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근위축성측삭경화증 환자의 수면 중 저산소증의 발현 양상과 인지기능 저하와의 연관성

The pattern of manifestation of nocturnal hypoxia and its relationship with cognitive dysfunction in patients with amyotrophic lateral sclerosis

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서울대학교 대학원

의학과 뇌신경과학 전공

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이 논문을 의학석사 학위논문으로 제출함

2012년 10월

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의학과 뇌신경과학 전공

박 수 연

박수연의 의학석사 학위논문을 인준함.

2013년 1월

위원장 남현우 (인)

부위원장 김상윤 (인)

위원 임재영 (인)

학위논문 원문제공 서비스에 대한 동의서

본인의 학위논문에 대하여 서울대학교가 아래와 같이 학위논문 저작물을 제공하는 것에 동의합니다.

1. 동의사항

① 본인의 논문을 보존이나 인터넷 등을 통한 온라인 서비스 목적으로 복제할 경우 저작물의 내용을 변경하지 않는 범위 내에서의 복제를 허용합니다.

② 본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제·배포 및 전송 시 무료로 제공하는 것에 동의합니다.

2. 개인(저작자)의 의무

본 논문의 저작권을 타인에게 양도하거나 또는 출판을 허락하는 등 동의 내용을 변경하고자 할 때는 소속대학(원)에 공개의 유보 또는 해지를 즉시 통보하겠습니다.

3. 서울대학교의 의무

①서울대학교는 본 논문을 외부에 제공할 경우 저작권 보호장치(DRM)를 사용하여야 합니다.

②서울대학교는 본 논문에 대한 공개의 유보나 해지 신청 시 즉시 처리해야 합니다.

논문제목: 근위축성측삭경화증 환자의 수면 중 저산소증의 발현 양상과 인지기능 저하와의 연관성

학위구분 : 석사 ▣· 박사 □

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서울대학교총장 귀하

Abstract

The pattern of manifestation of nocturnal hypoxia and its relationship with cognitive dysfunction in patients with amyotrophic lateral sclerosis

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Background: Amyotrophic lateral sclerosis (ALS) is a common neurodegenerative disease that leads to the progressive weakness of the respiratory muscles and limb muscles. Consequently, most patients with ALS exhibit progressive hypoventilation, which easily worsens during sleep. The aim of this study was to evaluate the effect of nocturnal hypoxia on the cognitive function of patients with ALS and assess the pattern of nocturnal hypoxia in the patients with ALS.

Method: Twenty-three patients with either definite or probable ALS were recruited for the study. The patients were grouped on the basis of the presence of nocturnal hypoxia, and their clinical characteristics. Cognitive functions including attention, executive function, and memory were measured.

Results: Ten of the 23 patients with ALS (43.5%) exhibited nocturnal hypoxia and a poor performance for memory retention ($p = 0.039$) and retrieval efficacy ($p = 0.045$). In addition, 7 patients in the nocturnal hypoxia group showed a cluster of

desaturation pattern for hypoxia.

Conclusions: Compared to a group of patients without nocturnal hypoxia, the ALS patients with nocturnal hypoxia showed significant defects in memory function tests. Further studies are required to examine the causal relationship of this phenomenon and to understand the mechanism underlying the intermittent hypoxia in these patients.

Key words: amyotrophic lateral sclerosis, nocturnal hypoxia, cognitive dysfunction, intermittent hypoxia

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a common progressive neurodegenerative disease that involves both upper and lower motor neurons and leads to progressive muscle weakness (1, 2). Weakness of the respiratory muscles in patients with ALS causes hypoventilation, which can worsen during sleep because of a weak diaphragm, sleep-disordered breathing, supine position, and central drive dysfunction (3-5).

