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Pain at the onset of Amyotrophic Lateral Sclerosis: a cross-sectional study

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ABSTRACT

Objective: We evaluated ALS patients reporting pain, either generalized or localized, at disease onset and determined whether this feature defined a specific ALS phenotype.

Patients and Methods: : We considered all consecutive ALS patients referred to our Motor Neuron Diseases Center between 2006 and 2016 and included only patients who fulfilled the El Escorial revised criteria for probable and definite ALS diagnosis. We then identified those cases who reported pain at disease onset and compared them to all remaining cases. Secondary causes of pain have been excluded.

Results: Our initial sample consisted of 108 patients (55 men and 53 women). We identified 5 cases with generalized pain and 16 cases with localized pain at disease onset, corresponding to 4.6% and 14.8% of the initial sample, respectively. Cases with generalized pain were all female and had an earlier disease onset (49.6 ± 1.5 vs 66.6 ± 10.2 yrs, $p = 0.002$). Cases with localized pain showed a preponderance of upper motor neuron symptoms/signs at disease onset. Patients with pain, either localized or generalized, had a significantly higher involvement of the limbs (82.6% vs 100%, $p = 0.022$), while the bulbar district was spared at disease onset (17.4% vs 0%, $p = 0.008$). More specifically, the proximal upper and distal lower limbs were more frequently affected by ALS in patients with pain at disease onset.

In two cases, the clinical presentation was notable for the resemblance with complex regional pain syndrome.

Conclusion: The presence of pain at disease onset seems to relate to peculiar clinical features of ALS and may be pathophysiologically associated with neurodegeneration.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease, characterized by the loss of motor neurons in the cortex, brainstem and spinal cord, with a fatal outcome, generally within 2–4 years from disease onset [1]. Although historically considered a pure motor disorder, growing evidences point toward an early involvement of non-motor systems, including the prefrontal cortex [2], the olfactory [3] and the somatosensory pathways [4–8]. The latter is suggested by different findings, including: a) MRI abnormalities of the posterior columns of the spinal cord [4]; b) neuropathological evidences of neural degeneration along the somatosensory pathway, i.e primary somatosensory cortex [5], posterior columns of the spinal cord [6], large-caliber myelinated fibers [7] and epidermal small fibers [8]; c) electrophysiological studies showing reduced sensory nerve potentials in up to 30% of ALS patients [9] (and probably in higher percentages if distal sensory nerves were registered [10]), altered somatosensory [11] and laser evoked potentials [12]. Furthermore, the degeneration of intraepidermal nerve fibers and dorsal root ganglion neurons has been observed in $SOD1^{G93A}$ mouse models of ALS, too [13].

Among sensory symptoms, pain seems to be quite common, being reported by 48%–85% of ALS patients in different cross-sectional surveys [14–19]. Although pain is known to occur at any stage of the disease [20], there is conflicting evidence whether the frequency and intensity of pain correlates with disease duration and functional impairment [19], with some studies suggesting no difference between early and late stages [17,18].

Pain can be localized or diffuse in nature; the former is pathophysiologically more relevant, because can be correlated with the site of motor involvement [20] and can suggest a possible underlying etiology, such as, for example, small fiber neuropathy in patients with foot pain [20].

In the present study, we retrospectively evaluated ALS patients reporting pain at disease onset, either isolated or in combination with "classical" motor symptoms, and verified whether the presence of pain defined a specific ALS phenotype.

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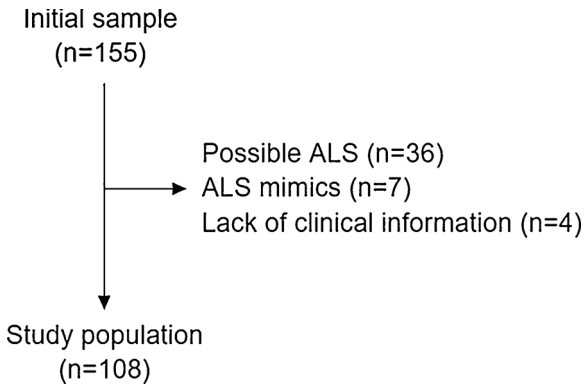

Fig. 1. Study population flow chart, including initial study sample, excluded cases (with respective reasons) and final study sample.

