ORIGINAL

Which muscle shows fasciculations by ultrasound in patients with ALS?

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INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that predominantly affects the upper and lower motor neurons. Fasciculations, that are localized and temporary muscle twitching, have been recognized as a hallmark of this disease entity, suggesting hyperexcitability of motoneurons and motor axons. Given the high sensitivity to detect fasciculations in comparison with clinical examination, needle electromyography has been utilized for the detection. Because of the diagnostic importance, Lambert proposed an electrodiagnostic criteria of ALS (“Lambert criteria”) that required the presence of fasciculation potentials (FPs) in the multiple body segments (1). The diagnostic weight of FPs in electrophysiology of ALS had been slightly downgraded by the subsequent diagnostic criteria (e.g., the revised El Escorial criteria (2, 3)). Given the low diagnostic sensitivity of the electrodiagnostic criteria, new electrodiagnostic criteria were awaited to achieve high diagnostic sensitivity, especially in the early disease stage (4). To take advantage of fasciculations as a highly characteristic, albeit non-specific, finding of ALS, widespread FPs in the presence of reinervation were recently included in the Awaji ALS electrodiagnostic criteria and validated by a number of studies (5, 6). Detection of FPs is of clinical significance, because FPs tend to appear earlier than other signs of reinervation (e.g., increased durations, amplitudes, and phases of motor unit potentials) and application of the Awaji criteria was reported to diagnose ALS earlier than the revised El Escorial criteria (7, 8).

Ultrasoundography (US) has also been recently utilized as a sensitive measure of muscle movements, including fasciculations. Because of its ability to observe a wide area of muscle tissues non-invasively, detection of fasciculations by US was reported to be superior to that by needle electromyography (9). However, there has no detailed analysis as to the distribution of fasciculations by US in order to set up an efficient and sensitive recording protocol. Thus, the aim of the study was to elucidate the distribution of fasciculations by US in patients with ALS and its possible association with clinical information.

MATERIALS AND METHODS:

Inclusion criteria of the ALS patients

In this retrospective study the patients with ALS were assessed from April, 2013 to April, 2015. The patients who fulfilled the criteria for definite or probable ALS according to the revised El Escorial ALS criteria (2) combined with the Awaji electrodiagnostic criteria (5). Briefly, Awaji electrodiagnostic criteria recognizes fasciculation potential as a sign of active denervation along with fibrillation and positive sharp wave, provided that concurrent evidence of reinervation is present in the same muscle (i.e., long-duration, high-amplitude motor units, late recruitment, polyphasia). Given the potential disagreement of how the Awaji criteria and the revised El Escorial criteria are to be combined (10), both clinically probable and laboratory-supported probable criteria were enrolled as originally stated in the revised El Escorial criteria (2). The patients were classified into four subtypes based on the initial

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region of clinical involvement (arm, leg, bulbar, and bibrachial), according to the clinical history and initial neurological examination by treating neurologists. The diagnosis of the bibrachial subtype was based on the classification by Wijesekera, et al. and those eventually met the above-mentioned ALS criteria (11). This study was approved by the Institutional Review Board of Vihara Hananosato Hospital and Tokushima University. The subjects or their caregivers gave written informed consent at the time of the testing.

Sonography

The sonographic examinations were performed using LOGIQ7 (GE) with an 11-MHz linear-array transducer. A single technician (N.T.) who was not aware of the clinical information performed the sonography. The participants were tested in the supine position. The room temperature was maintained at 23-25 degrees Centigrade. The skin temperatures at the neck and the limbs were measured and maintained >32 degrees Centigrade by covering a blanket. Similar to the previous study, all scans were made in the transverse plane with standard transducer locations corresponding to muscle bellies (9). We observed the muscle for 20 seconds to determine the presence or absence of fasciculations. The definition of fasciculations was made as involuntary twitching of small parts of the muscle, at least two of which were required to be classified as being present. We tested unilaterally on the side of the initial onset. In case of symmetric onset, the right side was selected.

Statistical analysis

The chi-square test and ANOVA with a Games-Howell post-hoc test were used for statistical analysis [SPSS software (version 22.0J) (Tokyo, Japan)]. A statistically significant P value was set at 0.05.

RESULTS:

Typical presentation of fasciculations is shown in Figure 1, that shows brief twitching of a part of the muscle. The clinical characteristics of the patients are shown in Table 1. Sonographic evaluation for fasciculations were performed in total of 640 muscles, averaging 11.4 muscles per patient [11.4±2.2 (range 7-15)]. Overall, approximately a half (48.8%) of the tested muscles showed fasciculations, ranging from 0 to 100% in each patient. Table 2 shows the frequencies of fasciculations in the 15 tested muscles. In comparison to the grand average of all the patients (48.8%), four muscles showed significantly different frequencies: biceps brachii and extensor digitorum communis had higher frequencies [66% and 68%, P=0.013 and 0.011, respectively (the chi-square test)], whereas sternocleidomastoid and rectus abdominis had lower frequencies (25% and 26%, P=0.002 and 0.0078, respectively (the chi-square test)). In addition, the medial head of gastrocnemius tended to have lower frequency than the grand average [30%, P=0.07 (the chi-square test)].