Although ALS has been considered to involve mainly the motor neurons, recent evidence has shown that more than 50% of the patients with ALS have cognitive impairments involving fronto-temporal lobe functions (6); this might be associated with nocturnal hypoventilation observed in these patients for the following reasons. (1) Cognitive dysfunction in ALS was associated with reduced vital capacity (4). (2) Cognitive dysfunction in ALS can be partially reversible with non-invasive positive pressure ventilation (3). (3) Cognitive dysfunction in patients with sleep-disordered breathing is characterized by the dysfunction of the fronto-temporal lobes and resembles that observed in patients with ALS (7).

The aim of this study was to evaluate the effect of nocturnal hypoxia on the cognitive function of patients with ALS and to assess the pattern of hypoxia in the patients with ALS by using nocturnal continuous oximetry and capnography.

METHODS

Patients

The ALS patients were recruited from the ALS clinic of the Seoul National University Hospital between March 2006 and July 2012. Twenty-three patients (8 women and 15 men; age, 38–82 years) with either definite or probable ALS (El Escorial criteria) (8) and subjective clinical symptoms of hypoventilation, namely, dyspnea, orthopnea, daytime drowsiness, and unrefreshing sleep, were included. We excluded patients who were on a ventilator, were supplied with oxygen, were tracheostomized, or had a pulmonary disease. Written informed consent was obtained from all the patients. This study was approved by the Institutional Review Board of Seoul National University Hospital.

Measurements

We used capnography (CO2SMO, Respironics Novametrix, USA) and pulse oximetry (CO2SMO, Respironics Novametrix) for overnight continuous respiratory monitoring. The gross respiratory pattern, average end tidal carbon dioxide ($ETCO_2$) level, average oxygen saturation (SpO_2) level, duration of nocturnal hypercapnia (percentage of sleep time when $ETCO_2$ > 47 mmHg per total sleep time), and duration of nocturnal hypoxia (percentage of sleep time when SpO_2 < 95% per total sleep time) were analyzed using NovaCARD software (Respironics Novametrix). The value of $ETCO_2$ obtained using capnography can reflect $PaCO_2$

reliably in patients who do not have dead space in the lungs or are on a non-invasive ventilator, and SpO_2 by pulse oximetry is determined mainly by using PaO_2 (5).

The manifestation of the respiratory pattern with desaturation was also evaluated. Desaturation was defined as a decrease in SpO_2 of 4% or more, and cluster of desaturation was defined as 5 or more desaturations occurring in a 10-min period, according to a previous study (9). Forced vital capacity (FVC) was measured, and the symptoms of orthopnea and dyspnea, degree of swallowing, speech, and salivation were evaluated using the ALS Functional Rating Scale-Revised (ALSFRSr) with total ALSFRSr (10).

For evaluating cognitive function, we used the Rey–Kim memory test, frontal assessment battery (FAB), verbal fluency test, and the Korean version of the mini-mental state examination (K-MMSE). The Rey–Kim memory test is the first standardized Korean version of the auditory verbal learning test (AVLT) and complex figure test (CFT), which were widely accepted as useful tools for evaluating memory function worldwide (11-13). K-AVLT consists of 15 nouns that were read to the patients in 5 successive trials (Trials 1 through 5), followed by free recall, delayed recall, and delayed recognition (11, 13). K-CFT is used for the evaluation of nonverbal memory and visuospatial function by drawing a Rey-complex figure, followed by immediate recall and delayed recall (12, 13). We evaluated the 3 components of "learning curve," "memory retention," and "retrieval efficiency" derived from the raw scores of the Rey–Kim memory test for the analysis of specific memory processes (i.e., registration, retention, and retrieval)

(13). FAB is a short and sensitive tool for evaluating frontal lobe function (14). We assessed each parameter of FAB (i.e., similarities, lexical fluency, motor series, conflicting instructions, inhibitory control, and prehension behavior) (14). The verbal fluency test was composed of 3 components: written verbal fluency test (for Korean words beginning with the sounds for "b" and "z"), spoken verbal fluency test (for Korean words beginning with the sounds for "s" and "k"), and written categorical verbal fluency test (for animals, foods, flowers, and objects in a supermarket) (4, 15). The patients are expected to write or say as many words as possible during the time limit for each fluency test.