2. Material and methods

We considered all consecutive patients referred to our Motor Neuron Diseases (MND) Center between January 2006 and December 2016 diagnosed with ALS by our team of trained neurologists. One of the Authors (GP) has been personally involved in the diagnosis of all reported cases.

ALS patients were exhaustively evaluated in face-to-face interviews to obtain valid and detailed information; all patients underwent neurological examination. In all cases, electrophysiological studies, including nerve conduction studies (NCS), needle electromyography (EMG), somatosensory and motor evoked potentials (SEP, MEP), and routine blood work were performed at our first evaluation; imaging studies, including brain and spinal cord MRI and second level laboratory tests, were performed when necessary to exclude ALS mimics; for cases with a positive family history, genetic tests were performed as well.

We then reviewed our patients' clinical records, and considered only patients who fulfilled the El Escorial revised criteria for probable and definite ALS diagnosis [21]. Of our initial sample (n = 155), 47 patients were excluded for a variety of reasons (Fig. 1), including: a diagnosis of possible ALS (36 cases), a misdiagnosis with ALS mimics (7 cases), which became evident during the subsequent follow-up, including a case of Multifocal Motor Neuropathy (MMN) and two cases of spondylotic cervical myelopathy, and a lack of sufficient clinical information (4 cases).

We then identified those patients who, during our first clinical interview, reported pain as an initial complaint, either isolated or in combination with “typical” motor symptoms. For our analysis, we distinguished between localized pain (i.e. referred to one of the topographical regions included in the El Escorial Criteria) and diffuse pain (i.e. pain that was not localized to a specific body area, or that included two or more topographical regions). We decided not to include patients reporting headache as a type of localized pain. This because, to our knowledge, neural circuits involved in primary headache disorders (such as, for example, the hypothalamus, the spinal trigeminal nucleus and the visual cortex) [22] have not been found to be altered in ALS.

During the initial work-up for the diagnosis of ALS, patients with localized pain were evaluated for secondary causes of neuropathic pain, including radiculopathy, entrapment neuropathy and polyneuropathy, through electrophysiological, laboratory and imaging studies, which proved to be normal. Similarly, for patients with generalized pain, an underlying rheumatologic disorder was excluded through appropriate laboratory tests.

2.1. Statistical analysis

We used ANOVA test for continuous variables and Pearson's chi-square test for categorical variables. The results were corrected for multiple comparisons.

The collected data were analyzed using SPSS, version 20.0 for Windows. We calculated two-tailed p-values and set the statistical significance at $p < 0.05$.

2.2. Ethics

All subjects gave written consent to use their personal and clinical data for research purposes.

3. Results

The overall study population included 108 subjects, 55 men and 53 women. The mean age-of-onset of the overall ALS cases was 66 ± 10 yrs (range 33–85 yrs), without gender differences (p = 0.467): namely, it was 67.4 ± 9.9 yrs among men (range 44–84 yrs) and 65.9 ± 10.9 yrs among women (range 33–85 yrs).

Five patients (4.6% of the initial sample) complained of generalized pain at disease onset. All cases were females, and the mean age of ALS onset was 49.6 ± 1.5 yrs. Pain had widespread localization, was ill-defined in nature and was associated with whole-body tiredness; the mean intensity of pain was 3.2 ± 0.8 in an 11-points numerical rating scale (NRS, scores from 0 to 10) [23].

Sixteen patients reported localized pain at disease onset, corresponding to 14.8% of the initial sample, and including eight men (14.5% of male patients) and eight women (15.1% of female patients). The mean age-of-onset was 66 ± 13 yrs (71.5 ± 10.9 yrs in men and 60.5 ± 11.5 yrs in women, p = 0.934).

In Table 1, we compared patients with and without pain according to different clinical and demographic features at disease onset; we also considered the presence of MEP abnormalities (i.e. increased central conduction time or decreased amplitude of cortical responses), of SEP alterations (increased central or peripheral conduction time, or decreased amplitude of cortical responses N20 and P37) and of decreased sensory nerve responses (sural and median nerves).

When considering the topographic distribution of weakness at disease onset, we found that patients with pain, either localized or generalized, had a significantly higher involvement of the limbs (82.6% vs 100%, p = 0.022), while the bulbar district was consistently spared (17.4% vs 0%, p = 0.008). More specifically, the strength in the proximal upper limbs and distal lower limbs was impaired in cases with pain more frequently than cases without pain (Table 1).

