Amyotrophic Lateral Sclerosis and Cervical Myelopathy overlap: a concise review for the spine surgeon

Sobrepósio de Esclerose Lateral Amiotrófica e Mielopatia Cervical: uma revisão concisa para o cirurgião de coluna

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ABSTRACT
Amyotrophic Lateral Sclerosis is a progressive condition caused by motor neuron deterioration in the spinal cord and brain. Cervical spondylotic myelopathy is a secondary spinal cord dysfunction, non-traumatic and progressive. Due to their similar initial symptoms and higher incidence in older individuals, it is not uncommon for an overlap of amyotrophic lateral sclerosis and cervical spondylotic myelopathy. The purpose of this paper is to differentiate amyotrophic lateral sclerosis of cervical spondylotic myelopathy and to elucidate, if possible, the overlap presentation of them. In summary, the amyotrophic lateral sclerosis and the cervical spondylotic myelopathy occur in similar epidemiology and can co-occur in almost half of amyotrophic lateral sclerosis patients. Their diagnosis must consider imaging exams, symptoms and clinical red flags that help to differentiate these two conditions, thus avoiding iatrogenic issues and misdiagnosis, which are associated with worse prognosis, inappropriate surgeries, and higher costs in healthcare.

Keywords: Amyotrophic lateral sclerosis; Spine surgery; Cervical myelopathy

RESUMO
A esclerose lateral amiotrófica é uma condição progressiva causada pela deterioração do neurônio motor na medula espinhal e no cérebro. A mielopatia espondilótica cervical é uma disfunção medular secundária, não traumática e progressiva. Devido aos sintomas iniciais semelhantes e maior incidência em indivíduos mais velhos, não é incomum a sobreposição de esclerose lateral amiotrófica e mielopatia espondilótica cervical. O objetivo deste trabalho é diferenciar a esclerose lateral amiotrófica da mielopatia espondilótica cervical e elucidar, se possível, a apresentação sobreposta destas. Em resumo, a esclerose lateral amiotrófica e a mielopatia espondilótica cervical ocorrem em pacientes com epidemiologia semelhante e podem coexistir em quase metade dos pacientes com esclerose lateral amiotrófica. O diagnóstico deve considerar os exames de imagem, sintomas e alertas clínicos que ajudam a diferenciar essas duas condições evitando, assim, iatrogenias e erros de diagnóstico, que estão associados a pior prognóstico, cirurgias inadequadas e maiores custos no atendimento.

Palavras-Chave: Esclerose lateral amiotrófica; Cirurgia na coluna; Mielopatia cervical

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INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive condition caused by the deterioration of motor neurons in the spinal cord and brain, which epidemiology is large but geographically limited. In a literature review made by Chiò et al., the most prevalent mean age of ALS onset was 62 years. ALS has a clinical spectrum that englobes spasticity, muscle atrophy, fasciculations, facial weakness, low palatal elevation, dysarthria, tongue fasciculations atrophy, slow speech, palm omental, and jaw jerk reflexes, as well as frontotemporal dementia. Cervical Spondylotic Myelopathy (CSM) is a non-traumatic and progressive secondary spinal cord dysfunction. According to Young, it is the most common cause of spinal cord dysfunction in adults. It presents clinical motor manifestations, similar to ALS symptoms, except for the absence of the bulbar deficits and frontal dementia.

Due to their similar initial symptoms and higher incidence in older individuals, it is not uncommon an overlap of ALS and CSM. When that happens, it can be late for the proper ALS diagnosis, resulting in inadequate treatment and, consequently, a possibility of iatrogenic action. The purpose of this paper is to differentiate ALS from CSM and to elucidate, if possible, their overlap presentation.

MATERIAL AND METHODS

A non-systematic review was performed with search on public databases: PubMed, Medline, ScienceDirect, SciELO and Cochrane. The searching process was performed using keywords related to Amyotrophic Lateral Sclerosis, Cervical Spondylotic Myelopathy and overlap of Amyotrophic Lateral Sclerosis and Cervical Spondylotic Myelopathy. The most relevant papers written in English were selected.