Statistical analysis

To analyze the association between nocturnal hypoxia and cognitive function, the patients were grouped on the basis of whether they did or did not have nocturnal hypoxia. Nocturnal hypoxia was defined by a SpO_2 value of <95% for at least 10% of the night-time (16, 17). The 2 groups were analyzed and compared using a paired *t*-test for respiratory and cognitive functions. We also evaluated the correlation between the degree of hypoxia and cognitive functions in the 23 patients by using Spearman's correlation coefficient. A p-value of <0.05 indicated a statistically significant difference. Computer software packages (SPSS 18.0 for Windows, SPSS, Chicago, IL) were used for the statistical analysis.

RESULTS

Ten of the 23 patients with ALS (43.5%) showed nocturnal hypoxia during capnography monitoring. The respiratory and neuropsychologic characteristics of the patients are summarized in Tables 1 and 2. The respiratory pattern with an intermittent cluster of desaturation was observed in 8 patients (7 of 10 patients of hypoxia group (70%), 1 of 13 patients of non-hypoxia group (7.7%)) (Figure 1). Compared to the patients without nocturnal hypoxia, the patients with nocturnal hypoxia showed a significantly longer duration of nocturnal hypercapnia ($p = 0.023$), lower mean SpO_2 ($p = 0.008$), higher mean $ETCO_2$ ($p = 0.037$), and poorer scores for memory retention ($p = 0.039$) and retrieval efficiency ($p = 0.045$). The 2 groups did not show significant differences in age, total ALSFRSr, duration of disease, and FVC.

Analysis of the association between the degree of hypoxia and cognitive functions showed that the duration of nocturnal hypoxia was significantly correlated to the retrieval efficiency (Spearman's correlation analysis, $p = 0.049$), but confounding factors such as age or education level, which could affect the degree of cognition, were not corrected in this analysis.

Table 1. Clinical and respiratory characteristics of the ALS patients

	Nocturnal *hypoxia group	Nocturnal non-hypoxia group	p-value
Gender (M:F)	7:3	8:5	1.000
Age (year)	51.8 ± 10.55	56.92 ± 13.39	0.332
Duration of disease (months)	26.2 ± 12.72	17.85 ± 12.44	0.129
FVC (% of normal)	69.4 ± 27.42	59.77 ± 22.17	0.362
ALSFRSr			
Dyspnea	2.30 ± 1.25	3.00 ± 0.91	0.135
Orthopnea	3.10± 0.74	3.31 ± 0.48	0.423
Speech	3.20 ± 0.42	2.54 ± 1.20	0.112
Salivation	3.60 ± 0.70	2.85 ± 1.28	0.109
Swallowing	3.6 ± 0.52	2.92 ± 0.76	***0.025***
Total score	32.5 ± 9.31	32.85 ± 8.49	0.927
% of sleep time when $ETCO_2$ > 47 mmHg	37.7 ± 41.37	2.02 ± 4.22	***0.023***
% of sleep time when SpO_2 < 95%	57.10 ± 28.95	4.46 ± 3.09	***0.000***
Average $ETCO_2$ (mmHg)	46.92 ± 10.36	38.67 ± 4.23	***0.037***
Average SpO_2 (%)	92.35 ±3.50	96.07 ± 0.28	***0.008***
Cluster of desaturation	7 (70%)	1 (7.7%)	

* Defined as the presence of a hypoxia period (SpO_2 value, <95%) of more than 10% of the total sleep time.
Abbreviation: ALSFRSr = Amyotrophic Lateral Sclerosis Functional Rating Scale Revised, $ETCO_2$ = end-tidal carbon dioxide, FVC = forced vital capacity, SpO_2 = arterial oxygen saturation measured using pulse oximetry, cluster of desaturation = 5 or more desaturations (a decrease in SpO_2 of 4% or more) occurring in a 10-min period
All continuous values are expressed as mean ± standard deviation