In Table 2 we focused on ALS patients with localized pain at disease onset. While upper motor neurons (UMN) symptoms/signs were present in all cases, only nine out of 16 cases showed an involvement of lower motor neurons (LMN).

When considering the localization of pain and the combination of LMN/UMN symptoms/signs at disease onset, we identified two specific subgroups of patients: (a) Five cases reported pain in an upper limb (involving unilaterally a hand or a shoulder) and showed exclusive UMN involvement; pain description resembled neuropathic pain. (b) Six cases reported pain involving lower limbs bilaterally, and showed involvement of both UMN and LMN; in the majority of these cases (i.e. four out of six) pain was described as painful cramping. The intensity of pain on an 11-points NRS was significantly higher in the former group when compared to the latter (i.e. 7.6 ± 2.1 vs 3.8 ± 0.8, p = 0.0054) (Table 2).

Case 2 (Table 2) was noteworthy, as pain preceded the onset of motor symptoms by two years, and the clinical presentation resembled that of complex regional pain syndrome (CRPS). Pain was located in the carpal and metacarpal joints of the left hand, was severe in intensity, poorly responsive to analgesics, and had a burning quality; it was associated with allodynia, local erythema, stiffness and swelling of hand joints. The patient had been surgically treated for a presumptive diagnosis of carpal tunnel syndrome, however, without benefit. A skin

Table 1
Comparison between patients with and without pain at disease onset; the former group is divided between patients reporting localized and generalized pain.

	Without pain (n = 87)	Localized pain(n = 16)	Generalized pain (n=5)	*p*
Male, nr (%)	55 (51)	8 (50)	0 (0)	***0.030***
Mean age-of-onset(*), (yrs ± SD)	66.6 ± 10.2	66 ± 13	49.6 ± 1.5	***0.002***
Diagnostic delay, (yrs ± SD)	1.1 ± 1.3	1.5 ± 1.5	1.4 ± 1.2	*0.309*
BMI at onset, (kg/m2 ± SD)	24.9 ± 3.7	25.8 ± 3	25.3 ± 2.5	*0.449*
ALSFRS-R (first evaluation), (/48 ± SD)	39.3 ± 6.3	39.2 ± 5.5	38.9 ± 4.8	*0.981*
Familial history of ALS, nr (%)	7 (8.1)	0 (0)	0 (0)	*0.316*
Comorbidities, nr (%)				
FTD or dementia	5 (5.4)	0 (0)	0 (0)	*0.464*
Diabetes	8 (8.7)	1 (6.3)	0 (0)	*0.628*
Cardiovascular diseases	41 (44.6)	9 (56.3)	1 (20%)	*0.387*
Site of onset(*), nr (%)				
Limbs	76 (82.6)	16(*) (100)	5 (100)	***0.022***
Bulbar	16 (17.4)	0 (0)	0 (0)	***0.008***
Respiratory	3 (3.2)	0 (0)	0 (0)	*0.464*
Limb onset(*), nr (%)				
Proximal upper limb	4 (4.3)	3 (18.8)	4 (80)	***0.040***
Distal upper limb	23 (25)	4 (25)	1 (20)	*1.00*
Proximal lower limb	16 (17.4)	3 (18.8)	0 (0)	*0.642*
Distal lower limb	35 (38.0)	11 (68.8)	0 (0)	***0.029***
Electrophysiological abnormalities, nr (%)				
MEP	30 (32.6)	8 (50)	3 (60)	*0.122*
SEP	7 (7.6)	1 (6.3)	0 (0)	*0.936*
Sural or median sensory study	16 (17.4)	3 (18.8)	0 (0)	*0.880*

MEP = motor evoked potentials.
SEP = somatosensory evoked potentials.
FTD = fronto-temporal dementia.
SD = standard deviation.
* Onset of motor symptoms/signs.

biopsy had excluded the presence of small fiber neuropathy. A plain radiograph disclosed patchy osteopenia in the carpal and metacarpal bones, with a periarticular distribution, which is consistent with CRPS [24]. The patient later developed prevalent UMN signs in the affected hand (i.e. loss of dexterity and spasticity).

