Clinical features of pain in amyotrophic lateral sclerosis: A clinical challenge

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Summary

Pain in amyotrophic lateral sclerosis (ALS) is paradoxical in this disease of the upper and lower motor neurons. As such, it remains an underestimated and neglected clinical problem because it is poorly identified by physicians, its mechanisms are numerous and its treatments are generally not effective. Pain may be primary in the form of cramps, spasticity and neuropathy, or secondary as nociceptive pain, and may arise before the first motor symptoms. It may also lead to depression and, in all cases, affect patients' daily activities and quality of life. Given the high frequency of pain in ALS, the use of analgesic or sedative drugs is necessary and should reduce the course of the disease. Nevertheless, it is important to understand the pathophysiological mechanisms of pain in ALS, and to train physicians how to detect ALS pain early on and provide dedicated treatments. In France, the implementation of ALS centers is a positive response to the public-health problem resulting from this disorder.

Keywords:

Amyotrophic lateral sclerosis; Pain; Analgesic drugs; Quality of life

Introduction

Amyotrophic lateral sclerosis (ALS) was first described by Jean-Martin Charcot [1], and is a rare but severe neurodegenerative disease, usually leading to death within 2 to 4 years [2,3]. Without treatment, involvement of the first- and second-order motor neurons induces palsy of the four limbs, dysphagia and dysarthria, with respiratory failure as the cause of the fatal outcome.

Besides these motor issues, other, non-motor symptoms may be a major problem, such as cognitive decline, semantic memory involvement [4], frontotemporal dementia [5], malnutrition and pain, although the latter is often underestimated by practitioners compared with fatal motor and respiratory failure [6]. In addition, the treatment of pain in ALS is not well managed [7] because its underlying mechanisms and assessment are still as yet unclear [2,8]. Yet, despite this, every practitioner in charge of patients with ALS is familiar with the negative effects of pain on quality of life for both patients and their caregivers [9].

To provide a clinical tool for practitioners, the present article reviews what is currently known of the clinical characteristics of pain in ALS, its underlying mechanisms and different treatments according to the mechanisms involved.

Clinical features of pain in ALS

These features are multiple and differ among patients because they depend on the patient's age, duration of disease, and clinical form of the disease and its underlying primary or secondary mechanisms. These differences explain the variable prevalence of cases, ranging from 15% [10] to 85% [10–12]. Indeed, a common observation is that pain is less frequent in bulbar forms of ALS [12,13].

Primary causes of pain

These are induced as a direct result of the neuropathological damage due to the disease.

Cramps and spasticity

Cramps are the most frequent type of pain in ALS, with rates between 25% [14] to 63% [10]. They usually affect the calf and other distal muscles, but also the abdomen, during the night. They are short-lasting and may be induced by movement and cold temperatures [10], but they are also often experienced for several months prior to the onset of motor weakness [2,10].

Cramps and fasciculations are due to hyperexcitability of motor units due to axonal sprouting [10], and are usually associated with muscle denervation as a consequence of involvement of second-order motor neurons at the level of the anterior horn of the spinal cord [14], as shown by needle electromyography (EMG) tests, with rare giant motor unit potentials.

Spasticity can produce paroxysmal, spontaneous, violent and hyperalgic contractures of hypertonic muscles, thereby suggesting involvement of first-order motor neurons. It is estimated to affect close to 6% of patients [10].

