Case Reports in Neurology

Case Rep Neurol 2021;13:145–156

DOI: 10.1159/000512810
Published online: March 4, 2021

Case Series – General Neurology

ALS Mimics due to Affection of the Cervical Spine: From Common Compressive Myelopathy to Rare CSF Epidural Collection

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Keywords
Amyotrophic lateral sclerosis · Mimic · Cervical spine · Myelopathy · Diagnosis

Abstract
Amyotrophic lateral sclerosis (ALS) is a clinically heterogeneous disease, with chameleon presentations and several mimics. Considering the poor prognosis of ALS, their precise and timely identification is pivotal. Affection of the cervical spine represents one potential source of ALS mimics that should never be missed, since it is potentially treatable. We hereby present 5 cases initially diagnosed as ALS but eventually found to have different kinds of cervical spine affection, from a common compressive myelopathy to a rare space-occupying cystic fluid collection.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a clinically heterogeneous disease with chameleon presentations and several mimics. Although being relatively rare, with a reported population incidence of 1.5–2.5/100,000 per year [1], giving its poor prognosis, it is of substantial importance that it be not confounded with other, potentially treatable, medical conditions.

The most distinct feature of many ALS mimics is slow progression over time, with symptom onset starting up to 12 months before the diagnosis. Therefore, the speed of symptom worsening may represent a helpful detail, but sometimes also a misleading element, due to the existence of rare, slowly progressive variants of motor neuron disease. According to the El Escorial criteria, the diagnosis of ALS is based on neurological examination and electrophysiological study, with highly sensitive and specific biomarkers still lacking; therefore, even nowadays, misdiagnosis of ALS remains a relevant issue, with about 10% false diagnoses [2].

One of the most common differential diagnoses from ALS are cervical myelopathies (CM), especially the degenerative ones (DCM) [3], where spondylotic changes lead to chronic compression of the spinal cord. The neurological manifestations of DCM usually include neck pain, sensory alterations such as hand numbness and paresthesia, motor dysfunction with loss of fine dexterity, amyotrophy and weakness of both the upper and the lower limbs, gait difficulties, Lhermitte's phenomenon, and sphincter incontinence. The progression of symptoms in case of DCM is highly variable, as they can remain stable over time, worsen in a slowly progressive fashion, or, rarely, even improve.

In certain circumstances, cervical spondylosis may present with so-called dissociated motor loss (DML), characterized by an isolated intradural compression of multiple motor roots, without damage to either the spinal cord or the sensory roots. First described by Keegan in 1965 [4], this condition is also known as cervical spondylotic amyotrophy, because it is characterized by a slowly progressive amyotrophy with weakness of the proximal extremity of one or both upper limbs, often preceded by a transient period of shoulder pain without sensory loss [5].

Another rare cause of CM is Hirayama disease (HD) [6, 7]; this is a self-limiting CM resulting from spinal cord compression by the posterior dural sac during neck flexion and primarily affecting adolescent males. Patients usually present with insidious and progressive, unilateral muscular atrophy and weakness of the upper limb extremity (sometimes bilaterally asymmetrically), followed by spontaneous arrest usually within several years. This condition may initially arise suspicion of ALS, but the early onset and the self-limiting course help distinguish it, together with several other clinical findings (albeit not always present) such as oblique amyotrophy, cold paresis, contraction fasciculations, and absence of upper motor neuron (UMN) signs. Due to their similarity to progressive muscular atrophy, both the DML variant of DCM and HD represent examples of how a dedicated imaging study is necessary in case of ALS suspicion to rule out any intradural or extradural compression and to achieve the correct diagnosis.

Among other kinds of cervical spine affection, a rare congenital or acquired condition that can mimic motor neuron disease is also represented by syringomyelia [8], especially when structural malformations associated with Arnold-Chiari syndrome are absent. In any case,

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even though syringomyelia may present with atrophy and weakness, it is often characterized by a dissociated sensory loss, a slower disease progression, and a younger age at onset than is ALS [8]. We hereby present 5 clinical cases, with the aim of illustrating some examples of ALS mimics due to cervical spinal cord affection.

