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Misdiagnoses in a Brazilian population with amyotrophic lateral sclerosis

Erros de diagnóstico em uma população brasileira com esclerose lateral amiotrófica

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects the upper and lower motor neurons. The correct diagnosis at the onset of the disease is sometimes very difficult, due to the symptoms being very similar to those of other neurological syndromes.

Objective This study aimed to analyze the initial manifestations, the specialty of the first physician visited due the initial complaint, the misdiagnoses, as well as the unnecessary surgical interventions in a new ALS Brazilian population.

Methods The medical records of 173 patients with typical ALS were reviewed.

Results The present study demonstrated that other symptoms, besides weakness, were very frequent as initial presentation of ALS, and orthopedics was the medical specialty most sought by patients at the onset of symptoms. Our frequency of misdiagnoses was 69.7%, and in 7.1% of them, an unnecessary surgical intervention was performed.

Conclusions Amyotrophic lateral sclerosis presents a very large pool of signs and symptoms; therefore, there is an urgent need of increasing the disease awareness to other specialties due to the high frequency of misdiagnoses observed in clinical practice.

Keywords
- Amyotrophic Lateral Sclerosis
- Motor Neuron Disease
- Diagnostic Errors
- Unnecessary Procedures

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Resumo

Antecedentes A esclerose lateral amiotrófica (ELA) é uma doença neurodegenerativa que afeta os neurônios motores superior e inferior. O diagnóstico correto no início da doença é, às vezes, muito difícil, pois os sintomas de início são muito semelhantes aos de outras síndromes neurológicas.

Objetivo Este estudo teve como objetivo analisar as manifestações iniciais, a especialidade do primeiro médico visitado devido à queixa inicial, os diagnósticos errôneos, bem como as intervenções cirúrgicas desnecessárias em uma nova população brasileira acometida por ELA.

Métodos Os prontuários médicos de 173 pacientes com ELA típica foram revisados.

Resultados O presente estudo demonstrou que outros sintomas, além da fraqueza, foram muito frequentes como apresentação inicial da ELA, sendo a ortopedia a especialidade médica mais procurada pelos pacientes no início dos sintomas. Nossa frequência de diagnósticos errôneos foi de 69,7%, e em 7,1% deles foi realizada intervenção cirúrgica desnecessária.

Conclusões A ELA apresenta um conjunto amplo de sinais e sintomas; portanto, há necessidade urgente de uma melhor educação de outras especialidades devido à alta frequência de diagnósticos equivocados observada na prática clínica.

Palavras-chave

- Esclerose Amiotrófica Lateral
- Doença dos Neurônios Motores
- Erros de Diagnóstico
- Procedimentos Desnecessários

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder affecting both upper and lower motor neurons, presenting with weakness, atrophy, spasticity, fasciculations and reflexes abnormalities.[1] The diagnosis of ALS is based upon clinical aspects,[2] supported by electromyography and image.[3] However, a definitive diagnosis may be difficult, at least in part due to the non-specificity of the disease manifestations and the lack of a diagnostic biomarker leading to a prolonged period of investigation and a frequent initial misdiagnosis.[4] In this context, these patients are frequently submitted to unnecessary investigations and medical interventions,[4–6] in addition to a heavy emotional distress.[7] On the other hand, an early diagnosis avoids unnecessary investigation and allows an early onset multidisciplinary care, which is known to be associated to a better prognosis, in addition to capacitate the patient to participate in clinical trials, that are becoming more and more frequent.[8]

In this study, we reviewed the initial diagnosis of ALS patients followed at our university hospital.

METHODS

The database of the neuromuscular and neurogenetics clinic of the university hospital of Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (HCFMRP-USP) was retrospectively accessed considering a period of 12 years. All patients included fulfilled the Gold Coast criteria for definite ALS.[9] Patients with autoimmune disorders, hereditary motor neuropathies, and possible and probable ALS were excluded.

Age, sex, and age of onset were determined for epidemiological analysis. For further analysis symptom at onset, the medical specialty of the first physician visited after the initial complain, the first diagnosis, and the surgeries undertaken during the study period were also considered.

All patients underwent rigorous neurological evaluation. Symptoms at onset were characterized as motor and non-motor. Motor symptoms included limb weakness, atrophy, dysphagia, or dysarthria (bulbar), respiratory distress, cramps, and fasciculation. Non-motor symptoms reported included paresthesia, clumsiness, pain, asthenia, and ankle strain. This study was approved by the local ethics committee (11558113.4.0000.5440).

RESULTS

A total of 250 patients diagnosed with ALS were found in the local database considering the selection period. One hundred seventy-three out 250 patients were classified as having a definite ALS. The missing points on the notes were verified by a phone call. There were 103 men and 70 women, and the age at onset ranged from 22 to 82 years old, with a mean of 51 years and a median of 51.9 years.