Table 1: patient characteristics and overall sonographic findings

<table>
<thead>
<tr>
<th>ALS</th>
<th>Number</th>
<th>Age (mean±SD; range)</th>
<th>Gender (men/women)</th>
<th>Disease duration (months)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body MassIndex</th>
<th>Region of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56</td>
<td>67.3±10.5 (38-88)</td>
<td>31/25</td>
<td>27.5±29.6 (1-110)</td>
<td>159±9.8</td>
<td>53.4±11.1</td>
<td>21.2±3.5</td>
<td>Arm 19 (34%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Leg 17 (33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bibrachial 8 (14%)</td>
</tr>
</tbody>
</table>

Table 2: frequencies of fasciculations in the 15 tested muscles

| Fasciculations present       | 312/640 (48.8%) |
| [individual patient]         | [range: 0-100%, 48.8±22.1%] |
| Number of muscles tested/patient | 11.4±2.2 (7-15) |

To study possible associations, multivariate analysis was performed between the overall frequency of fasciculations and the patients’ descriptive parameters. There was an inverse correlation between the disease duration and the frequency (Figure 2). Otherwise, no correlation was present between the frequency and the following: age, gender, height, weight, and the body mass index. Table 3 shows the frequencies of fasciculations according to the region of onset. There was no difference in the frequencies of the all tested muscles, the arm muscles, and the leg muscles. However, in the patients who were tested within one year since disease onset, the frequency of fasciculations in the arm tended

Figure 1: serial recording of muscle sonography showing typical fasciculations in a patient with amyotrophic lateral sclerosis. In comparison to the baseline image of the biceps brachii (left), there was brief twitching of a part of the muscle causing upward deflection (right).
to be lower in the bulbar-onset patients than the limb-onset patients \(P = 0.065\) (ANOVA with the Games-Howell post-hoc test).

**DISCUSSION:**

In this retrospective study we have performed sonographic evaluation up to 15 muscle groups to determine the relative frequencies of fasciculations. Biceps brachii and extensor digitorum communis had higher frequencies than the grand average, whereas sternocleidomastoid and rectus abdominis had lower frequencies.

**Sonographic evaluation of fasciculations in ALS**

Fasciculations are observed with a number of underlying conditions, including normal individuals, cramp-fasciculation syndrome, metabolic disorders (e.g., hyperparathyroidism, hyperthyroidism, hypomagnesemia), drug-induced conditions (e.g., caffeine, lithium, terbutaline, anti-cholinesterase, theophylline), motor neuropathies and motor neuron diseases (12). In ALS, fasciculations appear to originate from motor axons and neuronal bodies (13). Because the presence of fasciculations in progressive weakness and muscle atrophy highly indicates motor neuron disorders, fasciculations became an integral part of diagnosis of ALS.

**Possible mechanisms of variable frequencies of fasciculations in ALS**

The present study showed non-uniform frequencies of fasciculations in ALS; more specifically, of the 15 tested muscles biceps brachii and extensor digitorum communis had greater detection sensitivities, whereas sternocleidomastoid and rectus abdominis were lower than the ground average. This tendency (i.e., limb > truncal, upper extremity > lower extremity, possibly proximal limb > distal limb) was somewhat consistent with previous studies and will be discussed in detail.

Sonographically, Misawa, et al. reported sensitivities of fasciculations in six muscles (i.e., tongue, biceps brachii, first dorsal interosseous (FDI), low-thoracic paraspinalis, vastus lateralis, and tibialis anterior), the biceps being the most sensitive muscle and the paraspinalis the lowest (9). Overall, the sensitivities of their study were higher than ours (48-88%), possibly reflecting the different recording durations (20 seconds in the present study and at least 30 seconds by Misawa, et al.).

Electrophysiologically using needle electromyography, Misawa, et al. in the same study claimed FDI as the most sensitive among them, followed by biceps brachii and the tibialis anterior being the least sensitive, but the reason for inconsistency of the orders between the needle electromyography and sonography was unknown. Higashihara, et al. examined 11 muscles (3 in the cranial, 5 in the cervical, 1 thoracic (paraspinalis), and 2 in the lumbosacral segments), showing triceps brachii being the highest, followed by trapezius, biceps brachii, and vastus medialis (10). Sekiguchi, et al. reported the frequencies of FPsin 8 muscles (1 in the cervical, 1 in the thoracic, 1 in the lumbar, 1 in the thigh, 1 in the foot, 1 in the calf, and 1 in the foot). In this study, triceps brachii showed the highest frequencies, followed by biceps brachii, vastus medialis, and tibialis anterior.