Case Report

Case 1

A 44-year-old man was examined for a 2-year history of gait difficulty and distal weakness of the right upper limb. The neurological examination revealed impaired fine motility of both hands, atrophy of the right first dorsal interosseous muscle, proximal muscle atrophy and brisk deep tendon reflexes of both upper limbs, a positive Hoffmann sign bilaterally, and very brisk reflexes of the lower limbs with sustained ankle clonus bilaterally. Paraparetic gait could be recognized. The EMG study confirmed abundant spontaneous muscle activity and fasciculations throughout the upper limbs; furthermore, it also detected signs as of a slight radiculopathy of the C7-C8-T1 roots. A complete spinal cord MRI with gadolinium documented a severe spondylotic myelopathy of the cervical spine along the C4–C6 tract, with a shrunken spinal cavity and a spinal cord impingement (Fig. 1a). Thus, the patient was addressed to receive surgical treatment of the vertebral spondylosis.

Case 2

A 74-year-old man presented with a 5-month history of progressive weakness of all four limbs such that he had recently started using crutches for walking. On questioning, additional symptoms emerged: a 1-month history of shortness of breath, particularly on efforts, lower back pain, and episodic dysesthesia of the distal upper extremities.

On neurological evaluation, global weakness was appreciated, with severe weakness on the bilateral grip strength test and moderate right thenar muscle atrophy. No fasciculations were detected. Deep tendon reflexes were normal in the upper limbs, whereas they were brisk at the knees bilaterally, with normal plantar reflexes. Sensory testing was normal. Finally, a paraparetic gait was present. An ALS diagnosis was initially hypothesized.

An EMG study was carried out; the needle part showed signs of a chronic and diffuse neurogenic damage with active denervation and fibrillations at the first dorsal interosseous muscle of the right hand. The EMG neurographic testing evidenced diffuse slowing of both motor and sensitive action potentials. A brain MR scan described initial widening of both temporal horns. Cervical, dorsal, and lumbar spine MRI depicted multiple disc protrusions with reduction of the vertebral cavity and concentric compression of the spinal cord (Fig. 1b). The patient was surgically treated after a couple of months.

Case 3

A 46-year-old man presented with a 6-month history of progressive right upper limb muscle atrophy and weakness. The deltoid and triceps muscles were especially involved. Neither neck pain nor incontinence was present. Deep tendon reflexes were diffusely brisk. A

diagnosis of possible ALS was initially considered. The EMG study suggested chronic neurogenic damage primarily involving the distal extremity of the right upper limb.

Complete spinal MRI showed a very unusual ventral extradural intraspinal fluid-filled collection that extended from C2 to L4, with displacement of the C6–T1 tract of the spinal cord towards the right (Fig. 2). A dynamic CT myelogram failed to identify any dural defect; therefore, no surgical procedure was performed.

Case 4

A 20-year-old man complained of a sudden remote fine motor difficulty in both hands, followed by slowly progressive muscle wasting of the upper extremities. After 20 years, the motor impairment and the muscular atrophy had very slowly progressed to all four limbs, even though the left side remained the more affected one.

At the age of 42 years, the patient underwent his first neurological assessment together with an EMG, whose findings were consistent with a diagnosis of possible ALS. Therefore, he was started on riluzole.

A second EMG, performed 3 years later, was consistent with a diagnosis of definite ALS. At the age of 53 years, the patient was admitted to our neurology department for a thorough functional status assessment. The neurological examination evidenced bilateral severe motor impairment with both distal and proximal muscle atrophy, especially on the left side; absent deep tendon reflexes on both upper limbs and a negative Hoffmann sign bilaterally; and lower limb spasticity, associated with brisk reflexes, sustained ankle clonus, and a positive Babinski sign bilaterally. A paraparetic gait was present during ambulation. No dyspnea, dysarthria, and dysphagia were reported. Moreover, impairment of thermal sensitivity throughout the four limbs and the trunk was evident on neurological examination, confirming the history finding of several recent burns. A new EMG study confirmed abundant spontaneous muscle activity and fasciculations throughout all four limbs, especially in the upper ones.