Neuropathic pain

It is surprising to describe neuropathic pain in a disorder of the motor system that usually spares the somatosensory system [15]. In fact, only 9% of patients with ALS report neuropathic pain [2]. It may be spontaneous, presenting as burning feet, tingling, paroxysmal shooting pain and/or numbness, or

evoked, with allodynia, hyperalgesia and flashback algesia [2]. These sensations may be localized to the distal limbs (hands, feet) and either focal (abdomen) or diffuse.
This type of pain suggests involvement of the sensory tracts [16] affecting the posterior columns of the spine in ALS, as shown by familial cases [17–19], sensory evoked potentials [20], magnetic resonance imaging (MRI) of the spinal cord [21] and some animal models [22].
A recent study [23] found that sensory nerve conduction was altered in 44% of ALS patients, and up to 50% of patients had small fiber neuropathy [24]. The use of skin biopsies may be useful in ALS patients with neuropathic pain to analyze their intraepidermal nerve fibers [25].
Yet, despite these data, it is still difficult to clarify the relationship between neuropathic pain in ALS and the lesions observed in the sensory system. However, clinical experience has demonstrated positive responses to antiepileptic drugs, but a lack of efficacy of anti-inflammatory drugs for this type of ALS pain [2,15,26,27].

Secondary pain

This is induced by complications of the disease, and increase in intensity as the disease progresses [10,15,26]. Nociceptive pain is the main cause, induced by the involvement of non-neural tissue [28]. In ALS, this type of pain develops from the association of muscle atrophy, long-term reduced mobility, and involvement of smooth tissue, bone, tendon, ligament and joint contractures [10]. The most frequent joint pain is due to shoulder joint contractures, resulting from muscle weakness, loss of protective muscle sheaths due to atrophy and microtrauma induced by caregivers when helping patients to stand [2,16].
Decubitus ulcers (bed sores) are not classic symptoms in ALS despite long periods of immobility. When present, pain appears mainly during their care.
Non-invasive ventilation (NIV) using, for example, face or nasal masks, is another secondary pain induced by lesions on the skin around the nose and mouth, reported in ALS patients after beginning NIV.
Close to 80% of ALS patients report experiencing this type of pain [29,30], which is usually treated by non-steroidal anti-inflammatory drugs (NSAIDs) [31].

Unspecified pain

In some patients, it is not possible to identify either neuropathic or nociceptive types of pain except through the association of both organic and psychic pain [16,27]. This type of pain is known as ‘central sensitization’ [2], for which four mechanisms are currently suggested: (i) spontaneous increase in neuronal activation resulting in pain hypersensitivity [31]; (ii) increased response of cerebral neurons to light stimuli [32]; (iii) hypoxemia, which can stimulate nociceptive inhibitory control [33]; and (iv) greater susceptibility to pain by a decrease in pain threshold [30]. There are also new data [2] to explain how sensory light stimuli are able to create and amplify responses in non-stimulated nociceptive neurons [31].

Natural history of pain in ALS

It is important to bear in mind that pain may precede the onset of motor symptoms, by 2 years [2] in 25% of cases [9] and in up to 50% in other patients [10,34]. Cramps are the classic initial pain [35] along with low back pain. Similar results are reported even with the use of analgesic drugs 2 years prior to ALS onset [36].

Usually, there are also no differences in the frequency [9,11] and severity [10,37] of pain between early and late stages of the disease [10]. However, recent studies [38] have reported the presence of all-day-long moderate-to-severe pain in one patient out of two during the last month of life.
In addition, the natural history of pain in ALS associates pain with comorbidities such as depression [37,39]. Indeed, pain is more frequent in ALS patients with than without depression [40], whereas the same excess of depression is found in patients with ALS and pain [41]. This double association explains the poor quality of life of these patients. Other comorbidities, such as anxiety, apathy [2,42], and impaired memory [4] and cognitive functions [43], may also arise during the course of the disease.

Pain treatment in ALS

Given the importance of pain in terms of quality of life for patients with ALS, physicians need to be able to identify and reduce the pain quickly or even prevent it (Tables 1 and 2). Such strategies are mostly based on clinical experience, with pharmacological treatments being the more efficacious approach for neuropathic and secondary pain.
For neuropathic pain [15,44,45], gabapentin, pregabalin and tricyclic antidepressants are recommended. For cramps, quinine, benzodiazepine, magnesium and carbamazepine have proved significantly effective [10]. For severe spasticity, oral or intrathecal baclofen may be efficacious, as well as benzodiazepine and dantrolene [10,15,44]. Articular pain such as in the shoulder joints can be relieved by anti-inflammatory drugs and acetaminophen/paracetamol or by intra-articular injections of analgesics or corticosteroids.
Finally, in all cases, physiotherapy, massage, daily stretching, therapeutic ultrasound, laser therapy, transcutaneous electrical nerve stimulation (TENS) and acupuncture may also help patients with ALS and pain [2,10].

