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ORIGINAL ARTICLE

Under-recognized primary spontaneous pneumothorax in ALS: a multicenter retrospective study

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Abstract

Primary spontaneous pneumothorax (PSP) is not an uncommon disease, especially in patients with risk factors such as male gender, history of smoking, and low body mass index (BMI). Amyotrophic lateral sclerosis (ALS) is a rare disease caused by neurodegeneration of the motor neurons that share risk factors with PSP. The aim of this study was to determine the prevalence of PSP in ALS and find the significant risk factors related to PSP. We retrospectively reviewed the data from 86 patients with clinically probable or definite ALS from three different centers. Clinical characteristics, including age, sex, subtype, disease duration, body mass index, history of smoking, tracheostomy state, and ventilator use, were obtained. The ALS Functional Rating Scale-Revised Form (ALSFRS-R) total score and subscores were also retrieved from the medical records. In the results, six of the 86 patients (7%) had PSP. There were no statistically significant differences among the clinical characteristics and the ALSFRS-R scores between the patients with and without PSP, except for BMI and smoking ($p < 0.022$ and $p < 0.019$, respectively). A multivariate logistic regression analysis of smoking and BMI showed an odds ratio of 19.25. In conclusion, the existence of PSP in ALS may be under-recognized. Further well-designed, large studies are needed to elucidate the prevalence and pathophysiology of pneumothorax in ALS.

Keywords Amyotrophic lateral sclerosis · Dyspnea · Pneumothorax · Smoking · Body mass index

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease caused by the loss of motor neurons that eventually leads to muscle weakness and respiratory difficulty [1]. Clinical ALS-related respiratory symptoms include dyspnea, sleep-disordered breathing, and respiratory failure [1–3]. Pneumothorax is caused by the presence of gas within the pleural space, which is located between the lung and chest wall. Pneumothorax that is not associated with underlying lung disease is defined as primary spontaneous pneumothorax (PSP). The aim of this study was to determine the prevalence of PSP, which is an under-recognized respiratory complication of ALS, as well as the possible risk factors of PSP in ALS.

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Materials and methods

Participants

We enrolled patients with clinically probable/definite ALS according to the revised El Escorial criteria from three different tertiary hospitals in Korea. The patients' medical records were retrospectively reviewed, and patients with chronic obstructive pulmonary disease (COPD), tuberculosis, interstitial lung disease, lung cancer apparent on chest X-ray and/or CT, or past history of chest trauma (such as rib fracture) were excluded. To exclude iatrogenic pneumothorax, we also excluded ALS patients with a history of central venous catheter use. In addition, in order to exclude iatrogenic pneumothorax caused by ventilator use, ALS patients with insufficient medical records regarding ventilator mode, history of a change in ventilator mode, and less than 3 months of ventilator use at the time of the X-ray or CT evaluation were excluded. A total of 98 ALS patients were initially investigated. After exclusion according to the exclusion criteria stated above, there were 12 patients with ALS (11 ALS patients without admission history and 1 ALS patient with history of rib fracture), and finally a total of 86 ALS patients were enrolled. Each patient's chest X-ray and/or chest CT performed at any point of time were reviewed, and imaging performed during an adverse event was reviewed again in more detail by an experienced thoracic surgeon in order to confirm the presence of PSP. We defined PSP as the presence of pneumothorax without clinically apparent lung disease, as previously defined [4].

Clinical parameters

Clinical parameters, including age, sex, type of onset (bulbar or limb), disease duration, height, weight, body mass index (BMI), past history of smoking, presence of tracheostomy, and use of mechanical ventilation, were obtained. The most recent amyotrophic lateral sclerosis Functional Rating Scale Revised Form (ALSFRS-R) score was used. We defined an underweight BMI as that less than 18.5 kg/m^2 [5, 6].