A complete spinal cord MRI with gadolinium documented the presence of a wide syrinx within the spinal cord around the central canal from the cervical to the lumbar metamers (Fig. 3). The patient was therefore addressed to receive surgical treatment with syringoperitoneal shunting. The clinical manifestations and radiological findings improved after the intervention.

Case 5

A 20-year-old man came to our attention complaining of weakness and muscle wasting in his left hand. The symptoms had first been noticed one year before during (or just after) swimming and had subsequently slowly worsened. Both his family history and his past medical history were unremarkable.

An EMG study had been previously performed, which was consistent with a mild C8 and T1 right radiculopathy, while a spinal cord MRI study was unremarkable. Therefore, the patient was referred to us with clinical suspicion of "flail arm" syndrome, which is quite an infrequent, ALS-restricted phenotype. Neurological examination showed mild distal muscle atrophy and weakness in the intrinsic muscles of his right hand. Cranial nerve, sensory, and cerebellar examinations were unremarkable. Deep tendon and plantar reflexes were normal.

Repeated EMG revealed chronic neurogenic motor unit potentials in hand and forearm muscles innervated by the C8 and T1 right roots, with minor involvement of the C7 root, with no signs of active denervation, predominant on the symptomatic side but also detectable in the intrinsic muscles of his left hand.

A thorough laboratory examination, including screening for anti-nerve autoantibodies, was unremarkable. We repeated spinal cord MRI in both the neutral position and on full cervical flection; while the routine supine cervical MRI scans had unremarkable results, flection MRI clearly allowed a final clinicoradiological diagnosis of HD (Fig. 4), a rare form of upper limb nonneurodegenerative amyotrophy. We advised the patient to avoid neck flexion exercises as much as possible in the future.

Discussion

ALS is still a clinical diagnosis [9], and the lack of sensitive and specific instrumental or biological biomarkers often makes a differential diagnosis challenging (Table 1). According to the El Escorial Criteria (2000), a diagnosis of clinically defined ALS needs the presence of both UMN and lower motor neuron (LMN) clinical signs or electrophysiological evidence in three regions. Nonetheless, the coexistence of LMN signs in the upper limbs and UMN signs in the lower limbs should strongly point towards an alternative diagnosis to ALS (e.g., central cord syndrome in cases 2 and 4).

Moreover, the coexistence of UMN and LMN signs in the same limb segment strongly sustains a diagnosis of ALS; however, exceptional cases might exist, as in patient 1, who showed atrophy of arm and hand muscles together with brisk deep tendon reflexes of both upper limbs. As a matter of fact, a progressive impairment within both UMN and LMN in more than one body region has few differential diagnoses [10]; however, for several reasons, patients may not always clearly exhibit both UMN and LMN signs.

In our cases, an erroneous diagnosis of "possible ALS" in 3 patients and of "definite ALS" in 1 patient was initially made, due to the coexistence of both UMN and LMN signs. Only the last case had no signs of UMN involvement. Anyway, all patients exhibited asymmetric limb amyotrophy and chronic neurogenic damage with a progressive weakness mimicking ALS, even though they were all affected by intrinsic or extrinsic cervical spinal cord compression, which was responsible for their neurological deficits.

The results of spine MRI were crucial to reach a correct diagnosis in all cases: in the first 2 patients, a "common" severe spondylotic myelopathy was documented, whereas an unexpected result was discovered in patient 3: here, a ventral intraspinal fluid-filled collection compressing the spinal cord structure – and similar to those seen in spontaneous CSF leaks [11] – was documented, even though no orthostatic headache was reported by the patient and no clinical or radiological signs of CSF hypotension or leakage were detected. We retrospectively regarded the brisk tendon reflexes expressed by this patient either as constitutional, perhaps due to the young age, or due to an indirect compression of the pyramidal tracts by the cystic space-occupying lesion.

Few cases of intraspinal fluid-filled collection due to CSF leakage have been already described [12], with evidence of clinical and radiological improvement after treatment of the CSF leak, thus supporting a causative relationship between fluid collection and symptoms. In addition, while patient 4 displayed on the MR scan a classic well-recognizable mimic of ALS (i.e., syringomyelia), patient 5 had an initially normal standard scan, and only after the addition of image acquisition during neck flection could the final diagnosis of HD be reached.