**Table 2:** frequency of fasciculations by sonography

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Number of patients with present/absent fasciculations (% positive)</th>
<th>(P) value (vs. grand average : 48.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCM</td>
<td>11/33 (33%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Tongue</td>
<td>24/26 (48%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Deltoid</td>
<td>22/26 (44%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>37/19 (68%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Triceps brachii</td>
<td>30/25 (55%)</td>
<td>0.4</td>
</tr>
<tr>
<td>EDC</td>
<td>32/15 (68%)</td>
<td>0.011</td>
</tr>
<tr>
<td>FDS</td>
<td>12/11 (54%)</td>
<td>0.7</td>
</tr>
<tr>
<td>FCU</td>
<td>12/11 (54%)</td>
<td>0.7</td>
</tr>
<tr>
<td>FDP</td>
<td>11/11 (55%)</td>
<td>0.9</td>
</tr>
<tr>
<td>FDI</td>
<td>28/27 (51%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Quadriceps</td>
<td>30/23 (57%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Tibialis anterior</td>
<td>25/27 (48%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Gastrocnemius, medial head</td>
<td>19/34 (36%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Soleus</td>
<td>10/12 (45%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Rectus abdominis</td>
<td>9/26 (28%)</td>
<td>0.0078</td>
</tr>
</tbody>
</table>

SCM, sternocleidomastoid ; EDC, extensor digitorum communis ; FDS, flexor digitorum superficialis ; FCU, flexor carpi ulnaris ; FDP, flexor digitorum profundus ; FDI, first dorsal interosseous

**Figure 2:** there was inverse relation between the disease duration and the frequency of the muscles that showed fasciculations.

**Figure 2:** there was inverse relation between the disease duration and the frequency of the muscles that showed fasciculations.
translated persistent Na+ currents (17-20). Although regional differences, FPs imply axonal and/or neuronal hyperexcitability. axons, anterior horn cells, and supraspinal sites (16). As controversial, and is likely to be multifactorial, including distal proximal arm muscles and low frequency in truncal muscles has been reported to have dysfunctions in ionic channels, namely impaired potassium currents and upregulated persistent Na+ currents (17-20). Indeed, motor neurons and axons in the peripheral and central nervous systems have been reported to have dysfunctions in ion channels, namely impaired “slow” potassium currents and upregulated persistent Na+ currents (17-20). Although regional difference of axonal excitability has been reported in axons innervating a limb muscle as evidenced by in vivo “threshold tracking” (21-23), its application for a short paraspinal nerve is technically challenging, thus it is uncertain whether there is different excitability or channel properties between the axons innervating the limb muscles and paraspinals.

Clinical significance

The present data suggest several points that are relevant to clinical practice. First, the present data would guide the sonographic evaluation to detect fasciculations in a patient with suspected ALS in terms of selection of muscles. Although the position of sonography in the diagnosis of ALS has not been established in the recent criteria (2, 5), sonographic detection of fasciculations would anticipate the presence of FPs in the respective muscle and thus would reduce the total number of invasive needle examination as “echo-guided needle electromyography” (24). Second, our results showing lower frequencies of fasciculations with longer disease durations are consistent with electrophysiological observation (8), in that FPs could be the initial electrophysiological change by needle electromyography that precedes fibrillations and positive waves. It is possible that chronically denervated and degenerated muscles loses firing properties. Third, the present data have shown diffuse fasciculations beyond initially involved regions, even in patients with short disease durations. In an early disease stage when only focal muscular atrophy is evident in a single limb, sonographic evaluation of other, often strong, muscle groups might suggest diffuse neuron loss and axonal dysfunction.

Limitation of the study

This study has limitations. First, the numbers of the tested muscles were not uniform in each patient because of the retrospective methodology. Second, sonographic evaluation of fasciculations is operator-dependent, however, a recent report claimed high interrater agreement and ability to distinguish fasciculations from motion artifact (25). Third, there has been no uniformly accepted protocol on sonographic evaluation of fasciculations, such as a duration for observation and selection of a transducer and frequency ranges. In needle electromyography, Mills recommended 60 seconds of observation for fasciculation potentials (26). However, theoretically shorter time of observation could detect fasciculations effectively by sonography because sonography observes wider area of muscle tissues than needle electromyography. A prospective, large-scale study to compare electrodagnostic and sonographic features would clarify the issues.

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CONFLICT OF INTEREST STATEMENT:

None of the authors has conflict of interest.

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