Statistical analysis

Descriptive and frequency data are presented as means with standard deviations. Group comparisons were performed using the Wilcoxon rank sum test or Mann-Whitney and Pearson's chi-squared test where applicable. A multivariate logistic regression with forward stepwise selection was performed to assess the risk factors of PSP in patients with ALS. Variables significant at $p \leq .05$ in the Wilcoxon rank sum test or Mann-Whitney and Pearson's chi-squared tests were included in the multivariable stepwise logistic regression analysis. The final multivariate prediction model consisted of the variables selected from the stepwise regression. Odds ratios and 95% confidence intervals (CIs) were calculated. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software, version 22.0 (SPSS, Chicago, IL, USA).

Results

Among 86 patients with ALS, a total of 21 patients with ALS were admitted via emergency department. Among them, 2 patients were admitted due to aspiration pneumonia and the remaining 19 patients visited the emergency department due to dyspnea. PSP was present in 6 of the 86 ALS patients recruited. Among the 6 patients, 5 were male. The patients had a mean age of 57.3 years (range 46–75 years) (Fig. 1). Three patients had bulbar onset and the other 3 had limb-onset ALS. Five patients with PSP were smokers. The mean BMI of the 6 patients was 19.34 kg/m^2 (range 16.7–25.3 kg/m^2). All ALS patients with mechanical ventilation were applied by invasive mechanical ventilation for 24 h. For control hypercapnia, initially, the same ventilator mode (spontaneous timed mode biphasic positive airway pressure or inspiratory positive airway pressure (IPAP) 10 mmHg, expiratory positive airway pressure 5 mmHg, frequency 8, fraction of inspired oxygen 0.24) was applied by all ALS patients with invasive mechanical ventilators. Then, IPAP was modulated using arterial carbon dioxide level (< 45 mmHg). At the time of CT or X-ray examination, mean arterial carbon dioxide levels were 34.8 ± 3.63 mmHg in ALS patients without PSP and 38.6 ± 3.13 mmHg in ALS patients with PSP. In addition, mean tidal volume of ALS patients without pneumothorax was 454 ± 71.11 mL and 466.8 ± 54.53 mL in ALS patients with PSP at the time of CT or X-ray examination.

Demographic and clinical characteristics of ALS patients

Data from the 86 ALS patients were retrospectively reviewed. The mean age of the patients was 62.17 ± 11.02 years. The sex ratio was 52:34 (male:female), and 53 patients were smokers. The mean height was 162 ± 8.3 cm and the mean body weight was 57.18 ± 9.9 kg. Fourteen of the 86 patients had a low BMI (i.e., less than 18.5 kg/m^2), and the mean BMI was 20.80 ± 5.73 kg/m^2. The mean ALSFRS-R total score was 30.94 ± 13.67. Thirty patients had bulbar-onset ALS. We also evaluated the lipid profiles of 41 patients. The mean total cholesterol (TC) was 184.25 ± 42.4 mg/dL, the mean triglyceride (TG) level was 112.93 ± 75.71 mg/dL, and the mean low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels were 109.77 ± 37.06 mg/dL and 50.73 ± 16.39 mg/dL, respectively.

The clinical characteristics of ALS patients with and without pneumothorax

Based on radiological results, 6 patients had primary spontaneous pneumothorax. We compared the clinical, laboratory, and ALSFRS-R data of ALS patients with and without PSP (Table 1). We found no significant difference in age, sex, or ALS subtype between the two groups. There was no difference in disease duration or mean BMI. Interestingly, patients with PSP were significantly more likely to have a low BMI (i.e., < 18.5 kg/m^2) compared with patients without PSP ($p = 0.022$). The presence of smoking was also significantly more prevalent in ALS patients with PSP ($p = 0.019$). Among the patients with ALS included this study, chest CT was