As reported in several studies [13, 14], the proximity of UMN and LMN structures in the cervical spine makes cervical myeloradiculopathy (CM) one of the most common differential diagnoses in cases of suspected ALS. A recent retrospective study conducted in Argentina [15] reports that among 368 patients with initially suspected ALS, 11.7% were finally diagnosed with a different disease; among those, 32.6% of the cases (i.e., 3.8% of the whole sample, corresponding to 14 patients) were finally represented by compressive myelopathy. Nonetheless, several studies do not support these observations: Traynor et al. [16] analyzed the Irish ALS Register, reporting the most common ALS mimic to be multifocal motor neuropathy, closely followed by Kennedy's disease. A possible explanation for such contrasting evidence may be the easier recourse to MR scanning in the latter study, which ensured that the presence of CM was (almost) never missed, long before an ALS diagnosis might have been made for the patients. In an attempt to clarify this challenging diagnostic pathway, a recent review [10] classified ALS mimics according to the presence of either LMN-only (e.g., multifocal motor neuropathy) or UMN-only (e.g., hereditary spastic paraparesis) signs or mixed UMN and LMN signs, with CM being the only disorder inside the last category. A recent interesting analysis [17] identified the main clinical features more frequently leading to a revision of an initial diagnosis of ALS: false-positive cases were especially characterized by young age, symmetrical distribution of neurological deficits, limb weakness greater than atrophy, and symptomatic exacerbation.

Prominent neck pain and sphincter involvement are key clues to CM, and these symptoms should advocate this potential diagnosis. However, on the one hand, the absence of sensitive symptoms and incontinence is not uncommon in CM, and on the other hand, spondylotic changes might present as a comorbidity to ALS. Often, in the former case, the concomitant lack of clear UMN signs [18] – often concealed by the LMN involvement in ALS – forces one to consider DML as a potential ALS mimic [4], as eventually found in our first case.

Preferential wasting of the thenar eminence, the so-called split hand sign, is considered a useful clinical clue to an ALS diagnosis. However, pure motor wasting of the intrinsic hand muscles is also seen in patients with other disorders affecting the motor neurons, including CM, spinal muscular atrophy, peripheral neuropathy, and spinocerebellar ataxia type 3, and even in normal elderly individuals [17]. Given that it has been repeatedly reported that the electroneurographic split hand index (SHI) is significantly reduced in ALS patients compared to those with other neuromuscular disorders, including cervical radiculopathy [19, 20], it is likely that the SHI should be considered a useful instrumental – rather than clinical – sign, requiring a quantitative value.

In conclusion, no specific biochemical or instrumental tests are actually available to definitively confirm a diagnosis of ALS, although potential biomarkers are currently on trial for improving the diagnostic algorithm. Hopefully, this research will help clinicians in resolving

the complexities deriving from ALS phenotypic heterogeneity [21]; meanwhile, affection of the cervical spine should never be forgot.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All patients have given their written informed consent to publish their case (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding is reported.

Author Contributions

Management of patients: all authors; conception: L.T.; first draft preparation: B.S., S.D., L.T., C.L., and N.R.; manuscript discussion and critical evaluation: all authors.

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Case Rep Neurol 2021;13:145–156
DOI: 10.1159/000512810