RESULTS

Amyotrophic lateral sclerosis

ALS is a motor neuron disease (MND) characterized by degenerative changes of upper and lower motor neurons with the involvement of the brainstem and multiple spinal cord regions of innervation. ALS is caused by specific mechanisms of neuronal death that are currently unknown. Evidence supports the presence of autoimmune mechanisms that contribute to ALS pathogenesis.

Many clinical presentations of ALS have been described, including lower motor signs like weakness in members, muscle atrophy and fasciculations. Also, upper motor signs like spasticity, facial weakness, low palatal elevation, dysarthria, tongue fasciculations and tongue atrophy. Bulbar signs involve slow speech and palm omental and jaw-jerk reflexes. According to Picher-Martel et al., up to 50% of ALS patients may have symptoms of frontotemporal dementia, which include personality change, behavioral abnormalities, language dysfunction, and memory impairment.

Approximately 30% of patients with ALS have a cognitive impairment, and 10% of them have frontotemporal dementia, mostly the behavioral variant. The cognitive profile of ALS patients presents with deficits in fluency, language, social cognition, executive functions, and verbal memory with sparing of visual perception. The higher-level executive impairment does not follow the same rate of declines as physical disability. Scientific evidence reveals that the relative resistance of pure oculomotor function is an objective mean of assessing extra motor cerebral involvement in ALS.

Diagnosis of ALS is primarily determined by clinical manifestations, electromyography (EMG) and laboratory testing. It requires at least one of the following: the progression of upper motor neurons and lower motor neurons dysfunction in at least one limb or body region or lower motor neuron dysfunction in 1 region identified by clinical examination and/or by EMG in 2 regions (lumbosacral, bulbar, thoracic, cervical). The EMG findings consist of sharp waves and/or fibrillation and neurogenic potentials. Laboratory tests are done in patients with ALS to exclude other conditions.

ALS has no curative treatment, and there are no studies with significant scientific evidence for interventions to manage the symptoms resulting from lower motor signs. The cornerstones of the management of ALS patients are focused on symptom control: drug therapy in case of pain and/or spasticity, mechanical ventilation for supporting respiratory function, treatment for sialorrhea, enteral tube feeding for supporting nutrition, therapeutic exercise, and multidisciplinary care.
Cervical spondylotic myelopathy

Cervical Spondylotic myelopathy (CSM) is in the group of non-traumatic spinal cord injuries (NTSCI), which epidemiology varies around the globe. In a literature review made by New et al., the vertebral column degenerative disorders, including CSM, contribute to 64% of the cases of NTSCI in North America, while in Europe, the incidence is 31%; in North Africa/Middle East is 27%. In Asia, the South shows 16%, the Pacific 59%, Australasia 22%, while in Southwest and Oceania there are no numbers. Moreover, finally, Africa brings 27% in the East, 13% in the East, 22% in the West, and 4% in the Southern. Latin America has no data in this study. Thus, there is a lack of data on the exact incidence of CSM, with few population-based studies, except for those covering rates and discussions on surgical treatments of the condition.

CSM is caused by non-traumatic, progressive, and chronic cord compression. In other words, it is a secondary spinal cord dysfunction, which involves spasticity, hyperreflexia, neck pain or stiffness, wide-based ataxic gait, ascending paresthesia in the upper or lower extremities, lower extremity weakness, finger/hand clumsiness, pathologic reflexes, clonus and Babinski sign. Besides, in severe disease, there is a sphincter dysfunction. Degenerative disorders are more common at C5 and C6 or C6 and C7.

Diagnosis is suspected by one or more symptoms between hand clumsiness, gait imbalance, numbness, weakness, and bladder dysfunction besides cervical spinal cord signs like fine motor dysfunction of the hands, hyperreflexia, gait ataxia, sensory deficits, and focal weakness. Still, one must have the proof of compression on MRI, which is the standard criterion for current diagnosis, made by the view of the spinal cord and nerve. Computed tomography and radiographs are helpful only to bring information about dynamic changes, quality, and bone alignment, which can be used for surgical guidance. Electromyography, likewise, holds value in the differential diagnosis of other neurological disorders, excluding the hypotheses of peripheral disorders, neuropathy, amyotrophic lateral sclerosis, and multiple sclerosis. Furthermore, finally, the somatosensory evoked potential, due to the more direct assessment of spinal cord dysfunction, can collaborate to CSM diagnosis, as Milligan and the authors approached it in their review.

