Count of Fasciculation in Ultrasound Can Predict the Prognosis of Amyotrophic Lateral Sclerosis

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Abstract

Background: Although muscle ultrasound (MUS) is known to facilitate the diagnosis and evaluation of the severity of amyotrophic lateral sclerosis (ALS), the number of fasciculation has been scarcely examined as a predictive marker of the prognosis in ALS. **Objective:** The objective of this study was to examine the predictive value of fasciculation number for the prognosis of ALS. **Materials and Methods:** We examined fasciculation count (FasC), defined as the number of fasciculation per unit of time and area in MUS, of 11 patients with clinically probable or definite ALS. Thereafter, they were observed for maximally 2 years, unless they reached the endpoint of decease or receiving tracheostomy**. Results:** Six patients, who thereafter reached the endpoint within 2 years, had significantly higher FasC (223 [49.3] vs. 34 [13], $P = 0.0043$) and shorter disease duration (7 [2.3] vs. 33 [17], $P = 0.0022$) at MUS than the remaining five patients without reaching the endpoint. **Discussion and Conclusion:** Our study suggested that high FasC in MUS can predict rapid progression in ALS. Due to the limitations such as small sample size, suboptimal length of the observational period, and confounding factor of disease duration, further investigations are required.

Keywords: Amyotrophic lateral sclerosis, fasciculation, prognosis, tracheostomy, ultrasound

Introduction

Fasciculation is a manifestation of neuronal excitability, including both benign and pathologic origin. In amyotrophic lateral sclerosis (ALS), due to the feature of relentlessly progressive neurodegeneration, fasciculation is noticeable and almost inevitable.[1] Hence, fasciculation has been used as a diagnostic marker of ALS in physical examination (PE), in electromyography (EMG), and recently in muscle ultrasound (MUS). Reportedly, MUS has minimal invasiveness with higher sensitivity to detect fasciculation than PE and EMG in the diagnosis of ALS.[2,3] In addition, echo intensity, thinness, and echo variation of muscles in MUS can be biomarkers for the disease severity and the prognosis of ALS.[4-6] However, the number of fasciculation, which can be observed as small and irregular twitching of the muscles, has been not intensively examined as a prognostic factor of ALS, although one study made exploratory quantification in cranially innervated muscles (ALS was suspected if there was >5 fasciculation in 30 s).[2-5,7] Furthermore, prediction of the prognosis in ALS is often challenging because it can be several months or decades, although the typical natural course is 3–5 years.[8,9] Thus, a practical method to predict the prognosis ALS by MUS would be helpful for clinicians.

Objective

We designed this exploratory study for investigating the predictive value of "fasciculation count (FasC)" defined as the number of fasciculation per unit of time and area in MUS, for the prognosis of ALS.

Materials and Methods

Eleven patients with ALS were recruited and underwent MUS between June 17, 2016, and September 23, 2016. Thereafter, we observed their disease progression for the maximal length of 2 years. Inclusion criteria were as follows: (1) receiving the diagnosis as clinically probable or definite ALS based on the revised El Escorial criteria, (2) sporadic and adult-onset (>40 years old) cases without any family history of motor neuron disease, and (3) able to cooperate to take MUS in relaxing supine position.[10] Exclusion criteria were as follows: (1) comorbid pathologies that can affect motor neurons (e.g., vasculitis), (2) young onset (<40 years old), (3) enteral feeding or mechanical ventilation before the enrollment, and (4) orthopnea. We permitted the patients to start the treatment by riluzole and/or edaravone if indicated. This study was approved by the Ethics Committee of the National Hospital Organization Hyogo-Chuo National Hospital (approval number: 28–02). This trial was registered in the Japan Medical Association

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Submission: 04.10.2018 **Acceptance:** 10.10.2018 **Published:** 25.10.2019

