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The terminal latency of the phrenic nerve correlates with respiratory symptoms in amyotrophic lateral sclerosis

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HIGHLIGHTS

- The prolonged terminal latency of the phrenic nerve may reflect a distal axonopathy.
- The optimal cutoff value for the terminal latency of the phrenic nerve was 7.65 ms.
- Recognizing the usefulness of the terminal latency of the phrenic nerve in ALS is important.

ABSTRACT

Objective: The aim of the study was to investigate the electrophysiological parameters in phrenic nerve conduction studies (NCS) that sensitively reflect latent respiratory insufficiency present in amyotrophic lateral sclerosis (ALS).
Method: Forty-nine patients with ALS were examined, and after exclusion, 21 patients with ALS and their phrenic NCS results were reviewed. The patients were divided into two groups according to their respiratory sub-score in the ALS functional rating scale - revised (Group A, sub-score 12 vs. Group B, sub-score 11). We compared the parameters of phrenic NCS between the two groups.
Results: There were no significant differences in the clinical characteristics between the two groups. Using a multivariate model, we found that the terminal latency of the phrenic nerve was the only parameter that was associated with early symptoms of respiratory insufficiency ($p < 0.05$). The optimal cutoff value for the terminal latency of the phrenic nerve was 7.65 ms (sensitivity 80%, specificity 68.2%).
Conclusion: The significantly prolonged terminal latency of the phrenic nerve in our study may reflect a profound distal motor axonal dysfunction of the phrenic nerve in patients with ALS in the early stage of respiratory insufficiency that can be used as a sensitive electrophysiological marker reflecting respiratory symptoms in ALS.
Significance: The terminal latency of the phrenic nerve is useful for early detection of respiratory insufficiency in patients with ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurodegenerative disease that involves limb, axial, bulbar, and respiratory muscles (Haverkamp et al., 1995). Weakness and fatigue of the respiratory muscles eventually induce respiratory insufficiency, which is the main cause of death in this disease (Haverkamp et al., 1995). Since respiratory function is an important factor influencing the survival of patients with ALS, (Lechtzin et al., 2001, 2007) its assessment is essential for monitoring disease progression and determining the timing for non-invasive ventilation that is proven to increase the survival and quality of life of patients with ALS (Bourke et al., 2006; Andersen et al., 2007). Generally, forced vital capacity (FVC) has been suggested to be a prognostic factor for ALS (Fallat et al., 1979; Czaplinski et al., 2006). In patients with ALS with bulbar symptoms, however, respiratory function tests, such as FVC, are not always reliable in practice; these patients have weak lip seal that impairs the accurate evaluation of their respiratory function (Pinto et al., 2009). Moreover, assessment of respiratory function

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depends on cooperation, which is difficult to obtain in patients who are less motivated, depressed, or have behavioral changes as commonly observed in patients with ALS (Phukan et al., 2007).

In contrast, a phrenic nerve conduction study (NCS) can be used as an efficient and non-invasive tool in patients with ALS, even in those with bulbar symptoms (Pinto et al., 2007). Until date, several studies have reported that the phrenic NCS result could be a powerful predictor of survival and disease progression in patients with ALS (Pinto et al., 2007, 2009; Sathyaprabha et al., 2010; Kwon et al., 2015). The phrenic NCS parameters that have a more meaningful correlation with respiratory function in patients with ALS are still being debated. Pinto et al. reported that phrenic compound muscle action potential (CMAP) amplitude could be a marker for hypoventilation in patients (Pinto et al., 2007, 2009) and that it is an important predictor of survival in patients with ALS (Pinto et al., 2012). Contrary to these findings, Sathyaprabha et al. (Sathyaprabha et al., 2010) reported that the terminal latency of the phrenic nerve may be a better indicator of early respiratory muscle involvement and disease progression.

Recently, there have been several studies that have examined the early pathophysiology of ALS, using NCS as a tool (Noto et al., 2011; Shibuya et al., 2013; Park and Park, 2017). Based on these studies, we compared phrenic NCS results of patients with ALS between those with early respiratory symptoms and those without respiratory symptoms to determine an electrophysiological parameter that correlates with respiratory insufficiency.

