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Original Article

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Pattern of Respiratory Deterioration in Sporadic Amyotrophic Lateral Sclerosis According to Onset Lesion by Using Respiratory Function Tests

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Most amyotrophic lateral sclerosis (ALS) patients show focal onset of upper and lower motor neuron signs and spread of symptoms to other regions or the other side clinically. Progression patterns of sporadic ALS are unclear. The aim of this study was to evaluate the pattern of respiratory deterioration in sporadic ALS according to the onset site by using respiratory function tests. Study participants included 63 (42 cervical-onset [C-ALS] and 21 lumbosacral-onset [L-ALS]) ALS patients and 31 healthy controls. We compared respiratory function test parameters among the 3 groups. Age was 57.4±9.6 (mean±SD), 60.8±9, and 60.5±7 years, and there were 28, 15, and 20 male participants, in the C-ALS, L-ALS, and control groups, respectively. Disease duration did not differ between C-ALS and L-ALS patients. Sniff nasal inspiratory pressure (SNIP) was significantly low in C-ALS patients compared with controls. Maximal expiratory pressure (MEP) and forced vital capacity percent predicted (FVC% predicted) were significantly low in C-ALS and L-ALS patients compared with controls. Maximal inspiratory pressure to maximal expiratory pressure (MIP:MEP) ratio did not differ among the 3 groups. Eighteen C-ALS and 5 L-ALS patients were followed up. ΔMIP, ΔMEP, ΔSNIP, ΔPEF, and ΔFVC% predicted were higher in C-ALS than L-ALS patients without statistical significance. Fourteen C-ALS (77.8%) and 3 L-ALS (60%) patients showed a constant MIP:MEP ratio above or below 1 from the first to the last evaluation. Our results suggest that vulnerability of motor neurons in sporadic ALS might follow a topographic gradient.

Key words: Amyotrophic lateral sclerosis, Respiratory function test, Maximal inspiratory pressure, Maximal expiratory pressure, Progression

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that causes both upper and lower motor neuron loss [1]. Most ALS patients show focal onset of upper and lower motor neuron signs and spread of symptoms to other regions or

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the other side on neurological examination [2]. However, onset and progression mechanisms of ALS remain unclear [3]. Although the clinical presentation of ALS suggests a focal onset mechanism [2], multifocal [4] and generalized onset mechanisms remain possible, particularly in familial ALS with genetic defects [5-7]. Recent study has shown prion-like propagation of superoxide dismutase-1 misfolding [8, 9] and TDP-43 [10]. Another study suggests prion-like propagation of TDP-43 between upper and lower motor neuron regions through the synapse [11].

Respiratory function is an important factor for survival of ALS patients [12, 13] and can be used for predicting survival of these patients [14, 15]. Respiratory function tests include forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and sniff nasal inspiratory pressure (SNIP) [16].

MIP and MEP reflect inspiratory and expiratory muscle function, respectively. Humans use the diaphragm and external intercostal and internal intercostal muscles during relaxed respiration. However, additional muscles are recruited during forced inspiration and expiration; the diaphragm, external intercostals, scalenes, sternocleidomastoid, upper trapezius, and internal intercostals are used for forced inspiration, and the internal intercostals, rectus abdominis, external obliques, internal obliques, pectoralis major, and latissimus dorsi for forced expiration [17]. These muscles are innervated by the accessory nerve and cervical and thoracic nerve roots. Some spinal nerve roots innervate both inspiratory and expiratory muscles. Dysfunction of spinal nerve roots that innervate both inspiratory and expiratory muscles may result in reductions in both MIP and MEP. However, the diaphragm, the main muscle for inspiration, is innervated by the phrenic nerve from the C3, C4, and C5 nerve roots. Previous study has shown the importance of the phrenic nerve in survival of ALS patients [18], and that the diaphragm is used for inspiration and not expiration [19].

We hypothesized that the MIP:MEP ratio would differ between ALS patients with initial onset of symptoms in the cervical region (C-ALS) and those with initial onset of symptoms in the lumbosacral region (L-ALS) if the disease follows a course of focal onset and contiguous propagation. The aim of this study was to evaluate the pattern of respiratory deterioration in sporadic ALS according to the legion of onset by using respiratory function tests.