There are no studies with significant scientific evidence for its determination regarding treatment, but it is known that Cervical Spondylotic Myelopathy is a progressive disease. Therefore, at some point in the evolution of the disease, it will require surgical intervention, even with conservative treatment at first. Instead, it is empirical and presents scientific scarcity for further protocol, being made from physiotherapy, immobilization through the cervical collar, massages, medication with anti-inflammatories, and the removal of high impact activities. In surgical treatment, functional and clinical improvement are achieved, with some authors even indicating it for all patients diagnosed with CSM.

An overlap of CSM and ALS is not uncommon because they are two conditions with a higher incidence in older individuals. One study shows that 4.2% of patients with ALS are submitted to a surgical procedure before diagnosis. Retrospectively, 81% of patients' symptoms were classified as clearly related to ALS. An important feature was that unilateral foot drop represented the symptom that leads to surgery in 21% of the cases.

In a large national study in South Korea, it was found that ALS account for 0.19% of all myelopathies diagnosed patients, but 41.9% of ALS patients had concomitant myelopathy. CSM accounted
for 10% of these cases and associated higher surgery rates among other myelopathies diagnosed22.

In another study, Yamada et al.23 found similar results with a prevalence of 48% of CSM in patients who have already ALS diagnosis, showing that the overlap of the conditions is common, and the presence of one of them does not exclude the diagnosis of the other one. Another study found that 13% of patients with ALS undergo unnecessary surgery for many reasons, including CSM before ALS diagnosis24.

A more recent study with a larger sample found that 8.6% received inappropriate surgery, with CSM being the second more common reason before lumbar spine surgery. Interestingly, most of the patients (41/43) who undergo surgery had a limb onset ALS, and the other two patients with a bulbar onset had a cervical spine one25.

In the study of Kim et al.22, it was found that 10% of patients with ALS undergo surgery, with the cervical spine being the second most common reason. In this study, it was found that 11% of the patients underwent conservative treatment for their symptoms, with a precise diagnosis made just for 24% of them. The other ones received treatment for their symptoms only26.

Patients with ALS and myelopathy have higher surgery rates than patients with myelopathy isolated, showing that symptoms severity can mislead to inappropriate surgery22. A crucial piece of data found by Cellura et al.27 brings that CSM was the most common misdiagnosis in ALS patients made by a neurologist, showing that even fellowship-trained neurologists are prone to diagnostic confusion between ALS and CSM. On the other hand, ALS diagnosed patients that had a cervical disease, although unusual, have been reported as well. In addition, patients first diagnosed with ALS were further evaluated to have CSM from various causes28.

Surgery had no benefits in 89% of patients with ALS, and, obviously, even in the tiny sample that did refer to any benefits, these benefits were promptly overshadowed by ALS progression. Furthermore, the benefits of surgery in the small responsive sample were restricted to pain symptoms1.

Clinical, electrodiagnosis, and other differentiation tools
It is essential to address that sensibility symptoms are well-known differentiators between ALS and CSM1. However, the important overlap of the two conditions can shadow these differences because ALS patients can have sensibility symptoms, especially pain due to muscle atrophy and weakness29 or caused by CSM itself. Therefore, a careful sensory, physical examination can help to show a spine level characteristic pattern and help to support CM diagnosis over ALS, although it should not be the only sign to close the diagnosis30,31.

With that in mind, it is essential to remember that CSM can have a pure motor onset with no sensory symptoms, which, in this setting, should be borne in mind a particular CSM phenotype, the Cervical Spondylotic Amyotrophy (CSA) that presents with no sensory signs and is associated with upper limb atrophy30,32. In these cases of CSA, the disease tends to be restricted to one upper limb, although bilateral disease can be present, and there is not such atrophy or symptomatology in the lower limbs32. In addition, the hand muscle atrophy pattern can help to differentiate ALS and distal type CSA33.