2. Method

2.1. Participants

This was a retrospective study and medical records of patients who visited our ALS clinic between January 2014 and August 2017 were reviewed. The diagnosis of ALS was made on the basis of the revised El Escorial criteria (Ludolph et al., 2015). Twenty-one patients (forty-two phrenic nerve study results) with clinically definite, probable, or probable laboratory test-supported ALS were included in our study. Among the ALS functional rating scale - revised (ALSFRS-R) scores, bulbar, fine motor, gross motor, and respiratory sub-scores were further analyzed (Cedarbaum et al., 1999). "Non-respiratory symptom" patients (Group A) vs. "early respiratory symptom" patients (Group B) were defined as those with respiratory sub-score of ALSFRS-R 12 (no dyspnea, 4; no orthopnea, 4 and no respiratory insufficiency, 4) vs. those with respiratory sub-score of ALSFRS-R 11 (dyspnea, 3–4, orthopnea, 3–4, respiratory insufficiency, 3–4). We also recorded age, sex, height, weight, body mass index (BMI), region of initial presentation, total ALSFRS-R scores, and scores on the penetration-aspiration scale (PAS).

Exclusion criteria were (1) inability to perform the pulmonary function test (PFT) due to severe bulbar weakness; (2) previously diagnosed peripheral polyneuropathy; (3) previously diagnosed chronic obstructive pulmonary disease (COPD); (4) history of an autoimmune related disease; (5) presence of a tracheal tube; (6) diabetes mellitus.

2.2. Pulmonary function test

All patients underwent a phrenic NCS and PFT simultaneously. We performed the PFT using a spirometry kit (Pony FX, CosMed, Italy). FVC (liters), and forced expiratory volume in one second (FEV1) was measured. Ratio of forced expiratory volume in the first second to forced vital capacity (FEV1/FVC) was additionally calculated (Sathyaprabha et al., 2010). All enrolled ALS patients were requested to repeat each maneuver three times at an interval of 2 min between the tests, and the best result was considered for the analysis (Sathyaprabha et al., 2010).

2.3. Phrenic nerve conduction study

The NCS was performed using a Medelec Synergy device (CareFusion Corporation, San Diego, CA). The phrenic NCS was performed by using the Bolton's method with in both right and left phrenic nerves of the patients (Bolton, 1993; Chen et al., 1995). The active recording electrode was placed over the xiphoid process and the reference electrode along the costal margin, 16 cm from the active recording electrode. The phrenic nerve was stimulated with surface electrodes at the posterior border of the sternocleidomastoid muscle and the active stimulating electrodes being approximately 3 cm above the clavicle, at the end of the respiratory cycle (filter setting 20 Hz – 10 kHz) (Kwon et al., 2015). We retrieved the terminal latency of the phrenic nerve, and the phrenic CMAP amplitude. The response with the highest CMAP amplitude was used for the analysis.

2.4. Statistical analysis

Statistical analyses were performed using SPSS for Windows and R package for Windows (version 2.15.2, R Foundation for Statistical Computing, Vienna, Austria). The comparison between the two groups (Group A vs. B) was performed with either independent samples t-test or Wilcoxon rank sum test, depending on the distribution of the continuous variables. Chi-square test was used to assess the independence of the categorical variables. For the multivariate analysis, the variables with p-value < 0.05 from the univariate analysis were included in the logistic regression model. Using the receiver operator characteristic (ROC) curve, the cutoff value, was calculated for the significant parameter from the multivariable analysis (Youden, 1950). The results are presented as the mean ± standard deviation. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

The clinical characteristics of the patients with ALS in the two groups are summarized in Table 1. There was no significant difference in age, sex, BMI, region of onset, height, weight, phrenic NCS, CMAP amplitude, FEV1/FVC, and PAS between the two groups. On the contrary, FVC, FEV1, total ALSFRS-R score, ALSFRS-R sub-scores (orthopnea, dyspnea, and swallowing), and terminal latency of the phrenic nerve were significantly different between the two groups (Table 1).

3.2. Multivariate analysis between two groups

In the multivariate model, early symptoms of respiratory insufficiency were only associated with the terminal latency of the phrenic nerve ($p < 0.05$), but not with other parameters, such as FVC or FEV1 (Table 2).

3.3. ROC curve analysis

The area under the ROC curve (AUC) for the terminal latency of the phrenic nerve, as a continuous variable, was 0.825. For the optimal cutoff value, a phrenic latency of 7.65 ms showed the highest Youden's index. The sensitivity and specificity of the terminal latency of the phrenic nerve (ROC-AUC, 0.825) were 85.0% and 68.2%, respectively. (Fig. 1).