MATERIALS AND METHODS

Subjects

Clinical and respiratory function test data obtained from a cohort of consecutive sporadic ALS patients from March 2012 through October 2014 were retrospectively analyzed. ALS patients were diagnosed with clinically probable or clinically definite ALS by revised El Escorial criteria [1]. Data from each patient were collected at the time of initial respiratory function testing. One hundred forty-four patients were included (bulbar onset [n=44], cervical onset [n=72], lumbosacral onset [n=23] both cervical and lumbosacral onset [n=5]). Patients were excluded who (1) had clinical onset with bulbar symptoms (n=44), (2) showed predicted FVC% values below 50% (n=26), (3) had simultaneous onset in the cervical and lumbar region (n=5), (4) could not undergo respiratory function tests because of severe bulbar weakness (n=4), or (5) had co-existing pulmonary disease (e.g., chronic obstructive pulmonary disease; n=2). Subsequently, 63 patients were included in this study. Onset region was cervical in 42 and lumbosacral in 21 patients. A revised ALS functional rating scale (ALSFRS-r) and ALSFRS-r bulbar subscore (three questions about speech, salivation and swallowing) was assessed [20]. Thirty-one healthy age and sex-matched subjects who did not have pulmonary disease were recruited as controls. Eighteen C-ALS and 5 L-ALS patients underwent follow-up respiratory function tests (Fig. 1). For these patients, we calculated and compared parameter changes for MIP, MEP, SNIP, pulmonary expiratory flow (PEF), and FVC% predicted. For example, ΔMIP was calculated as follows: value of MIP at the first examination - value of MIP at the last examination/time gap between the examinations (months). The study was approved by the ethics committee of Seoul National University Hospital (IRB No.1405-105-580).

Respiratory function tests

All procedure techniques and interpretive values were in accordance with American Thoracic Society/European Respiratory Society recommendations [16].

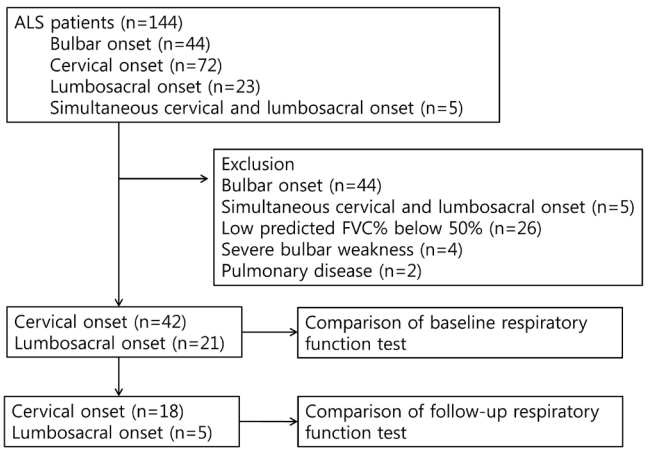

Fig. 1. Flow chart of this study.

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Forced vital capacity

FVC was measured in the sitting position with a spirometer (Flowscreen® CT; ERT, Philadelphia, PA, USA). The highest value among 3 or more repeated measurements was selected for comparison with values predicted from age, sex, and height (FVC% predicted) [21].

Sniff nasal inspiratory pressure

SNIP was determined with the patient seated by measuring the pressure through a plug occluding one nostril during sniffs performed through the contralateral nostril (Micro respiratory pressure meter; VIASYS Healthcare [CareFusion Corporation], San Diego, CA, USA). The highest value among at least 3 repeated measurements was selected as SNIP.

Maximal inspiratory pressure and maximal expiratory pressure

MIP and MEP were measured using a standard mouthpiece connected to a pressure transducer (Micro respiratory pressure meter; VIASYS Healthcare [CareFusion Corporation], San Diego, CA, USA). The highest values among at least 3 repeated measurements were selected as MIP and MEP.

Peak expiratory flow

Peak expiratory flow was measured using a commercially available device (MicroPeak® peak flow meter, CareFusion Corporation, San Diego, CA, USA).

Statistical analysis

Student's *t*-test and the chi-square test were used to analyze demographics and respiratory function test results between C-ALS and L-ALS patients. ANOVA with post hoc testing was used for comparisons between C-ALS patients, L-ALS patients, and controls. Pearson's correlations and corresponding p-values were used to evaluate the relationships between respiratory parameters in the C-ALS and L-ALS patients. We compared changes of respiratory function parameters per month between C-ALS and L-ALS patients by using Student's *t*-test. SPSS ver. 22.0 was used for data analysis, and the significance level was set at $p<0.05$.

RESULTS

Study participants included 42 C-ALS patients, 21 L-ALS patients, and 31 age and sex-matched healthy controls. Ratios of male to female participants were as follows: 28/14 (2:1) for C-ALS, 15/6 (2.5:1) for L-ALS, and 20/11 (1.8:1) for controls. Age was 57.4±9.6 (mean±SD), 60.8±9, and 60.5±7 years in the C-ALS, L-ALS, and control groups, respectively. Disease duration did not differ between C-ALS and L-ALS patients (18.5±14.5 vs. 18±13.8 months).