Similarly, case 4 presented with CRPS-like pain, whose distribution resembled post-stroke “shoulder-hand” syndrome. Pain involved the right shoulder more than the right hand, it was severe in intensity, had a throbbing quality, and was associated with swelling of the proximal arm. An MRI of the shoulder excluded periarthritis, electrophysiological studies proved negative for brachial plexopathy, while a skin biopsy excluded a small fiber neuropathy. A short course of oral steroids (prednisone 1 mg/kg/day PO, tapered over 2 weeks) proved effective for pain and edema, consistent with previous reports on CRPS [25]. At disease onset, the patient complained of weakness of the right shoulder, and to a lesser degree, of the right hand, which was initially attributed to pain; however, the presence of UMN signs, the lack of response to steroids, and the subsequent progression of the motor impairment to the contralateral arm pointed toward a diagnosis of ALS.

Table 2
Clinical features of ALS patients with localized pain at disease onset.

Case	Sex	Age at onset (yrs)	Location of pain	Description of pain	Intensity of pain (NRS)	Location of motor signs/symptoms	UMN	LMN
1	F	64	Right leg	Electric shock	8	Right lower limb (distal > proximal)	Yes	No
2	F	55	Left hand	Burning; CRPS-like	10	Left hand	(Yes)*	No
3	M	69	Both feet	Dull	4	Lower limbs (distal > proximal)	Yes	Yes
4	F	52	Right shoulder and hand	CRPS-like	9	Left arm (proximal > distal)	Yes	No
5	M	85	Right hand	Painful cold	6	Right upper limb (distal > proximal)	Yes	No
6	M	77	Right shoulder	Paroxysmal shooting	8	Right upper limb (diffuse)	Yes	No
7	F	66	Both feet	Cramping	3	Lower limbs (distal > proximal)	Yes	Yes
8	M	57	Both feet	Cramping	4	Lower limbs (distal > proximal)	Yes	Yes
9	M	56	Left shoulder	Dull	5	Upper limbs (diffuse)	Yes	No
10	M	81	Both feet	Cramping	5	Lower limbs (distal > proximal)	Yes	Yes
11	F	44	Right foot	Throbbing	2	Right lower limb (distal > proximal)	Yes	No
12	F	65	Both feet	Cramping	4	Lower limbs (distal > proximal)	Yes	Yes
13	F	56	Left leg	Stabbing	4	Left lower limb (diffuse)	Yes	Yes
14	M	79	Right foot	Cramping	5	Lower limbs (distal > proximal)	Yes	Yes
15	F	82	Both feet	Dull	3	Lower limbs (diffuse)	Yes	Yes
16	M	68	Left leg	Cramping	4	Left lower limb (diffuse)	Yes	Yes

NRS = 11-points numerical rating scale.
UMN = upper motor neuron signs/symptoms.
LMN = lower motor neuron signs/symptoms.
CRSPS = complex regional pain syndrome.
* UMN signs/symptoms appeared after pain onset.

4. Discussion

The occurrence of pain at the onset or as presenting symptom of ALS has been reported in few literature studies [20,26–30], and pathophysiologically suggests a primary mechanism, directly correlated to neurodegeneration. Primary sources of pain could be spasticity, (painful) cramps or lesions along the somatosensory pathway causing neuropathic pain [20].

In the largest survey on this topic (n = 424), 34% of ALS patients reported that pain was present during the early stages of the disease [27]. This percentage is higher than our 20.4% (including cases with localized and generalized pain), probably due to different inclusion criteria [27]. Similarly, a recent epidemiological study [31] showed that ALS patients used drugs for neuropathic pain more frequently than the general population, and this occurred up to 2 years before disease onset.

In our study, generalized pain was uniformly associated with fatigue, and may represent a somatic descriptor of fatigue itself. In accordance with previous studies focusing on fatigue in ALS [32], our cases had an earlier age-of-onset, and were females. Though their number is too low to draw definitive conclusions, ALS phenotype among these patients was peculiar, more specifically, they had a spinal onset and an exclusive involvement of upper limbs (proximal > distal).

In accordance with our findings (Table 1), various studies [14,16,18] have demonstrated that pain in ALS is more frequently located in the extremities (arms or legs), independently from the stage of disease.

