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Pain in amyotrophic lateral sclerosis: a population-based controlled study

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Background and purpose: To assess the prevalence and characteristics of pain in an epidemiological series of patients with amyotrophic lateral sclerosis (ALS) compared to population-based controls.

Methods: Of the 183 patients with ALS resident in the province of Torino, Italy, 160 accepted to be interviewed. Controls were randomly selected from the lists of general practitioners. Pain was assessed using the Brief Pain Inventory.

Results: Patients with ALS reported pain more frequently than controls [91 (56.9%) vs. 53 (33.1%); $P = 0.001$]. Pain frequency and intensity were correlated with a worse functional score and a longer disease duration. In patients with ALS, pain was more frequently located at the extremities ($P = 0.006$). Pain interfered with all areas of daily function, but patients reported a greater interference than controls in the domains of enjoyment of life and relation with other people. Sixty-four patients (70.3% of those with pain) and 24 controls (45.3% of those with pain) ($P = 0.003$) were treated for pain, most frequently with non-steroidal anti-inflammatory drugs. ALS cases were also more frequently prescribed non-opioid analgesics and opioids than controls.

Conclusions: Our study indicates that pain is frequent in all stages of ALS, but that it often goes underrecognized and undertreated. It is significantly more frequent in patients with ALS than in population-based controls. Future studies need to clarify the mechanisms of pain in ALS and determine the most effective treatment strategy.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of unknown aetiology, characterized by the progressive loss of upper and lower motor neurons, causing weakness and hypotrophy of upper and lower limbs, dysphagia and dysarthria, and respiratory failure. Classically, pain has been considered relatively rare in ALS, in particular in the early stages of the disease. Recent guidelines on the treatment of ALS have recognized that pain may be present and should be carefully treated [1]. However, to the best of our knowledge, no studies have analysed the characteristics of pain and its effect on patients' daily functions at different stages of ALS [2].

Our aim was to evaluate the frequency and the characteristics of pain in a series of patients with ALS identified through an epidemiological register, compared to a population-based control cohort randomly selected from the lists of general practitioners (GPs).

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Materials and methods

Participants

We contacted all the patients with ALS resident in the province of Torino, Italy, at the prevalence day (1 November 2009). Patients were identified through the Piemonte and Valle d'Aosta register for ALS (PARALS) [3]. The PARALS is a prospective epidemiological register established in 1995 collecting all ALS incident cases in two Italian regions. All patients were contacted by telephone. Of the 183 prevalent patients, 165 accepted to be interviewed. Interviews were performed between 1 November 2009 and 30 June 2010; five patients who accepted to be interviewed passed away before the interview was performed. Only patients with definite, probable and probable laboratory-supported ALS

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according to El-Escorial criteria were included. The 18 patients who refused to be interviewed were demographically and clinically similar to the patients who accepted to participate to the study. Patients were interviewed in person, either during the scheduled clinic visits or at home. Tracheotomized patients were interviewed with the support of augmentative communication devices, including eye-tracking instrumentations.

Controls subjects were randomly identified from the lists of the patients' GPs and matched to patients with ALS by age (±3 years) and gender. Controls were also interviewed in person, either at their GP office or at home. All persons resident in Italy are obligatory enlisted in the lists of GPs, which therefore represent a unique database of all Italian population.

Procedures

Pain was evaluated using the Italian version of the Brief Pain Inventory (BPI) [4,5]. BPI is a structured qualitative and quantitative questionnaire that provides basic information of pain in the last week, indicating the worst, least, average perceived pain intensity as well the pain perceived at the time of the interview (scale from 0, 'no pain', to 10, 'pain as bad that you can imagine'). BPI also gives information about the quality of pain, the type and site of pain, and the performed treatments. Patients are also asked to indicate the relief from pain during the last week because of pain treatment on a scale going from 0% (no relief) to 100% (complete relief). Lastly, BPI evaluates the interference of pain with seven daily functions (general activity, mood, walking ability, normal work, relation with other people, sleep and enjoyment of life) (scale from 0, 'does not interfere', to 10 'completely interferes'). However, because ALS causes the loss of walking ability and interferes with work, these two functions were not considered for the analyses. A Pain Severity Index (PSI) was derived by averaging the following pain severity items: worst and average pain and pain perceived at the time of the interview [6]. Pain was considered severe when PSI ratings were ≥7. A Pain Interference Index (PII) was derived by averaging the interference of pain on daily functions [6].