Results of respiratory function tests are summarized in Table 1. The C-ALS and L-ALS groups showed no statistical difference in ALSFRS-r (36.5±6.6 vs. 38.7±7.9) or ALSFRS-r bulbar subscore (10.4±1.3 vs. 10.8±2.1). C-ALS patients showed significantly low MIP compared with L-ALS patients and controls. SNIP was significantly low in C-ALS patients compared with controls, but not with L-ALS patients. MEP and FVC% predicted was significantly low in C-ALS and L-ALS patients compared with controls. The MIP:MEP ratio did not differ among the 3 groups (1.15±0.87, 1.1±0.4, and 1±0.3 in the C-ALS, L-ALS, and control groups, respectively).

SNIP of the C-ALS and L-ALS patients showed positive correlation with MIP ($r=0.62$ and $r=0.72$, respectively; $p<0.05$), MEP ($r=0.37$ and $r=0.56$, respectively; $p<0.05$), PEF ($r=0.64$ and $r=0.48$, respectively; $p<0.05$), and FVC% predicted ($r=0.56$ and $r=0.51$, respectively; $p<0.05$).

Table 1. Results of respiratory function tests of ALS patients according to the onset region and control

	C-ALS (n=42)	L-ALS (n=21)	Control (n=31)
Sex (M:F)	28:14	15:6	20:11
Onset Age (years)	57.4±9.6	60.8±9	60.5±7
Disease duration (months)	18.5±14.5	18±13.8	
ALSFRS-r	36.5±6.6	38.7±7.9	
ALSFRS-r bulbar	10.4±1.3	10.8±2.1	
Height	162.5±7.1	164.1±7.1	164.4±7
Weight	61.4±10.1	60±8.6	63.3±7
BMI	23.2±3.2	22.2±2.4	23.5±2.9
MIP (cmH_2O)	43.2±23.9[a,b]	57.9±22.3	71.4±31.4
MEP (cmH_2O)	44±22.1[a]	53.4±22.3[a]	67.4±18.2
MIP:MEP ratio	1.15±0.87	1.1±0.4	1.05±0.3
SNIP (cmH_2O)	43.4±23.8[a]	59.1±35	72.9±37.8
PEF (L/min)	367.9±127.8	358±120	389.1±124.2
FVC% predicted	80.4±15.1[a]	82.2±16.3[a]	99.7±7.7

Values are expressed as mean±SD.
C-ALS: cervical-onset amyotrophic lateral sclerosis, L-ALS: lumbosacral-onset amyotrophic lateral sclerosis, M: male, F: female, ALSFRS-r: revised amyotrophic lateral sclerosis functional rating scale, ALSFRS-r bulbar: revised amyotrophic lateral sclerosis functional rating scale bulbar subscore for speech, salivation, and swallowing, BMI: body mass index, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure, SNIP: sniff nasal inspiratory pressure, PEF: peak expiratory flow, FVC: forced vital capacity.
[a]$p<0.05$ compared with control. [b]$p<0.05$ compared with L-ALS.

The 18 C-ALS and 5 L-ALS patients who attended follow-up did not show differences in sex, age, or the number of follow-up examinations. Respiratory function parameters showed serial decline on follow-up studies. ΔMIP, ΔMEP, ΔSNIP, ΔPEF, and ΔFVC% predicted were higher in C-ALS than L-ALS patients without statistical significance (Table 2). Fourteen C-ALS patients (77.8%) and 3 L-ALS patients (60%) showed a constant MIP:MEP ratio above 1 or below 1 from the first examination to the last examination (Fig. 2 and 3).

Table 2. Results of respiratory function tests at follow-up

	C-ALS (n=18)	L-ALS (n=5)	p-value
Sex (male:female)	11:7	4:1	0.41
Age	55.4±8.4	60.4±8	0.25
Number of examinations	2.4±1.1	3.4±1.3	0.13
ΔMIP (cmH_2O)	2.5±3	0.4±1.6	0.16
ΔMEP (cmH_2O)	1.7±3	0.3±1	0.30
ΔSNIP (cmH_2O)	1.5±2.1	0.02±2	0.17
ΔPEF (L/min)	12.3±14.7	0.5±9.7	0.11
ΔFVC% predicted	2.3±2.4	1.8±1.2	0.62

Values are expressed as mean±SD.
Δ means change per month calculated as follows: (value at last examination - value at first examination)/time gap between the examinations (months).