Conclusion

Pain is a major clinical complaint reported by ALS patients, and physicians need to be trained to identify the different causes, including neuropathic pain, cramps, spasticity and nociceptive pain. In addition, pain may be reported by patients before the first motor symptoms of ALS; it then increases throughout the course of disease and, in most cases, is accompanied by depression, thereby worsening patients' quality of life.
Thus, pain is a major challenge in the management of ALS that now requires good clinical practices such as those developed in France, thanks to the creation of specific ALS centers by the Ministry of Health.

Disclosure of interest

The authors declare that they have no financial or personal conflicts of interests concerning this article.

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Table 1 – Pharmacological treatment of pain in patients with amyotrophic lateral sclerosis (ALS).

Types of pain	Indication	Efficacy	Side-effects	Contraindications
Cramps (lower limbs, hands, abdomen):				
Quinine sulfate	First line	+++	0	Cardiac arrhythmia, bradycardia, long Q–T interval, liver/renal failure, hypokalemia
Mexiletine	Second line	0	Drowsiness	0
Levetiracetam	First line	+++	0	Cardiac arrhythmia, atrioventricular block
Dronabinol	First line	+++	Fatigue, drowsiness, headache	Depression
Gabapentin	Second line	0	0	Psychiatric disorders
Spasticity (lower limbs):				
Levetiracetam	First line	+++	Fatigue, sleepiness	Depression
Intrathecal baclofen	Second line	+++	Headache	NA
Tizanidine	NA	NA	NA	NA
Dantrolene	NA	NA	NA	NA
Benzodiazepine	NA	NA	NA	NA
Neuropathic pain (extremities):				
Gabapentin	First line	+++	Drowsiness, fatigue, dizziness, weight gain	0
Pregabalin	First line	+++	Drowsiness, fatigue, dizziness, weight gain	0
Tricyclic antidepressants	First line	+++	Drowsiness, fatigue, dizziness, weight gain	Long Q–T interval, prostate hypertrophy, glaucoma, cardiac arrhythmia
Secondary pain (shoulder, other joints):				
Intra-articular injections (lidocaine, steroids)	First line	+++	NA	NA
Intra-articular injections (steroids)	First line	+++	Facial flushing	NA
Unspecified pain (diffuse):				
NSAIDs, acetaminophen/paracetamol	First line	+++	NA	NA
Opioids	Second line	+++	Facial flushing	Severe cardiac failure
Cannabis	Second line	NA	Constipation, confusion	NA

NA: not available; NSAIDs: non-steroidal anti-inflammatory drugs.

Table 2 – Non-pharmacological treatments of pain in patients with amyotrophic lateral sclerosis (ALS).

Types of pain	Indication	Efficacy	Contraindications
Cramps (lower limbs, hands, abdomen):			
Stretching	Adjuvant	+	NA
Massage	Adjuvant	+	NA
Spasticity (lower limbs):			
Daily stretching + ROM exercises	Adjuvant	+	Risk of falls
Moderate physical activity		++	NA
Secondary pain (shoulder joints):			
Assistive ROM exercises	Adjuvant	++	Severe motor weakness
Acupuncture	Adjuvant	0	
Neutral-position splints for hands, ankles	Adjuvant	+	
Unspecified pain (diffuse):			
Daily stretching + assistive ROM	Adjuvant	+	0
Osteopathic manual treatment	Adjuvant	±	NA

NA: not available; ROM: range of motion.