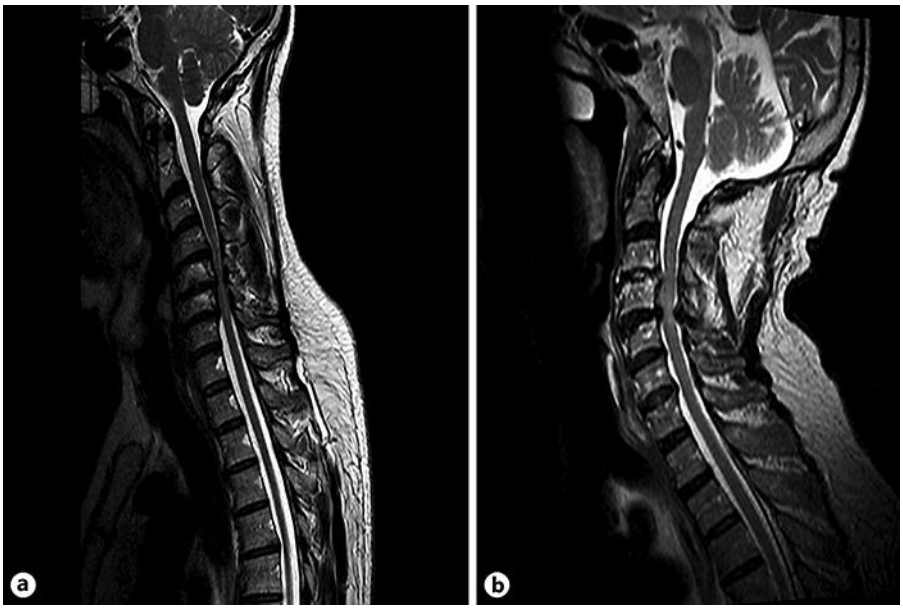

Fig. 1. **a** Case 1. T2-weighted sagittal section of cervicodorsal spine showing diffuse spondylarthrosis and posterior longitudinal ligament thickening of the C4–C6 tract, leading to shrinking of the spinal cavity and spinal cord impingement with a hyperintense signal of compressive damage. **b** Case 2. T2-weighted sagittal section of the cervicodorsal spine showing disk protrusion and thickening of the yellow ligaments at the C4–C5 level, determining shrinking of the spinal cavity and concentric compression of the spinal cord that exhibits a T2-hyperintense signal of local suffering.

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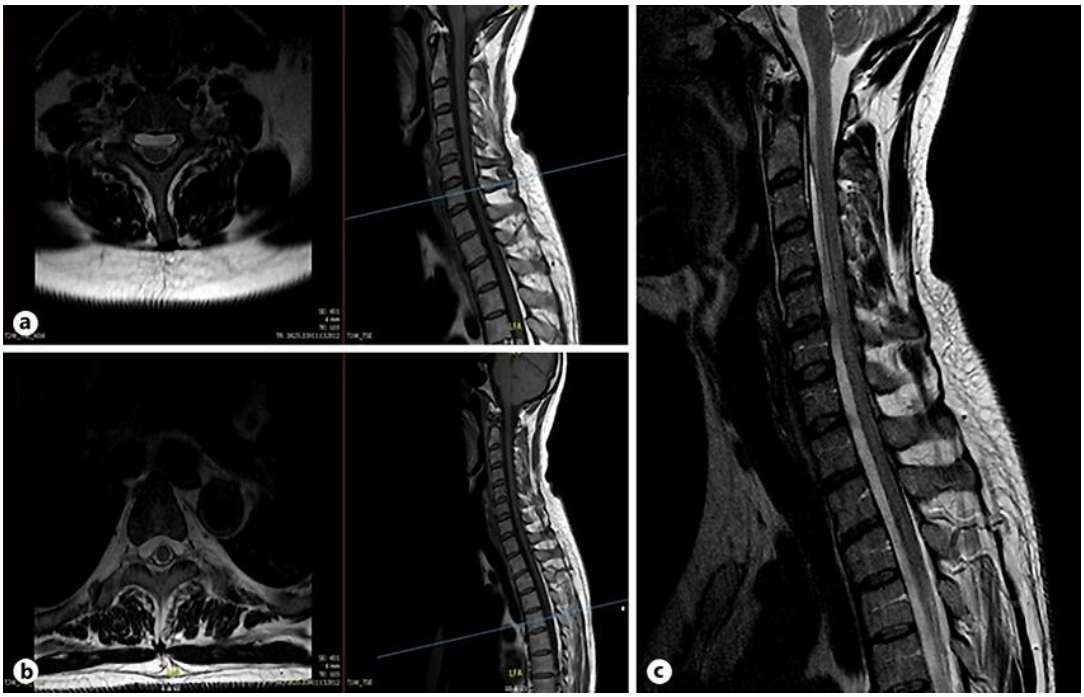

Fig. 2. Case 3. **a**, **b** T2-weighted transverse sections of the cervicodorsal spine documenting an isointense fluid-filled collection anterior to the spinal cord, determining an impingement of the anterior roots bilaterally, without signs of spinal cord compression. **c** T2-weighted sagittal section of the spine showing the whole epidural cyst extending from C2 to L4.