The initial complaint could be recovered for 171 patients. The most often initial complaint was limb weakness (83 patients, 48.5%), frequently accompanied by other manifestations, such as fasciculations and cramps. Thirty-eight patients (22%) reported atrophy and clumsiness, followed by bulbar onset manifestations (28 patients, 16.8%). In 22 patients (12.8%), the initial manifestations could not be attributed directly to a motor neuron dysfunction. The most frequent was pain (15 patients), localized at the limbs or at the cervical or lumbosacral column. Some other non-specific complaints were asthenia, ankle strain, paresthesias and, very occasionally, dyspnea.

One hundred thirty-eight patients had the spinal presentation (79.8%), including the upper limbs in 72 (42%) and the

lower limbs in 66 (38%); the bulbar presentation was seen in 32 patients (18.5%); the respiratory onset in 2 (1.16%), and 1 patient presented a generalized weakness when first seen (0.6%).

In 99 patients, a clear initial diagnosis and the medical specialty searched by the patient could be established. The 2 most frequent specialties were orthopedics (ankle strains and limb or column pain) for 35 patients (35.4%), followed by neurology in 33 patients (33.3%) (►**Table 1**). The list of the remaining specialists is long: general practitioner, occupational doctor, psychiatrist, geriatrician, gastroenterologist, pulmonologist, endocrinologist, and gynecologist. For the bulbar onset disease, dentists, otolaryngologists, and head and neck surgeons were often sought at the disease onset (►**Table 1**).

Table 1 Amyotrophic lateral sclerosis diagnostic route: medical specialty and diagnosis at the beginning of the disease

Specialty	Number (%)	Mistaken diagnosis (number of patients)
Orthopedist	35 (35.4)	Radiculopathies/vertebral column (17) Repetitive strain injury (4) Joint sprain (2) Hand trauma (2) Carpal tunnel syndrome (1) Median nerve mononeuropathy (1) Fibular nerve injury (1) Surgery trauma (1)
Neurologist	33 (33.3)	Stroke (7) Multiple sclerosis (3) Multiple mononeuropathy (2) Multisystemic atrophy (2) Cervical plexopathy (1) CIDP (1) Garcin syndrome (1) Hereditary spastic paraplegia (1)
General practitioner	10 (10.1)	Depression/anxiety (2) Gastroesophageal reflux (1) Multiple mononeuropathy (2) Parkinson's disease (2)
Otolaryngologist	08 (8.1)	Stroke (2) Dental prosthesis dysfunction (1) Vocal cord injury (1) Gastroesophageal reflux (1)
Head and neck surgeon	02 (2)	Vocal cord injury (1)
Occupational doctor	02 (2)	Depression/anxiety (1) Repetitive strain injury (1)
Psychiatrist	02 (2)	Depression/anxiety (2)
Geriatric	02 (2)	Lung disease (1)
Gastroenterologist	01 (1)	Gastroesophageal reflux (1)
Pulmonologist	01 (1)	Lung disease (1)
Dentist	01 (1)	Dental prosthesis dysfunction (1)
Endocrinologist	01 (1)	Thyroid disease (1)
Gynecologist	01 (1)	Depression/anxiety (1)

Abbreviations: ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory poliradiculoneuropathy.

Amyotrophic lateral sclerosis was the initial diagnosis in only 30 of them (31%), most of them performed by neurologists. Common alternative diagnoses were radiculopathies and other spinal cord disorders (17 patients), occupational lesions (5 patients), and focal neuropathies (2 patients), most of these performed by orthopedists. One patient was submitted to wrist surgery due to "severe carpal tunnel syndrome," and five to cervical spine surgeries. None of them presented benefit with these surgical procedures. Other common initial diagnoses were cerebrovascular disease (nine patients) and psychiatric disturbances (six with depression or anxiety), commonly performed by general clinicians. Most of the patients with bulbar onset disease received multiple diagnoses, including denture prosthesis dysfunction (two patients), gastroesophageal reflux disease (three patients), or a psychiatric condition (►**Table 1**). Only eight patients with bulbar onset received a correct diagnosis when first seen. One of these patients with an initial diagnosis of turbinate hypertrophy was also submitted to nasal surgery.