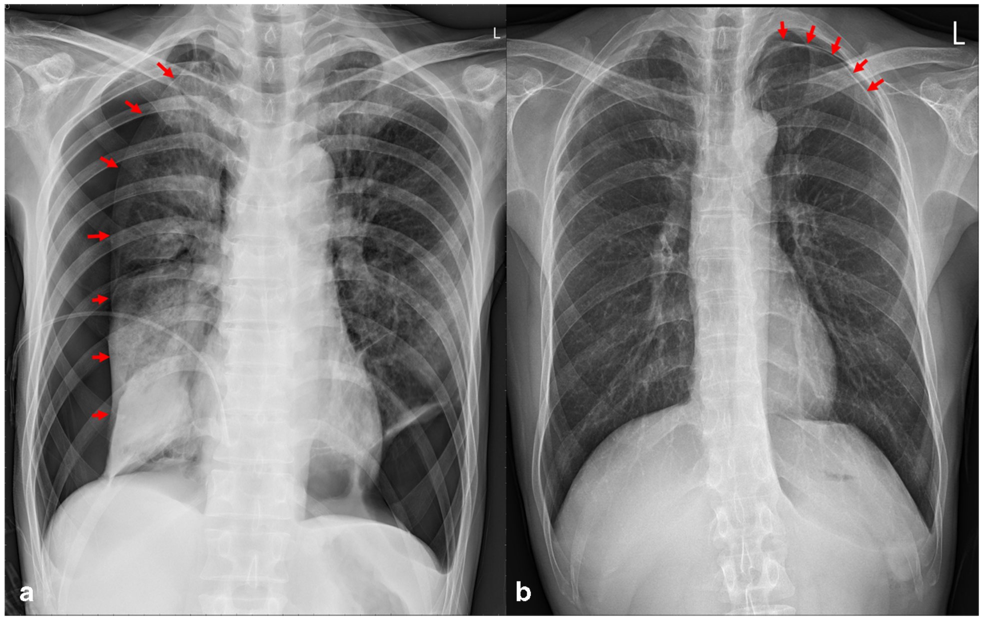

Fig. 1 Chest plain radiographs of amyotrophic lateral sclerosis (ALS) patients with pneumothorax. **a** 75-year-old man with ALS bulbar onset. **b** 46-year-old man with ALS bulbar onset

performed in 20 ALS patients without PSP (25%) and 2 ALS patients with PSP (100%). In ALS patients with PSP, there was an increased number of emphysema in chest CT compared with ALS patients without PSP (9/20; 45% vs. 2/2; 100%) (Table 1). However, it is not statistically significant (Table 1). In addition, ALS patients with PSP were significantly more likely to admit via emergency department ($p = 0.029$) (Table 1).

We also evaluated the level of the systemic inflammation biomarker, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, there was no statistically significant difference between the two groups (Table 1).

We also evaluated the use of ventilators and the presence of tracheostomy and found there was no statistically significant difference between the two groups ($p = 0.545$ and 0.912, respectively). The lipid profiles, including TC, TG, HDL, and LDL, also were not different between the two groups.

We further analyzed the risk factors of smoking and low BMI using a multivariate logistic regression analysis. The analysis showed odds ratios of 9.11 and 5.52 for smoking and low BMI, respectively (Table 2). The odds ratio observed in patients who were both smokers and underweight was 19.25, which was statistically significant (Table 3).

Discussion

Amyotrophic lateral sclerosis (ALS) is a progressive disease that involves the motor neurons [7, 8]. Involvement of the respiratory muscles is an important clinical feature that needs to be considered, as it is the leading cause of death in ALS [1, 9–11]. Although ALS has no direct effect on the lungs, disease progression eventually leads to devastating mechanical dysfunction of the respiratory system. The muscles involved in ALS can be divided into inspiratory, expiratory, and upper airway muscles [12]. Until recently, the clinical respiratory symptoms of ALS that received the most focused were dyspnea, hypercapnia, and respiratory failure. There have been only a few case reports related to pneumothorax in ALS.