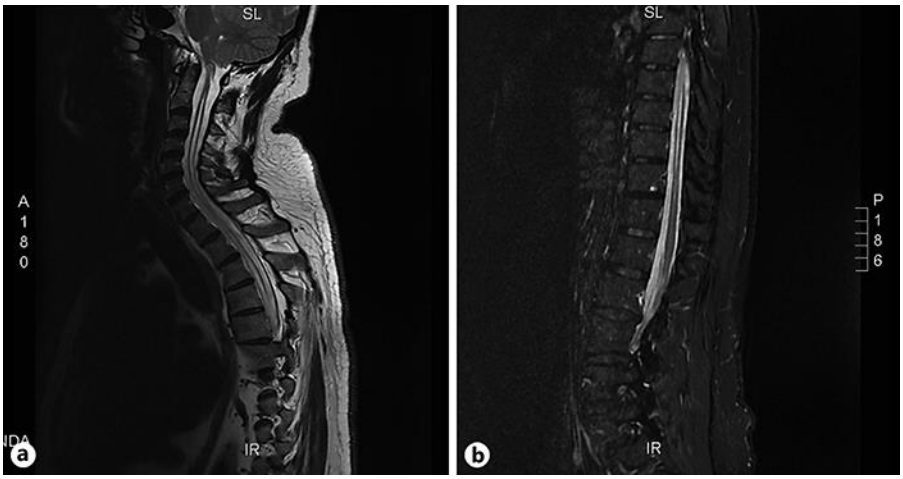

Fig. 3. Case 4. **a**, **b** T2-weighted sagittal sections of the whole spine showing a wide syrinx within the spinal cord, located around the central canal and extending from the cervical to the lumbar metamers.

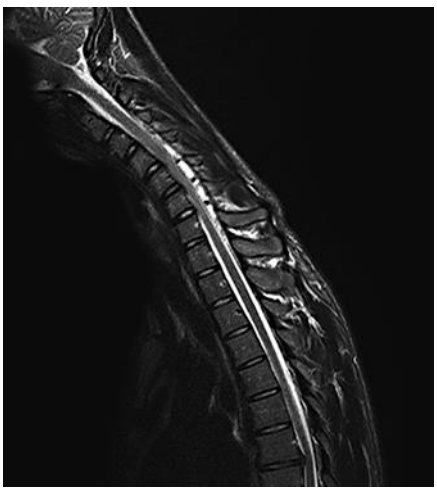

Fig. 4. Case 5. Sagittal cervical spinal cord STIR (short tau inversion recovery) flection MRI, showing anterior shift of the posterior dura with displacement from the cervical lamina between C3 and T2, associated with a minimally reduced anteroposterior diameter, predominant at the C5/C6 level, and the presence of posterior epidural venous structures.

Table 1. Red flags pointing out the need for further investigation in an ALS differential diagnosis

Red flags	Differential diagnosis
Sensitive symptoms and/or signs	Spinal cord pathology, radiculopathy, plexopathy, polyneuropathy, peripheral neuropathy
Prominent neck pain	Cervical spondylosis
Coexistence of LMN signs in upper limbs and UMN signs in lower limbs	Central cord syndromes
Abnormalities at sensory nerve conduction test	Postganglionic pathology
Dissociated sensory loss (preservation of fine touch and proprioception with selective loss of pain and temperature)	Syringomyelia
Conduction blocks at multiple motor nerves	Multifocal motor neuropathy
Sphincter disturbances	Spinal cord or cauda affection
Family history, very slow progression	Hereditary spastic paraparesis
Young age, men, very slow progression, limited number of myotomes	Monomelic amyotrophy, Hirayama's disease

ALS, amyotrophic lateral sclerosis; LMN, lower motor neuron; UMN, upper motor neuron.