12.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>50 to &lt; 65 years</td>
<td>69 (45.7)</td>
<td>30 (45.5)</td>
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<td>2 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>65 years and over</td>
<td>46 (30.5)</td>
<td>26 (39.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (100.0)</td>
<td>1 (50.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Death</th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tr>
<td>Yes</td>
<td>76 (50.3)</td>
<td>31 (47.0)</td>
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<td>2 (100.0)</td>
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<tr>
<td>No</td>
<td>75 (49.7)</td>
<td>35 (53.0)</td>
<td>2 (100.0)</td>
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<td>1 (50.0)</td>
</tr>
</tbody>
</table>

ALS: Amyotrophic lateral sclerosis.

### Table 3. Distribution of cases between the time of diagnosis to death and the beginning of non-invasive mechanical ventilation among patients diagnosed with ALS.

<table>
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<tr>
<th>Time between Diagnosis and Death (Year)</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>9</th>
<th>10</th>
<th>20</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>NIV Start time (Year)</td>
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<td></td>
<td></td>
<td></td>
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<td>0</td>
<td>0</td>
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<tr>
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<tr>
<td>Total</td>
<td>17</td>
<td>30</td>
<td>26</td>
<td>14</td>
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<td>1</td>
<td>1</td>
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</table>

NIV: Non-invasive ventilation.

**Figure 1.** Photographic panel showing the main clinical signs and interventions found in ALS patients. A: Spasticity and atrophy of the thenar and dorsal interosseous muscles of the hands. B: Atrophy and spasticity of muscles in the lower limbs and feet in plantar flexion. C: Atrophy and lingual sulcus. D: Atrophy of muscles in the upper limbs and anterior trunk. E: Arm muscle atrophy, also known as Flail-arm syndrome (FAS), an atypical variant of MND; and subcutaneous fat loss with redistribution to the abdominal region. F: Patient undergoing gastrostomy surgical procedure. G: Patient undergoing tracheostomy surgical procedure.
DISCUSSION

Population-based studies reveal that ALS affects more men than women, in the proportion of 1.2–1.5:1, and individuals between 50 and 75 years old\(^2,7,11\). Men were more affected by the disease (51.8%), which is in agreement with the literature. The evaluated sample showed a higher prevalence of ALS in the age group between 50 and 65 years (45.1%). Studies in mixed populations, such as the Brazilian, demonstrate the onset of the disease at around 55 years\(^7\), which explains the involvement of younger individuals in the country, as observed in our study.

This influence of gender and age on the risk of developing ALS is likely due to a neuroprotective factor of endogenous estrogen in women. Relevant fact for the increase of occurrences of the disease in the female sex from the post-menopausal period\(^14\). Gender also influences the clinical manifestation of the disease, in which the bulbar form is more prevalent in females\(^2,12,14\).

The classic form of the disease with initial symptoms, mainly in the lower (37.9%) and upper limbs (33.5%), was found in our study. According to these findings, there was a higher prevalence of the classic form (70.5%). A Brazilian study showed that the initial symptoms of ALS were more expressive in the upper (37.7%) and lower limbs (32.8%)\(^15\). Although Brazil is the fifth largest country in the world, clinical-epidemiological studies, such as that of Prado et al.\(^15\), are scarce.

The main clinical signs and surgical interventions found in patients with ALS were demonstrated in this study. Atrophy of the thenar and dorsal interosseous muscles (the so-called ‘Split hand’), is a typical feature in ALS. The mechanisms underlying this atrophy remain unclear; however, a corticomotoneuronal origin has been described because these muscles receive extensive corticospinal connections and may be subject to the mechanism of glutamatergic excitotoxicity\(^5,16\). This mechanism is due to the accumulation of glutamate, an important excitatory neurotransmitter, whose accumulation in the extracellular environment contributes to neurodegeneration\(^16\).

Atrophy of the tibialis anterior and gastrocnemius muscles of the legs and intrinsic muscles of the feet. Atrophy, fasciculation, and muscle weakness are classified as signs of LMN degeneration. Early in the disease, the involvement of LMN is generally more evident than in UMN\(^5,17\). Atrophy and lingual sulcus were also observed. Supporting the hypothesis of corticomotoneuronal origin, the tongue is disproportionately more affected when compared to other oropharyngeal muscles, especially in patients with bulbar ALS\(^5\).

Atrophy of the muscles of the anterior trunk was also observed, highlighting the atrophy of the supraspinatus, infraspinatus, and deltoid muscles. Consequently, there is an increase in cases of subluxation due to the prominence of the glenohumeral joint\(^5\). In addition, atrophy of the arm muscles, also known as Flail-arm syndrome (FAS), and the loss of subcutaneous fat, with subsequent redistribution of fat to the abdominal region, can be observed. The amount of subcutaneous fat was related to functional status and survival. In contrast, morbid obesity, associated with increased visceral fat, can decrease the survival of patients with ALS. More studies are needed to understand the occurrence of this change in body composition and how it relates to the neurodegenerative process\(^18\).