Patients' physical status was evaluated with ALS Rating Functional Scale-revised (ALSFRS-R), a 12-item scale assessing various physical functions potentially compromised in ALS. Each item is rated from 0 (worse) to 4 (best), corresponding to a total score ranging from 0 to 48.

Statistical analysis

Comparisons between means were performed with Student's *t*-test. Frequencies were compared with Yates' chi-square. Correlations were calculated using Pearson's and Spearman's coefficients. All tests were two-tailed. A P level <0.05 was considered significant. Analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

The study has been approved by the Ethical Committee of our institution, and each participant signed a written informed consent.

Results

The ALS population included 160 patients, 91 men and 69 women, with a mean age at the time of the interview of 62.4 years (SD 10.6) and a mean disease duration of 31.0 months (SD 15.4, median 25.5). The 160 controls (91 men and 69 women) had a mean age of 62.7 years (SD 11.0). A comparison of patients with ALS and controls and patients' clinical data are given in Table 1.

Pain in the preceding week was more frequently reported by patients with ALS (91, 56.9%) than controls (53, 33.1%) ($P = 0.001$). Mean maximum pain score was 7.0 (SD 2.1) in cases and 6.2 (SD 2.7) in controls ($P = 0.06$). Fifty-nine (36.9%) patients and 37 (23.1%) controls reported pain at the time of the interview ($P = 0.007$). Mean PSI was 5.0 (SD 1.8) for patients and 4.6 (SD 2.6) for controls ($P = 0.09$). Severe pain (PSI ≥ 7) was reported by 22 cases (13.8%) and 13 controls (8.1%) ($P = 0.11$).

Patients with or without pain had a similar age at the time of the interview [62.4 years (SD 10.6) vs. 62.3 years (SD 11.0); $P = 0.86$]. Pain was slightly, but not significantly, more frequent amongst patients with spinal onset [79 (59.8%) vs. 12 (41.4%), $P = 0.07$]. No differences were found in the both the genders. The presence of pain was correlated with a lower ALSFRS-R score [patients with pain, 26.7 (SD 12.2) and patients without pain 31.0 (SD 12.2), $P = 0.04$] and with a longer disease duration [patients with pain, 36.3 months (SD 14.3) and patients without pain,

Table 1 Comparison between cases and controls and clinical characteristics of cases

	Cases ($n = 160$)	Controls ($n = 160$)	P value
Gender (women) (n, %)	69 (43.1)	69 (43.1)	n.s.
Mean age at interview, years (SD)	62.4 (10.6)	62.7 (11.0)	n.s.
Site of onset (bulbar, %)	28 (17.5)	–	
Mean disease duration, months (SD)	31.0 (15.4)	–	
Mean ALSFRS-R score (SD)	28.7 (12.2)	–	

ALSFRS-R, Amyotrophic Lateral Sclerosis Rating Functional Scale-revised.

24.1 months (SD 9.5), $P = 0.02$]. PSI score was significantly higher in patients with lower ALSFRS-R score ($P = 0.008$).

Localization of pain in cases and controls is given in Table 2; patients with ALS reported pain more frequently at the extremities ($P = 0.006$).

Pain interference on daily functions

Pain interfered with all areas of daily function (Table 3). All areas of function and the summary score PII were significantly correlated with PSI at $P < 0.001$ level (data not shown). Mean PII score was not different in patients and controls, but patients referred a greater interference in the domains of enjoyment of life and relation with other people.