DOI: 10.4103/aian.AIAN_429_18

Center for Clinical Trials Clinical Trial Registry (ID: JMA-IIA00370). We obtained written informed consent from all the enrolled patients or their representative family members. Each patient underwent MUS of 12 limb muscles, that is, bilateral biceps brachii (BB), extensor carpi radialis, abductor digiti minimi, quadriceps femoris (QF), tibialis anterior, and soleus (Sol) to examine FasC. The transverse imaging of these muscles was obtained by real-time B-mode MUS using 17-MHz linear probe of Prosound α7® (Hitachi Ltd., Tokyo, Japan). In BB, QF, and Sol, the medial side of the muscles was examined because these muscles were wider than the probe. In each muscle, three quadrisection points between the origin and insertion of each muscle were assessed for 10 s since precedent studies suggested that 10 s observation had rational sensitivity to detect fasciculation, resulting in the examination of 30 s in each muscle and 6 min in each patient.[2-5,7] We defined fasciculation as involuntary twitching of small parts of muscle as the preceding study.[3] After the examination by MUS, these patients were observed maximally for 2 years unless they reached the endpoint of decease or receiving tracheostomy (TS). Further, the monthly declining rate (⊿) of revised ALS functional rating scale (ALSFRS-R) was examined in surviving patients 2 years after the MUS evaluation because in case of decease, it is quite arbitrary to regard the ALSFRS-R as zero.[3,11,12] The patients were classified as rapidly progressive group (RPG) if they reached the endpoint within 2 years, otherwise slowly progressive group (SPG). For statistical analysis, we used Chi-square test was used for categorical variables and Kruskal–Wallis test with *post hoc* analysis by Mann–Whitney U-test for continuous variables to compare RPG and SPG. We used Excel-Toukei software (version 2018; SSRI Co. Ltd., Tokyo, Japan). Shapiro–Wilk test was performed to examine the normality. Continuous variables were shown in median (interquartile range) because of the small sample size. Significance level was defined as $P < 0.05$ in two-tailed P value.

Results

At the time of initial evaluation by MUS, the age was 72 [20] years, disease duration of ALS was 9 [24] months, ALSFRS-R (0–48, full score = 48) was 37 [9.5], forced vital capacity (FVC) for predicted value (%FVC) was 79.8% [23.3], and FasC per patient in 6 min was 101[188] [Table 1]. For the treatment of ALS, case 2, 3, 5, 7, and 9 received riluzole and case 3 and 9–11 received edaravone. Within the continuous variables, only disease duration showed normality ($P < 0.05$). All the members of RPG (case 1–6) reached the endpoint within 8 months after the MUS. Case 5 received TS due to systemic muscle weakness including respiratory muscle, and other patients in RPG deceased by respiratory failure or dehydration by dysphagia as the natural course of ALS. In SPG (case 7–11), ⊿ALSFRS-R in 2 years observation was 0–0.58/month. To compare RPG and SPG, RPG had significantly higher FasC (223 [49.3] vs. 34 [13], $P = 0.0043$) and shorter disease duration of ALS (7 [2.3] vs. 33[17] months, $P = 0.0022$) than SPG at the initial evaluation by MUS [Table 2]. Retrospective review of their medical records showed that the time from symptom onset to fulfill the criteria of clinically probable or definite ALS was <7 months in all of RPG, while more than 12 months in all of SPG. Follow-up of MUS was unable in several patients who deceased, developed dementia or dyspnea, or could not visit our hospital in the adequate timing.

Discussion and Conclusion

We showed the positive predictive value of FasC for the subsequent progression of ALS from the MUS evaluation. Considering the reported mean of ⊿ALSFRS-R was 0.7–0.9/month, the value of case 5 (1.5/month) and in SPG (0–0.58/month) could be plausible to manifest their progressive speed.[4] The advantage of our protocol was small burden on the patients because MUS is painless unlike needle EMG, and the examination time of MUS was short (6 min per patient). In addition, sonographic evaluation can have higher spatial resolution than PE and EMG.[3] We excluded the patients with orthopnea due to the concern that respiratory distress could induce contraction fasciculation. If the patients have orthopnea, it might be better to perform MUS in the sitting position; however, our investigation was not enough on this point. Since this is an exploratory study, we have several challenges and limitations for further examinations. The sample size ($n = 11$) was small, and the observational period (2 years) was not enough to confirm the time to reach the endpoint in SPG or perform Cox regression analysis or correlation analysis for the contribution of FasC for the prognosis. The independent value of FasC needs further examination because the concurrent presence of shorter disease duration in RPG than SPG could be a confounding factor for poorer prognosis.[8] We included the patients who were previously diagnosed as probable or definite ALS; however, longer time to manifest necessary findings to fulfill the criteria in SPG might decline FasC.[13] Therefore, we should have examined the patients in the same duration of ALS, for example, approximately 1 year after the onset, even if the patient did not fulfill the criteria initially. In the precedent studies, the longitudinal sonographic positivity, not the number, of fasciculation in the same patients had variable change, and EMG showed the firing frequency of fasciculation potential does not decline overtime.[4,14] Therefore, we speculate FasC in the initial phase of SPG could be also small; however, there is no established knowledge on this point. Furthermore, since it was observational study, the presence of treatments by riluzole and/or edaravone in several patients could affect the prognosis. For the methodology, the validity of muscle selection in our protocol needs more examination. Since the selected muscles were different from the reports, although BB and QF were commonly selected, we selected on the basis of different innervations, functional importance (e.g., antigravity contraction), and easiness in sonographic observation for