Pneumothorax is caused by abnormal air collection in the pleural space. The etiology of pneumothorax varies, but when pneumothorax occurs in the absence of trauma, it is known as spontaneous pneumothorax (SP). SP is further classified into primary and secondary SP. When SP occurs without underlying lung disease, it is termed PSP. The incidence of PSP is under-recognized, and unlike trauma-related or secondary pneumothorax, the clinical symptoms of PSP are mild and non-specific. The prevalence of PSP varies, with an annual incidence rate between 18–28 and 1.2–6 per 100,000 men and women, respectively [13]. The risk factors of PSP are tall height, low BMI, male gender, and smoking [13]. To the best of our knowledge, this is the first study that attempted to determine the prevalence of PSP. We showed a PSP prevalence of 7% in ALS patients.

Respiratory involvement in ALS can be divided into three areas. First, the upper airway muscles, which constitute the tongue, pharyngeal, and laryngeal muscles, play an important role in swallowing. Second, the expiratory muscles that contract the abdominal muscles increase intrathoracic pressure, which is eventually expelled at a high velocity in the form of a cough. The third set of muscles is the inspiratory muscles, which includes the diaphragm and external intercostal muscles. Dysfunction of any of the three areas can result in respiratory dysfunction in ALS. However, pneumothorax in ALS has previously only been studied in case reports [14, 15].

Table 1 Characteristic of patients with amyotrophic lateral sclerosis in this study

	No pneumothorax Group A ($n = 80$)	Pneumothorax Group B ($n = 6$)	p value
Age	62.54 ± 10.98	57.33 ± 11.43	0.206
Sex (M:F)	47:33	5:1	0.235
ALS subtype (bulbar:limb onset)	27:53	3:3	0.408
Disease duration (months)	14.04 ± 16.10	24.60 ± 13.99	0.111
Height (cm)	161.95 ± 8.28	166.0 ± 7.97	0.459
Body weight (kg)	57.52 ± 9.92	53.00 ± 9.19	0.288
BMI	21.88 ± 3.71	19.34 ± 3.97	0.155
Underweight (BMI < 18.5)	11:69	3:3	0.022
Smoking (non-smoker:smoker)	52:28	1:5	0.019
Presence of tracheostomy	12:68	1:5	0.912
Mechanical ventilator usage:non usage	18:62	2:4	0.545
ALSFRS-R total score	31.09 ± 13.55	29.50 ± 16.06	0.729
Speech	2.79 ± 1.13	2.50 ± 1.76	0.893
Salivation	3.18 ± 1.18	3.17 ± 1.33	0.865
Swallowing	2.79 ± 1.40	2.67 ± 1.37	0.844
Writing	2.33 ± 1.55	2.17 ± 1.72	0.728
Feeding	2.38 ± 1.46	2.33 ± 1.21	0.262
Dressing	2.30 ± 1.40	1.83 ± 1.47	0.389
Turning	2.61 ± 1.56	2.50 ± 1.98	0.97
Walking	2.28 ± 1.37	2.50 ± 1.64	0.595
Climbing	1.96 ± 1.60	2.00 ± 1.67	0.981
Dyspnea	2.63 ± 1.63	2.83 ± 1.47	0.95
Orthopnea	2.81 ± 1.68	2.67 ± 2.07	0.894
Respiratory insufficiency	3.00 ± 1.49	2.83 ± 1.60	0.458
Total cholesterol	136.00 ± 31.00	189.24 ± 40.57	0.061
TG (mg/dL)	108.33 ± 47.25	113.44 ± 78.86	0.756
LDL (mg/dL)	76.33 ± 31.21	113.48 ± 36.24	0.09
HDL (mg/dL)	39.33 ± 15.89	52.00 ± 16.24	0.226
LDL/HDL (mg/dL)	2.06 ± 0.68	2.39 ± 1.05	0.863
ESR (mm/h)	26.5 ± 15.99	30 ± 25.70	0.452
CRP (mg/dL)	4.45 ± 6.61	4.81 ± 4.52	0.912
Presence of subclinical emphysema on CT	9/20 (45%)	2/2 (100%)	0.476
Pts diagnosed by X-ray:CT	60:20	4:2	0.782
Pts admitted via emergency department	17/80 (21%)	4/6 (66%)	0.029

A recent randomized controlled study of 74 patients assessed diaphragm pacing in ALS [2]. The study found pneumothorax in 4 patients, with a prevalence of 5% in both the treated and untreated group and no statistical difference between them. The results from our study are in accordance with this large prospective study, as we also found no statistically significant difference in the occurrence of PSP between patients with or without ventilator usage ($p = 0.545$). These data indirectly illuminate that mechanical ventilator–related pneumothorax may play a minor role in ALS; however, further well-designed, large studies are needed to confirm these findings.