Therapy for pain

Sixty-four patients (70.3% of those with pain) and 24 controls (45.3% of those with pain) ($P = 0.003$) received a therapy for pain. In both patients and controls, the probability to be treated increased with higher PSI and PII scores [cases: PSI, treated, 5.2 (SD 1.9), untreated 4.2 (SD 1.5); $P = 0.01$; PII, treated 4.0 (SD 2.2), untreated 2.7 (SD 2.6); $P = 0.01$] [controls: PSI, treated 5.4 (SD 2.0), untreated 3.5 (SD 2.3), $P = 0.003$; PII, treated 4.2 (SD 2.5), untreated 2.1 (SD 2.1), $P = 0.002$].

Sixty-three patients with ALS (69.2% of those with pain) used pharmacological treatments for pain; eight patients underwent physical therapy for pain treatment and in one case, without concomitant pharmacological therapy. Twenty-four controls (45.3%) underwent drug therapy for pain control. In both cases and controls, non-steroidal anti-inflammatory drugs (NSAIDs) were the drugs more commonly used for the treatment of pain. However, ALS cases were more frequently prescribed non-opioid analgesics and opioids, alone or in association (Table 4). The efficacy of therapy was rated similarly in cases [58.1% (SD 27.1)] and controls [60.9% (SD 31.3)] (P = n.s.). No differences were found between therapies in the rating of pain control (data not shown).

Table 2 Localization of pain in patients with amyotrophic lateral sclerosis and controls

Localization of pain	Patients ($n = 91$)	Controls ($n = 53$)	P value
Head/Neck	18 (19.8%)	11 (20.8%)	n.s.
Trunk	5 (5.5%)	7 (13.2%)	n.s.
Back	26 (28.6%)	21 (39.6%)	n.s.
Upper/Lower limbs	69 (75.8%)	29 (54.7%)	0.009

Total is higher than 100% because more sites could be indicated.

Table 4 Therapies performed by patients for the control of pain

Therapy	Patients ($n = 91$)	Controls ($n = 53$)
NSAIDs	24 (38.1%)	13 (54.2%)
Non-opioid analgesics	15 (23.8%)	2 (8.3%)
Opioids	5 (7.9%)	0
NSAIDs and non-opioid analgesics	7 (11.1%)	3 (12.5%)
NSAIDs and opioids	4 (6.3%)	0
Muscle relaxants	2 (3.2%)	2 (8.3%)
Other drugs	12 (19.0%)	6 (25%)
Physical therapy	8 (12.7%)[a]	0
Treated patients	63 (69.2%)	24 (45.3%)
Not treated patients	28 (30.8%)	29 (54.7%)

Total is higher than 100% because patients could indicate more therapies; Other drugs include: in patients with amyotrophic lateral sclerosis, pregabalin (4), quinine sulfate (4), gabapentin (1) zinc oxide (1), medicinal (true) aloe (1), phytotherapy (1); in controls: homeopathic drugs (2), steroids (2), botulin toxin (1), vitamins (1); NSAIDs, non-steroidal anti-inflammatory drugs. [a]All but one patient undergoing physical therapy also used drugs for pain.

Table 3 Interference of pain on daily functions. All subjects with pain

Pain interference item (mean value, SD)	All subjects with pain			Subjects with severe pain (PSI ≥ 7)		
	Patients ($n = 91$)	Controls ($n = 53$)	P value	Patients ($n = 22$)	Controls ($n = 13$)	P value
General activity	3.6 (3.1)	3.8 (3.2)	n.s.	5.8 (3.5)	6.6 (2.3)	n.s.
Mood	4.8 (3.2)	4.0 (3.5)	n.s.	7.4 (2.1)	7.7 (2.9)	n.s.
Relation with other people	3.4 (3.0)	2.1 (3.0)	0.02	6.0 (3.1)	4.6 (3.1)	0.03
Sleep	2.9 (3.3)	2.9 (3.5)	n.s.	4.5 (3.4)	4.8 (3.1)	n.s.
Enjoyment of life	3.9 (3.2)	2.1 (2.9)	0.0009	6.8 (2.8)	3.6 (3.6)	0.006
Pain interference index	3.7 (2.4)	3.0 (2.5)	n.s.	5.9 (2.0)	5.5 (2.2)	n.s.

PSI, pain severity index.