In cases with no sensory affection and only motor presentation, the differentiation of ALS from CSM is clinically easier to be made when patients have a bulbar onset. In these cases, the misdiagnosis can occur but it is rarely made26. The problem is that only 23% of ALS have bulbar onset in disease, although bulbar symptoms are common with disease progression and should be actively investigated in older patients reaching a spine surgeon for cervical pathology complaints with limb weakness3.

Other symptom that may help differentiate ALS from CSM is sphincter dysfunction, that points towards CSM in detrimental to ALS30.

Although it is still challenging to be evaluated in inexperienced hands, an emerging picture that is growing is that of cognitive and executive function alterations in ALS3. As a neurodegenerative condition that shares pathophysiological mechanisms with frontotemporal dementia, ALS when presented with this board can be helpful in a diagnostic challenge between ALS and CSM. Among the signs, it presents deficits in verbal fluency, semantic memory, and in almost every other cognitive domain29,34.
In this field, executive dysfunction – eye-tracking alterations, anti-saccadic tests, and other oculomotor alterations – can be altered in ALS patients compared to controls. Therefore, it may pose an additional sign to differentiate ALS and its mimics, even though further studies results are needed.

Usual imaging studies should not differentiate ALS and CSM once the overlap between these conditions is not uncommon. However, diffusion coefficient in MRI evaluation apparently can differentiate CSM from ALS, as demonstrated in a study conducted by Koike et al.

The main exam used to differentiate ALS and CSM is the electroneuromyography (EMG). With that aim, especially in lower limbs, EMG can show lower motor neuron degeneration in areas with clinically preserved function. Important sensory nerve conduction alterations are not uncommon in ALS and should not exclude the diagnosis when present.

Hand muscle's pattern of affection in EMG is different in ALS and CSA and can help to differentiate the conditions. The ulnar/median compound muscle action potential (CMAP) ratio is a helpful tool as well. It is customary in patients with CM and less in patients with motor neuron disease. The repetitive nerve stimulation with CMAPs decrements in at least one proximal muscle is again much more common in ALS patients (91%) than CSA patients (32.6%).

In a recent study, Zheng et al. evaluated the motor unit number index (MUNIX) to quantify the split hand phenomenon to help to differentiate CSA and ALS. The authors found a larger area under the curve using MUNIX when compared to CMAP.

**DISCUSSION**

ALS and CSM are conditions that occur in similar patient's epidemiology and can co-occur in almost half of ALS patients. Once ALS is an inexorably severe condition, surgery in these patients brings no results except diagnostic delay and an iatrogenic procedure. Surgery is associated with diagnostic delay as well.

As exposed earlier, ALS diagnosis is not simple, and confusion with CSM is not restricted to a single specialty and occurs even with fellowship-trained neurologists.

Limb-onset disease accounts for significant diagnostic errors and a higher risk of surgery. Specifically, orthopedists were associated with diagnostic delay in limb onset ALS patients, and it could be associated with a higher surgery rate in patients with ALS overlapped with CSM.

Even though ALS is an incurable condition nowadays, multidisciplinary care in reference is associated with lower costs in disease conduction and better outcomes for the patients.

This fact highlights the importance of being aware that symptoms can help to differentiate cervical spine affections from ALS, since spine surgeons are frequently the first or second physicians seen by an ALS patient. In addition, by relying solely on imaging techniques to diagnose, CSM can severely affect patients if they have ALS overlapped. Thus, spine surgeons should be aware of clinical aspects that help to differentiate these two conditions and their significant EMG alterations, thus preventing unnecessary surgery and improving care in such burdensome conditions.

Importantly, when facing a patient with signs of MND which might be attributed to a cervical myelopathy, the Ockham rule doesn't fit. Therefore, the only and simplest answer that addresses all the symptoms is perhaps the wrong one.

**CONCLUSIONS**

In conclusion, imaging studies cannot be the only reliable exam to diagnose CSM, especially in patients with suspected ALS. Misdiagnosis is associated with worse prognosis, inappropriate surgeries, and higher costs in ALS patients' care.
REFERENCES


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