DISCUSSION

Our study demonstrated that there were no differences in the MIP:MEP ratio between C-ALS and L-ALS patients. If sporadic ALS has a single region of onset followed by contiguous progression, MIP:MEP ratio should be lower in the C-ALS patients compared with the L-ALS patients. Therefore, the results of our study suggest that focal onset and contiguous progression are not likely.

Both C-ALS and L-ALS patients showed a decline in respiratory function on follow-up examination. However, ΔMIP, ΔMEP, ΔSNIP, ΔPEF, and ΔFVC% were higher in C-ALS than L-ALS patients although there was no statistical significance. From our results, we speculated that vulnerability of the motor neurons to degeneration in ALS might differ by topographical region, resulting in apparent progressive loss of motor neurons according to initial topographical gradient. Progression rate of FVC differed among patients, even those with ALS in the same onset region (Fig. 2 and 3).

ALS patients were excluded from this study if they had an FVC% predicted of <50%, respiratory failure or a possible need for assisted ventilation, or bulbar symptoms [22]. We only enrolled

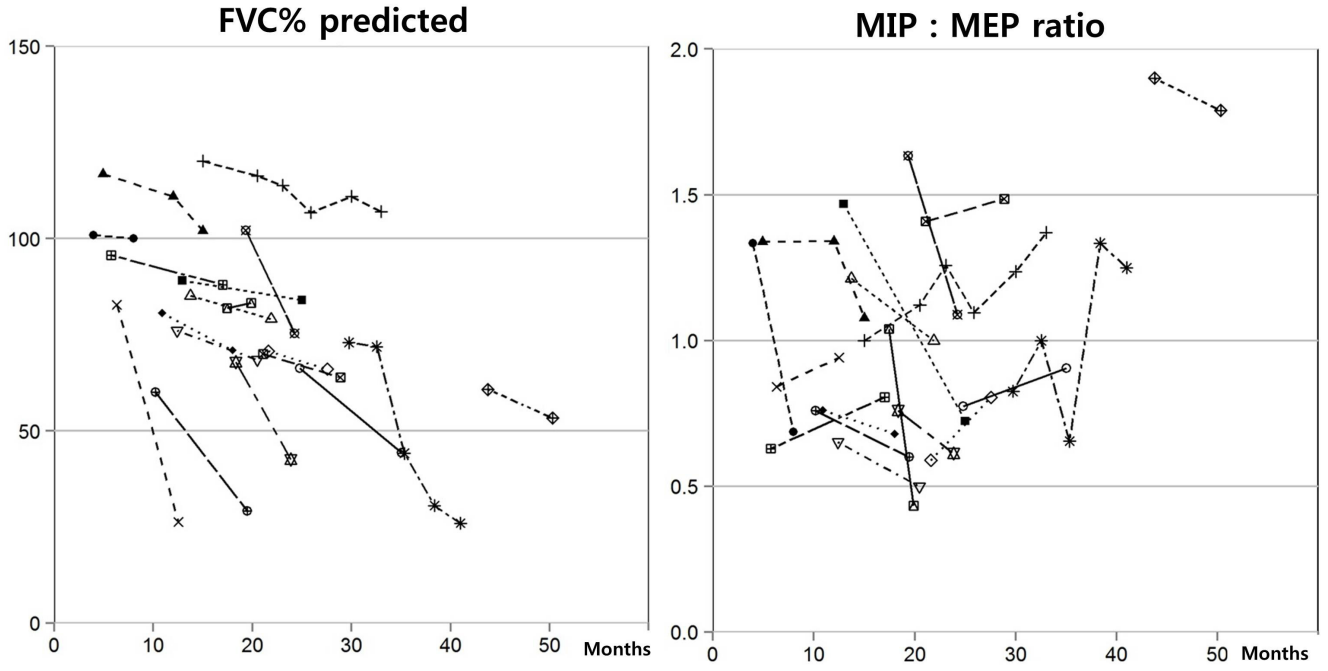

Fig. 2. Follow-up analysis of forced vital capacity percent predicted (FVC% predicted) and minimal inspiratory pressure to minimal expiratory pressure (MIP:MEP) ratio in the cervical-onset amyotrophic lateral sclerosis (C-ALS) patients. Decreased FVC% predicted was found on follow-up. Four patients showed a change in the MIP:MEP ratio to above or below 1. Fourteen patients (77.8%) showed a constant MIP:MEP ratio above or below 1 from the first to the last examination.