Discussion

In this population-based controlled study, pain was found to be significantly more frequent in patients with ALS than in age- and gender-matched controls. Furthermore, more patients than controls rated pain as severe (score ≥ 7) and reported pain at the time of the interview; however, the PSI score was only slightly higher in patients with ALS than in controls. The presence of pain was not related to patients' gender or age, but it was more frequent in subjects with a more severe clinical picture and a longer disease duration, confirming the concept that in ALS, pain is mostly related to reduction of mobility [7]. However, even if less frequently, pain was also reported by patients in the early phases of ALS, usually in the form of cramps or painful muscle spasms [8,9].

The frequency of pain in our epidemiological series is in the high range of the values reported in literature [10–13] including the studies performed on patients with severe disability or terminally ill [14–16]. The low frequency of pain reported in the ALS C.A.R.E. database (21%), when compared to previous literature, indicates that pain is a 'hidden' symptom, often not reported by patients [17].

In patients with ALS, compared to controls, pain was more often localized at the extremities, in particular shoulders and hips. In both patients and controls, pain severely interfered on daily functions. Interestingly, in both groups, the most affected areas were mood and general activity; however, in patients with ALS, enjoyment of life and relation with other people were more severely affected by pain in patients than those in controls. Although this finding may be weakened by the fact that we have no information about mood in both patients and controls, as depression may confound both pain and daily functions, we think that it may also indicate that patients with ALS attribute a higher value than the general population to interpersonal relationships.

To the best of our knowledge, no study has formally evaluated the influence of pain on ALS patients' quality of life and depression. However, in a study on patients with ALS interested in assisted suicide, pain was frequently reported as a reason of general discomfort and desire for hastened death [18]. Conversely, in a larger Dutch study comparing patient with ALS and patient with cancer, who requested euthanasia [19], pain was significantly less often indicated as being unbearable in patients with ALS than in patients with cancer, and physicians of patients with cancer indicated pain and fatigue significantly more often as being unbearable than did physicians of patients with ALS. A cross-sectional study found that ALS patients with pain were more likely to be in depression than ALS patients without pain [20]. Lastly, the absence of pain has been considered an explanation for the low frequency of depression in ALS [21].

Pain was more frequently treated in patients with ALS than in controls, but treatment-related pain relief was similar in the two cohorts. The frequency of treatment reported by our patients with ALS (69%) was similar to that indicated in other series [12,22]. Both in patients with ALS and in controls, NSAIDs were the most commonly prescribed drugs, whilst non-opioid analgesics were more frequently prescribed to ALS cases. Opioids were prescribed only to ALS cases, alone or in association with NSAIDs. The diversity of drug prescriptions in ALS cases reflects both different manifestations of pain in ALS and the uncertainty about the effectiveness of different analgesics in ALS [2].

No differences were found in pain relief comparing different treatments. Mean pain relief rating (58.1%) was similar to that reported in other studies on neuromuscular diseases [12]. For both cases and controls, the main determinant for starting the treatment of pain was a higher rating of pain severity and a higher subjective level of interference with daily functions.

We did not formally assess the pathophysiology of pain in our cases and controls. Different mechanisms for pain in ALS are reported, including muscle spasms, contractures and spasticity, abnormal stresses on the musculoskeletal system imposed by weak musculature, joint pain because of immobilization or articular blocks [2]. In a few cases, complex regional pain syndrome and reflex sympathetic dystrophy have been also described in ALS [23,24].

A limit to our study is that it has a cross-sectional design; therefore, we could not determine the course of pain over time in our patients. However, because the study includes all patients prevalent in an Italian province, who are compared to a population-based series of controls, it has the advantage to avoid selection bias and to fully represent the ALS population. A second limit is the absence of a formal evaluation of depression in our patients.

Our findings indicate that pain is a common and substantial problem for many persons with ALS and is significantly more frequent than in population-based controls. Patients with ALS appear to be particularly sensitive to the effects of pain on their lives, especially regarding mood, social relationships and enjoyment of life. Our study indicates that pain is an underrecognized and undertreated symptom in ALS; therefore, every effort should be made to identify pain in patients with ALS and to treat it appropriately. Moreover, studies

are urgently needed to determine the best treatment for pain in patients with ALS.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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