Table 2. Neuropsychologic characteristics of the ALS patients

	Nocturnal *hypoxia group	Nocturnal non-hypoxia group	p-value
MMSE	25.6 ± 3.63	25.58 ± 4.32	0.992
RAVLT			
Learning trial			
1	4.10 ± 1.45	4.60 ± 2.32	0.570
2	6.90 ± 2.33	6.00 ± 2.31	0.397
3	7.40 ± 1.78	7.10 ± 3.03	0.790
4	8.10 ± 1.91	8.30 ± 3.43	0.874
5	9.50 ± 2.55	9.20 ± 3.19	0.819
Learning curve	36.3 ± 36.68	34.55 ± 29.26	0.907
Memory retention	***20.78 ± 12.94***	***49.00 ± 36.00***	***0.039***
Retrieval efficiency	***27.80 ± 18.83***	***54.36 ± 33.31***	***0.045***
Verbal fluency			
Spoken verbal fluency s	7.89 ± 2.85	8.57 ± 3.64	0.680
Spoken verbal fluency k	8.67 ± 2.12	6.71 ± 2.93	0.143
Written verbal fluency b	7.50 ± 2.59	6.33 ± 3.20	0.504
Written verbal fluency z	7.83 ± 2.40	6.5 ± 3.73	0.478
Category fluency: animals	11.80 ± 4.02	10.25 ± 4.03	0.429
Category fluency: foods	10.67 ± 3.28	7.38 ± 4.57	0.105
Category fluency: flowers	8.00 ± 3.27	6.83 ± 3.06	0.522
Category fluency: objects in a supermarket	8.43 ± 3.26	8.17 ± 3.49	0.891
FAB	13.8 ± 4.71	14.28 ± 4.94	0.825

* Defined as the presence of a hypoxia period (SpO_2 value, <95%) of more than 10% of the total sleep time.
Abbreviation: MMSE = Mini Mental State Examination, RAVLT = Rey Auditory Verbal Learning Test, FAB = frontal assessment battery
All continuous values are expressed as mean ± standard deviation

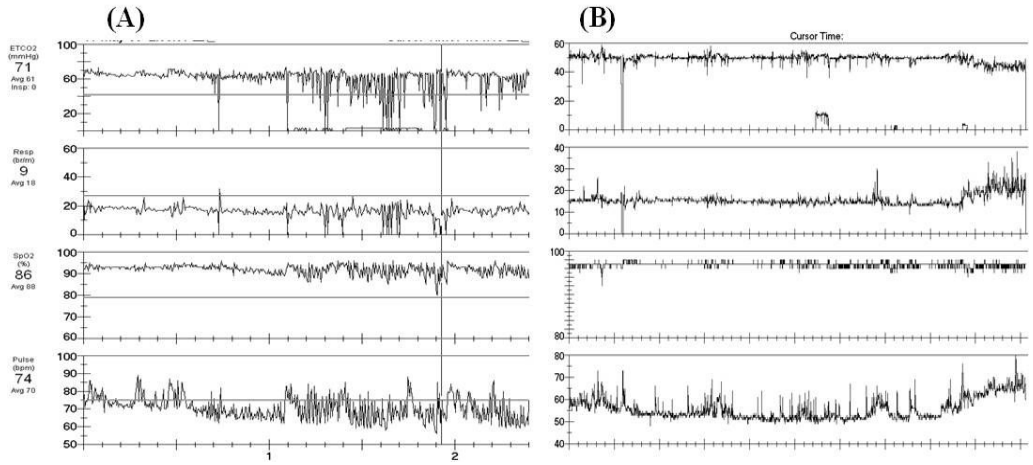

Figure 1. A capnography recording showing intermittent desaturation (A) and no intermittent desaturation (B). The upper trace – $ETCO_2$. Second line-Respiratory rate. Third line-SpO2. Bottom line-Pulse rate.