Finally, gastrostomy, and tracheostomy stand out as the main surgical procedures found. ALS leads to weakness and atrophy of the oropharyngeal and respiratory muscles, triggering dysphagia and respiratory failure, the main causes of death in ALS patients. Respiratory failure usually has a late onset, so most patients are assisted by NIV or undergo tracheostomy to improve and prolong life\(^19\). Dysphagia, in turn, can cause choking, dehydration, malnutrition and weight loss, making gastrostomy one of the main procedures used for the symptomatic treatment of this condition\(^20\).
In our study, although to a lesser extent, there were still forms of ALS associated with Parkinson’s (0.9%) and dementia (0.9%). Studies reveal that approximately 15% of the patients diagnosed with ALS have concomitant frontotemporal dementia\(^1,7,12\). These results are higher than those found in our analyses. Regarding ALS-Parkinson, the information found is rare.

Regarding etiology, 90% of the cases have no defined cause, while 10% correspond to fALS\(^1,15\). Corroborating the description found, our sample revealed similar values. A low frequency of fALS was also found in Ireland (4%)\(^21\) and the Italian regions of Piedmont (3.2%) and Apulia (2%)\(^22\).

Among surgical procedures, tracheostomy is indicated when the patient needs prolonged mechanical ventilation, and to facilitate the removal of secretion and hygiene of the airways, improving pulmonary ventilation and gas exchange\(^23\). In our study, 45.5% of the patients underwent a tracheostomy. Likely, the high rate was associated with the severity of the disease in the patients evaluated, who presented a rapid evolution to respiratory complications.

Gastrostomy intervention was performed in 60.3% of patients. This rate is higher than that found in the study by Kirstein et al.\(^24\) (52.4%). The severity of the disease in the sample analyzed would justify this high percentage, as gastrostomy is probably necessary to achieve the benefits of ventilatory treatment. This intervention used in cases of severe dysphagia improves the nutritional quality of the patients and promotes the survival of six months or more in 75% of the registered cases\(^25\).

Interventions aim to improve the patient’s quality of life. However, ALS shows rapid advance, progressing to death three to five years after the onset of symptoms\(^7\).

Due to its rapid progression, a variation of three to five years was found between the onset of the first symptoms and death in most patients. This finding is comparable to that of Benjaminsen et al.\(^26\), which also revealed a lower mean survival in patients with bulbar ALS (2.4 years). However, approximately 10% of ALS patients can survive over a decade. Thus, variations in the ALS phenotype and natural history influence the reports of disease survival\(^12\).

Studies have frequently reported \(\leq 1\) year between the onset of symptoms and the diagnosis of ALS on average\(^2,28\). However, our findings revealed that the initial symptoms preceded the diagnosis by one and two years, which leads to late treatments.

Most patients with ALS have limited survival after diagnosis\(^27\). Studies report an average lethality of one year up to variations in the average survival when the diagnosis is made under 40 years (4.8 years) or above 60 years (2.6 years)\(^28,29\). The patients examined had an average survival of two years after diagnosis; hypothetically this fact may have occurred due to the severity of the disease of the individuals selected for the study.

Respiratory failure, resulting from progressive diaphragmatic dysfunction, is responsible for the majority of deaths recorded ALS-related deaths\(^11\). Therapeutic interventions, such as NIV, are crucial in the treatment of patients diagnosed with the disease, prolonging survival from six to 15 months in patients without severe bulbar ALS\(^30\).

Thus, although a higher frequency of classic ALS was found in this study, the possible severity of the disease culminated in the early death of patients undergoing NIV (1-year period) regardless of the use of this intervention, noting that the use of NIV did not increase survival of the patients analyzed.

Most epidemiological ALS studies are performed in Europe and the United States. Nevertheless, although Brazil is the fifth largest country in the world, both by geographic area and population, there are few clinical and epidemiological studies on the disease. Considering the socio-economic and population differences among regions of the country, the representativeness of the data exposed in these studies remains inconclusive when characterizing the clinical profile of patients with ALS from other Brazilian regions. Thus, there is a clear need for more clinical and epidemiological studies on ALS in Brazil.

**CONCLUSION**

The evaluation of the patients diagnosed with ALS revealed a clinical profile similar to that reported in the literature. However, the time between the first symptoms and the diagnosis was longer in our study, resulting in late treatments. Since ALS has a rapid progression to respiratory complications, the use of NIV may improve patient survival. However, in this study, there was no satisfactory result in terms of survival with the use of this therapeutic intervention.
Therefore, trained professionals are required to recognize the clinical signs of ALS associated with the dissemination of the disease to raise awareness and reduce the delay in diagnosis. Also, the correct identification of the characteristics of ALS may help the transdisciplinary team carry out early and more efficient interventions.

REFERENCES


Author contributions
DCPB, RPDO, KFS, RMA, LBM, YMFT, AASR and RSS participated in the design, planning, data collection, analysis, and interpretation and contributed to the elaboration, review, and approval of the final version of the manuscript.

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Declaration of interest
The authors declare no conflicts of interest.

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