Among cases with localized pain, we identified a subgroup of patients with pain and weakness involving the upper limbs, and showing exclusive UMN symptoms/signs at disease onset (Table 2). Pain was severe in intensity, and had neuropathic pain descriptors, though we could not confirm this nature through focused questionnaires, nor we found lesions along the somatosensory pathway.

The presence of neuropathic pain in ALS has been described only by few case series [12,28], but not at disease onset. A case-control study [17] investigated neuropathic pain in ALS through focused questionnaires and found it in 9% of patients; this percentage, however, seems to be comparable to the prevalence of neuropathic pain in the general population, which ranges between 6.9% and 10% [33]. ALS phenotype among these patients was not different to ALS cases reporting nociceptive pain or without pain [17].

Shoulder pain seems to be quite frequent in ALS, and has been described as a presenting symptom in up to 10% of cases, without, however, any correlation with ALS phenotype [34].

In our study, painful cramps involving the feet identified a second pattern of localized pain. Pain intensity, as measured by an 11-points NRS, was significantly higher in this group when compared to patients with upper limbs pain. These cases reported lower limbs weakness at disease onset, with an equal representation of UMN and LMN signs/symptoms (Table 2).

Cramps have been reported as a source of pain in up to a quarter of ALS patients during the course of the disease [20]. Pain seems to originate from motor units instability and muscle denervation [20]. Accordingly, we found that LMN involvement was a distinguishing feature of patients with painful cramps, whereas the presence of UMN symptoms/signs was a common feature of all patients reporting localized pain (Table 2).

The involvement of feet intrinsic muscles rather than calves seems to be typical of ALS and to differentiate it from benign cramps [35].

A CRPS-like presentation has been previously associated with ALS in single case reports [36–38], and seems to be a late complication of severe limb paresis and immobilization. However, one of the cases described by De Carvalho et al [37] presented with CRPS-like symptoms at disease onset.

A possible role of the central nervous system (CNS) in the etiology of CRPS has been suggested by MRI studies showing changes in sensory and motor cortical areas [39]. On the other hand, CRPS in non-ALS patients may be associated with motor defects (weakness, atrophy and brisk reflexes) [39], while the occurrence of CRPS-like symptoms in ALS patients seems to accelerate the disease progression [37]. Taken altogether, these evidences suggest that CRPS itself may contribute to motor neuronal death, presumably through a sympathetic hyperactivity [37,39].

In 12 out of 16 cases, localized pain was apparently primary in nature, either with neuropathic features or related to cramping. This finding, together with the localized nature of pain, its early onset, and the association, in at least some cases, with a peculiar pattern of UMN vs LMN involvement suggest that pain may be directly associated with neurodegeneration.

As showed by electrophysiological test results (Table 2), pain was not explained by an involvement of peripheral large diameter fibers, while normal imaging studies seemed to exclude macroscopic abnormalities in the central somatosensory pathway. However, we could not perform skin biopsies or more focused electrophysiological studies (such as laser evoked potentials) in all patients reporting pain to exclude a small fiber neuropathy.

In accordance with some previous observations [14,16], we found that ALS patients experiencing localized pain have more frequently a spinal onset of their motor deficits, with sparing of the bulbar district. Similar to our observations on pain location, motor involvement was more frequent in the shoulder and in the feet (Table 1). These findings support the hypothesis that common mechanisms are involved both in motor impairment and pain genesis.

The strengths of our study are: a) this is the first literature report on pain, divided in localized and generalized, at ALS onset; b) a thorough clinical and electrophysiological evaluation was performed in all cases; c) all reported cases were personally seen by one of the authors (GP); d) ALS diagnoses were performed using the revised El Escorial criteria.

However, some limitations of our study need to be addressed: a) due to the retrospective study design, the presence of pain and its features were not identified through focused questionnaires, but through a clinical interview at the moment of our first evaluation; b) a recall bias cannot be excluded; c) the group of patients with pain, especially those with generalized pain, is small, and, therefore, we could not perform a multivariate regression analysis; d) we could not rule out a small fiber neuropathy through skin biopsy or focused electrophysiological studies.

5. Conclusion

In conclusion, the presence of pain at disease onset seems to relate to peculiar clinical features of ALS and may be pathophysiologically associated with neurodegeneration. Further studies, with larger populations and a prospective design are needed for a better understanding of this association.

Declaration of Competing Interest

We certify that there is no actual or potential conflict of interest in relation to this article.

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