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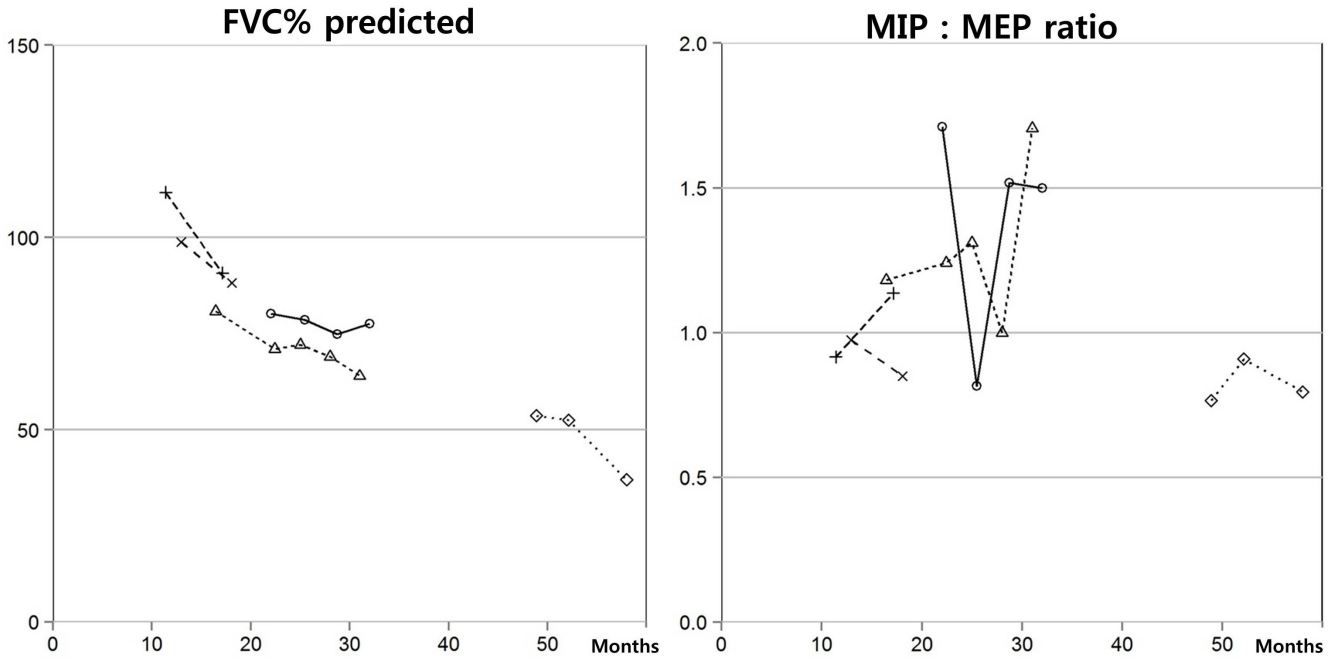

Fig. 3. Follow-up analysis of FVC% predicted and MIP:MEP ratio in the lumbar-onset ALS (L-ALS) patients. Decreased FVC% predicted was found on follow-up. Two patients showed a change in the MIP:MEP ratio to above or below 1. Three patients (60%) showed a constant MIP:MEP ratio above or below 1 from the first to the last examination.

patients without respiratory failure because the aim of this study was to evaluate changes in MIP and MEP between patients with different onset regions.

SNIP could be a good option for monitoring ALS patients with bulbar weakness [23, 24], who may not be able to undergo certain respiratory function tests. MIP and MEP in our study population showed statistical correlation with other respiratory function parameters including SNIP in the Pearson's correlation analysis. However, SNIP reflects only inspiratory function and shows delayed decline compared with FVC [25]. Therefore, we used the MIP:MEP ratio instead of the SNIP:MEP ratio in the present study.

This study has several limitations. First, not all patients underwent follow-up examination. Of note, only 5 patients were followed up in the L-ALS group. Results of follow-up examination in the L-ALS group might be of no relevance because of the small numbers of patients. However, 14 C-ALS patients showed a similar pattern for the MIP:MEP ratio as the L-ALS patients in the follow-up study. Second, because this study was conducted retrospectively, we could not enroll very early stage ALS patients. However, MIP and MEP do not decrease in ALS until significant loss of motor neurons. Third, we did not enroll bulbar-onset ALS patients. Severe bulbar weakness in the early stages of ALS would have affected the ability of the patient to carry out respiratory function testing; therefore, MIP and MEP would not have accurately reflected respiratory function in these patients.

Despite these limitations, this study is the first to use respiratory function parameters to investigate the theory of a disease course of focal onset and contiguous progression in sporadic ALS. This theory cannot be explained by our results. Sporadic ALS might have multiple or generalized onset sites, and vulnerability of motor neurons in sporadic ALS might follow a topographic gradient. Further study is warranted to investigate this hypothesis.

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