DISCUSSION

In this study, we showed that nocturnal hypoxia was associated with cognitive dysfunction in patients with ALS and that the pattern of hypoxia could exhibit an intermittent desaturation pattern.

In our study, the ALS patients with nocturnal hypoxia showed significantly lower values with respect to memory retention and retrieval efficiency in the Rey–Kim memory test than the patients without nocturnal hypoxia. Fronto-temporal dysfunction has been known as a common form of cognitive impairment in ALS patients (6, 15, 18). Previous studies have reported that the cognitive dysfunction observed in patients with ALS was associated with reduced vital capacity, as well as the primary irreversible degenerative process (4), and was partially reversible with non-invasive positive pressure ventilation (3). Cognitive dysfunction in patients with sleep-disordered breathing is also characterized by the dysfunction of the fronto-temporal lobes and resembles that observed in patients with ALS (7). Our results, which characterized the significant memory dysfunctions in the nocturnal hypoxia group, were consistent with those of previous studies that proposed an association between cognitive impairment and nocturnal hypoventilation (3, 4). These findings can provide a basis for the application of NIV treatment (3, 5). Further studies on the causal relationship of this phenomenon are required.

The results of FAB did not show significant impairment in the nocturnal hypoxia group. However, this test could have yielded false positive results because of the limb muscle weakness in the ALS patients who could not perform the test accurately. Several studies have reported that the verbal fluency test is useful in detecting cognitive dysfunction in patients with ALS, but there are some discrepancies in the detailed results (4). Our results demonstrated no significant differences between the groups with respect to the verbal fluency test. The MMSE scores also did not differ between the groups, but this test had a low sensitivity and specificity in the detection of specific cognitive impairment in patients with ALS.

We also found that 70% of the ALS patients with nocturnal hypoxia showed a cluster of desaturation pattern for hypoxia. Hypoxia is known to affect various body functions via 2 cellular pathways, namely, the hypoxia inducible factor (HIF) pathway and nuclear factor-kB (NF-kB) pathway (19, 20). Continuous hypoxia activates the HIF and the vascular endothelial growth factor, but intermittent hypoxia leads to the activation of NF-kB in vivo and in vitro (20, 21). The activated NF-kB induces increased proinflammatory mediators such as tumor necrosis factor alpha, interleukin 6, and prostaglandin E2 (20). Until recently,, studies have identified that acute intermittent hypoxia may be related to oxidative stress, with a greater production of superoxides, than a sustained hypoxic episode through different cytotoxic mechanisms (19, 22). The pathogenesis and progression of ALS was known to be closely related to hypoxia (20, 23), but this was not verified using

an in vivo continuous hypoxia ALS model. Our results suggest that intermittent hypoxia models will contribute to the identification of the effects of hypoxia on ALS pathogenesis.

Episodic desaturation during REM sleep or periodic respiratory patterns of mild O_2 desaturation in ALS were documented as sleep-disordered breathing by using polysomnography (24, 25). In our study, the cluster of desaturation pattern, which is similar to that observed in previous studies, was manifested, but a large proportion of this pattern was observed in the hypoxia group than in the non-hypoxia group. The intermittent hypoxia may be caused by dysregulation of the respiratory responses associated with neurodegeneration, but the exact mechanism is unclear. The effects of obstructive sleep apnea due to bulbar weakness might be minimal because the respiratory muscles of the ALS patients were too weak to close the upper airway, and our results showed a higher swallowing score in the hypoxia group than in the non-hypoxia group (24).