DISCUSSION

The diagnosis of classical ALS presenting with upper and lower motor neuron signs is straightforward. However, this scenario is different in patients evaluated when motor neuron dysfunction is not clear, and complaints are vague and nonspecific, or the onset manifestations are unusual. In addition, the same manifestations present in the early stages of ALS are shared with several other mimicking diseases, increasing the difficulties.[10] Additionally, it has been recently shown that those professionals who initially see the patients may not be properly prepared to recognize the presence of the motor neuron syndromes.[11]

In the present analysis, we focused on the initial diagnosis ALS patients received, and the medical specialty of the physician in charge of it. Approximately ⅔ (69.7%) of the patients seen in the study period were misdiagnosed. In the literature, this rate varies from 13 to 68.4%.[3,4,6,12–16] Radiculopathy and spinal cord disorders, stroke, depression, repetitive strain injury, and mononeuritis multiplex are some of the most frequent diagnoses received by our patients, similarly to those observed in other studies.[6,13–18] Grouping the similar diagnoses under the same denominator, the main groups were radiculopathies and other spinal cord/spine disorders, neuropathies, stroke, oropharyngeal dysfunctions, and neurodegenerative disorders/systemic diseases. This list is also shared with the same studies listed above.[6,13–18]

This long list of diagnoses is probably associated with the large number of the professionals that have seen these patients. Orthopedists were the most frequent specialists initially searched by these patients, followed closely by

neurologists, and then by a myriad of other specialists. In the study by Kano et al.,[19] more than 50% of ALS patients did not look for a neurologist initially. Similar to our findings, most of their patients had a limb onset disease and were seen by an orthopedist, resulting in a diagnosis delay of more than 10 months.[19] In a recent review about time to diagnosis and diagnosis delay in ALS, Richards et al.[10] found that in most studies, but not in all, time to diagnosis was shorter for those patients seen initially by neurologists. The misdiagnoses were much less frequent, although the final diagnosis may have required a second or even a third neurologist.[10]

Patients with bulbar onset deserve an individual analysis. Although their time to diagnosis is usually shorter,[4,6,20] they are usually seen by a variety of specialists, including dentists, otolaryngologist, head and neck surgeons, and gastroenterologists. This tends to result in unappropriated diagnosis as gastroesophageal reflux, dental prosthesis dysfunction, and vocal cord injury. The same situation has been reported in other studies.[6,21] In addition, symptoms might be remained isolated to the bulbar territory since the bulbar-onset is not uniformly associated with a rapid progression, increasing the average delay between symptom onset and diagnosis.[22]

Misdiagnosis may also imply in unnecessary interventions. In 7.1% of our patients with an initial incorrect diagnosis, a surgery was performed with no apparent benefit. Most of them were spinal cord surgeries, followed by carpal tunnel surgeries. The same has already been described by several other authors. Pinto et al.[23] showed that 111 patients (16.9%) had at least one eligible surgical intervention before disease onset. Srinivasan et al.[24] described 34 cases (13%) of surgeries in a group of 260 ALS patients due a wrong initial diagnosis. Bakola et al.[5] also described that 13 (7.9%) among 164 consecutive patients with ALS underwent unnecessary surgical procedures. As in five of our patients, a spinal surgery was performed in nine of their patients. Another one of their patients suffered a vocal cord polypectomy,[5] a procedure not performed in any of our patients. In three patients, a carpal tunnel syndrome surgery was performed,[5] as in one of our patients.

Pinto et al.[23] suggested that ALS patients who underwent surgical procedures less than 3 months after the clinical disease onset were at risk of a more rapid progression of their disease, in addition to postponing proper diagnosis by approximately 5 to 6 months.[4,5] Srinivasan et al.[24] reported that initial evaluation by a surgeon rather than a neurologist increases the possibility of an unnecessary surgery being performed.

Diagnosing ALS is still based on clinical skills, and there is no doubt it may be a very difficult task at the very early stages of the disease. However, according to Poon et al.,[25] 95% of the diagnostic problems are, in general, related to physician cognitive error that results from lack of knowledge about the disease and inadequate decisions, including investigation strategy and inappropriate interpretation of the results. A poster presented at the 2021 American Academy of Neurology arrived to the same conclusion.[11] It seems that the problem relies in not recognizing the motor neuron syndromes themselves, not in the differential diagnosis between the different motor neuron diseases. This observation probably explains the absence of important differential diagnosis that should be considered, including multifocal motor neuropathy and late onset spinal muscular atrophies.

It seems to us that ALS teaching should receive more attention at medical schools and resident training programs. Additionally, the referring system to a neuromuscular center should be optimized as it has been demonstrated that this action improves diagnosis and decreases the time spent on it.[26]

Authors' Contributions

VB: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, and writing - original draft; VPC: data curation, formal analysis, investigation, validation, and writing - review & editing. JOR: data curation, formal analysis, writing - review & editing; VDM, PTO, CFRS: data curation, formal analysis, and investigation; VASS, LFPB, PJT: data curation, validation, writing - review & editing; ACJS: data curation, visualization, writing - review & editing; WMJ: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, writing - review & editing.

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Conflict of Interest

The authors have no conflict of interests to declare.

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