The results of several evidence-based studies have shown that smoking is the only probable risk factor in the epidemiology of ALS [16, 17]. However, the pathomechanism of smoking in ALS remains to be elucidated. Another study

Table 2 Multivariate logistic regression analysis for assessing risk factor of pneumothorax in patients with ALS

	Beta coefficient	Standard error	Odds ratio (95% CI)	p value
Smoking	2.21	1.12	9.11 (1.01–81.86)	0.049
Underweight (BMI < 18.5)	1.71	0.92	5.52 (0.90–33.68)	0.064

Table 3 Multivariate logistic regression analysis for risk factor of pneumothorax in patients with ALS

	Beta coefficient	Standard error	Odds ratio (95% CI)	*p* value
Smoking + underweight	2.96	1.12	19.25 (2.13–174.19)	0.008

demonstrated a strong relationship between low BMI and ALS and found that low BMI was an independent prognostic factor of ALS [18, 19]. Interestingly, PSP shares common risk factors with ALS, including smoking and low BMI [20–22]. In our study, we found a statistically significant odds ratio of 9.11 for smoking, and a non-significant odds ratio of 5.52 for low BMI. However, when we included smoking and low BMI in a multivariate logistic regression analysis, we found an odds ratio of 19.25, which was statistically significant ($p = 0.008$).

There are several explanations for the role of low BMI in ALS. One possible explanation is that energy deficiency, which is commonly observed in ALS along with low BMI, leads to alpha 1 antitrypsin deficiency, which in turn leads to emphysema-like changes, eventually causing PSP [23]. In accordance with this hypothesis, a recent study found a significant reduction in alpha 1 antitrypsin in the cerebrospinal fluid of ALS patients [24]. The data suggesting that smoking is a risk factor for ALS also consolidates this theory, as smoking is also known to reduce alpha 1 antitrypsin [25]. Another possible hypothesis is that with a significant reduction of BMI there is a comparative increase in body height and chest height, thereby increasing negative chest pressure and causing PSP. We analyzed the lipid profile of some of the patients in our study as it generally reflects nutritional status. In ALS, hypolipidemia is known to be a poor prognostic factor [26]. As shown in Table 1, there was no statistically significant difference in the lipid profile of ALS patients with or without pneumothorax. Therefore, explaining the nutritional status via the lipid profile may not be an accurate marker with respect to pneumothorax. Other markers, such as alpha 1 antitrypsin, may be more accurate.

Our study is not without limitations. First, although it was a multicenter study, the data were collected retrospectively, thereby lowering its statistical power. Second, the diagnosis of pneumothorax was made based mainly on X-rays, so minor or equivocal pneumothorax may have been under-recognized. We excluded patients with known lung disease, history of chest trauma, and underlying autoimmune disease through a review of medical records, radiologic, and laboratory findings; however, this strategy may not have been sufficient to absolutely exclude the preexistence of these conditions. Finally, we enrolled ALS patients who were on mechanical ventilators. However, we excluded all patients in which the ventilator mode was changed more than once, those who had been using a ventilator for less than 3 months at the time of the study, and those whose medical records suggested that the ventilator mode was insufficient.

In summary, this is the first study to attempt to determine the prevalence of pneumothorax in ALS, which may be under-recognized due to the presence of other severe respiratory conditions. We also assessed the risk factors of PSP in ALS and tried to extrapolate the possible pathomechanism of PSP in ALS. Further well-designed, large studies are needed to elucidate the role of PSP in ALS. During the evaluation of ALS patients, clinicians should be aware of primary spontaneous pneumothorax as a respiratory complication.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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