According to our results, the ALS patients with nocturnal hypoxia presented statistically significant lower mean SpO_2 values, higher mean $ETCO_2$ values, and a longer duration of nocturnal hypercapnia than those without. The 2 groups did not show significant differences in the parameters of duration of disease, age, total ALSFRSr, and FVC. Thus, the degree of respiratory muscle weakness and disease severity is probably similar. Therefore, we can assume that nocturnal hypoxia may

be an independent factor that reflects the respiratory functions in patients with ALS. Our study has some limitations. First, this study had a retrospective design. Second, the number of patients was so small that we could not verify the differences in the other indices of the Rey–Kim memory test and word fluency tests between the groups. Third, we did not validate the causal relationship between the nocturnal hypoxia and the cognitive dysfunction because this was a cross-sectional analysis. Another common cause of hypoxia and cognitive dysfunction may exist, but we think it is reasonable to consider nocturnal hypoxia as, at least in some part, a cause of the cognitive dysfunction according to previous studies (3, 4). Fourth, we did not use polysomnography for assessing sleep-disordered breathing. Therefore, we could not use the apnea–hypopnea index as a parameter of respiratory dysfunction or assess the stages of sleep.

In conclusion, we identified that nocturnal hypoxia in patients with ALS is associated with their cognitive dysfunctions through intermittent hypoxia, rather than continuous hypoxia. Further studies are required for the identification of the causal relationship of this phenomenon and the cellular and molecular mechanisms underlying the effect of intermittent hypoxia.

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요약 (국문 초록)

배경: 근위축성측삭경화증은 사지의 근력 및 호흡근의 약화를 초래하는 대표적인 퇴행성 신경질환이다. 근위축성측삭경화증 환자는 호흡근의 약화로 인해 진행하는 저환기를 경험하는데, 이는 수면 중 악화될 수 있으며 일부 가역적인 인지 기능 저하와 관련이 될 수 있다. 본 연구에서 우리는 근위축성측삭경화증 환자에서 수면 중 나타나는 저산소증이 인지 기능에 미치는 영향과 저산소증의 양식에 관해 연구하고자 한다.

방법: 임상적으로 확실하거나 추정 진단을 받은 근위축성측삭경화증 환자 23명이 본 연구에 포함되었다. 호기말 이산화탄소분압 측정술과 맥박-산소측정법을 이용하여 수면 중 과탄산증과 저산소증의 지속 시간, 평균 호기말 이산화탄소분압 농도, 평균 산소포화도 농도를 측정하였다. 강제 폐활량을 측정하였으며, 기좌호흡이나 호흡 곤란 등을 비롯한 저환기의 증상에 대해 루게릭병 임상점수로 평가하였다. 인지기능평가를 위해서 레이-김기억검사, 전두엽기능평가, 언어유창성검사 및 간이정신상태검사를 시행하였다.

결과: 23명의 환자 중, 수면 중 저산소증을 보이는 환자는 10명이었다 (43.5%). 저산소증이 인지 기능에 미치는 영향을 분석하기 위하여 수면 중 저산소증이 있는 환자들과, 그렇지 않은 환자들 두 그룹으로 나누었다. 수면 중 저산소증이 있는 환자들은, 그렇지 않은 환자들과 비교하였을 때,

수면 중 과탄산증 (p=0.023)의 지속 시간이 더 길었으며, 평균 산소포화도가 더 낮았고(p=0.008), 평균 호기말 이산화탄소 분압이 높았으며(p=0.037), 레이-김기억검사의 기억유지도(p=0.039) 및 인출효율성(p=0.045) 에서도 유의하게 낮은 점수를 보였다.

결론: 수면 중 저산소증은 근위축성측삭경화증 환자에서 인지 기능 저하와 유의한 관련성을 보였다. 추후 이러한 현상의 인과 관계를 밝히고, 간헐적 저산소증의 작용기전을 밝히기 위한 보다 많은 연구가 필요하다.

주요어: 근위축성측삭경화증, 수면 중 저산소증, 인지기능 이상, 간헐적 저산소증

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