Table 1: Profiles and clinical data of the enrolled patients with amyotrophic lateral sclerosis

	Case number											Total
	1	2	3	4	5	6	7	8	9	10	11	
Age (years old)	86	78	72	87	64	89	79	61	51	55	72	72 (20)
Sexuality (male/female)	Male	Female	Male	Female	Male	Female	Male	Female	Male	Male	Female	Male:female=6:5
ALS onset site	Leg	Arm	Bulbar	Leg	Arm	Arm	Arm	Leg	Arm	Leg	Leg	Bulbar:arm:leg=1:5:5
Onset to decease or TS (month)	10	13	11	9	17	13	None	None	None	None	None	Undetermined
Baselines at MUS evaluation												
ALS duration (month)	9	7	7	4	9	6	14	46	29	78	33	9 (24)
ALSFRS-R	20	30	42	30	42	29	39	36	40	37	38	37 (9.5)
%FVC	23.7	37.1	85.2	60.8	83.7	80.6	92.3	79.8	66.4	61.6	114.7	79.8 (23.3)
FasC/patient	277	262	224	222	197	101	87	36	34	23	14	101 (188)
⊿ALSFRS-R (/month)	NA	NA	NA	NA	1.5	NA	0.58	0.46	0.29	0.21	0	Undetermined

Median (IQR) of continuous variables and number of categorical variables are shown in the right column. ALS: Amyotrophic lateral sclerosis; ALSFRS-R: Revised ALS functional rating scale; FasC: Fasciculation count; %FVC: Forced vital capacity for predicted value; IQR: Interquartile range; MUS: Muscle ultrasound; NA: Not available; TS: Tracheostomy

Table 2: Profiles of rapidly versus slowly progressive group

Group	Rapid	Slow	*P*
Number of patients	6	5	
Age (years old)	82 (13)	61 (17)	0.0584
Male: female	3:3	3:2	0.7401
ALS onset site (bulbar: arm: leg)	1:3:2	0:2:3	0.5169
ALS duration (month)	7 (2.3)	33 (17)	0.0022*
ALSFRS-R	30 (9.8)	38 (2)	0.3983
%FVC (%)	70.7 (39.9)	79.8 (25.9)	0.3290
FasC/patient	223 (49.3)	34 (13)	0.0043*

Median (IQR) of baseline characters at sonographic evaluation is shown in rapidly versus slowly progressive group which were classified by the presence of decease or tracheostomy within 2 years. *Statistical significance ($P<0.05$). ALS: Amyotrophic lateral sclerosis; ALSFRS-R: Revised ALS functional rating scale; FasC: Fasciculation count; %FVC: Forced vital capacity for predicted value; IQR: Interquartile range

the origins and insertions.[2-5,13] We did not select tongue and respiratory muscles for the examined muscles due to difficulty in the observation due to swallowing motion and respiratory motion. However, considering the contribution of these muscles for the prognosis, additional investigation in tongue and respiratory muscles can lead to better prediction of the prognosis.

In conclusion, we suggested the positive predictive value of FasC to manifest the prognosis in ALS. Due to the limitations of small sample size, insufficient observational period, concurrent use of riluzole and/or edaravone, unestablished methodology for muscle selection and sonographic observation, and confounding factor of shorter disease duration in RPG than SPG, further investigations are required.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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