Clinical Neurophysiology 126 (2015) 820–827

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Muscle ultrasonography as an additional diagnostic tool for the diagnosis of amyotrophic lateral sclerosis

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See Editorial, pages 651–652

ARTICLE INFO

Article history:
Accepted 27 June 2014
Available online 21 August 2014

Keywords:
Myosonography
Amyotrophic lateral sclerosis
Electromyography
Neuromuscular
Ultrasound

HIGHLIGHTS

- Muscle ultrasonography (MUS) is highly sensitive in detecting fasciculations—even in the muscles of full strength—and fibrillations, especially in the bulbar muscles of patients with amyotrophic lateral sclerosis (ALS).
- MUS shows significantly increased echo intensity and fasciculations in clinically and electrophysiologically affected and unaffected muscles in ALS patients.
- When combined with electromyography (EMG), MUS can provide additional information about specific muscles and increase the diagnostic yield.

ABSTRACT

Objective: We aimed to determine the utility of muscle ultrasonography (MUS) in addition to electromyography (EMG) in the diagnosis of amyotrophic lateral sclerosis (ALS).
Methods: In all, 60 patients with ALS and 20 with other neuromuscular disorders underwent MUS and EMG. In addition, 30 healthy controls underwent only MUS. Occurrence of fasciculations and fibrillations was evaluated. Ultrasonic echogenicity was graded semiquantitatively.
Results: The incidence of fasciculations was significantly higher in patients undergoing MUS than in those undergoing EMG ($p < 0.05$), even in muscles of full strength ($p < 0.001$). However, EMG was more sensitive in detecting fibrillations ($p < 0.05$). MUS had an overall higher sensitivity in detecting spontaneous activity in the tongue ($p < 0.05$). Patients with ALS showed significantly increased muscle echo intensity (EI) compared to patients who were initially suspected as having ALS and normal controls ($p < 0.05$), irrespective of the clinical or electrophysiological status.
Conclusion: Our results showed that the sensitivity and specificity of MUS in diagnosing ALS was almost equivalent to those of EMG, using the Awaji criteria. Combination of MUS and EMG enhances the diagnostic accuracy compared to EMG alone ($p < 0.05$).
Significance: The combination of EMG and MUS can be used to evaluate the lower motor neuron affection by reducing the use of the often painful and uncomfortable EMG examinations but without decreasing the diagnostic sensitivity and specificity.

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale in its revised form; APB, abductor pollicis brevis muscle; BB, biceps brachii muscle; EI, echo intensity; EMG, electromyography; ER, extensor muscles of the forearm; MND, motor neuron disease; MMN, multifocal motor neuropathy; MUNE, motor unit number estimation; PSW, positive sharp wave; RA, rectus abdominis muscle; RF, rectus femoris muscle; SMA, spinal muscle atrophy; TA, tibialis anterior muscle.

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http://dx.doi.org/10.1016/j.clinph.2014.06.052
1388-2457/

1. Introduction

Diagnosis of amyotrophic lateral sclerosis (ALS) is based on the anamnesis of progressive muscular weakness, clinical examination, and exclusion of other conditions. Various clinical onsets and courses often delay the diagnosis of ALS (Kraemer et al., 2010). However, early diagnosis is important for the initiation of treatment and enrollment into clinical trials. Electromyography (EMG) is essential to identify the loss of lower motor neurons (LMN), typically seen as fibrillations and positive sharp waves (PSWs), i.e., pathological spontaneous activity. Another typical phenomenon in ALS is the presence of fasciculations, which are not classified as pathological spontaneous activity when present in healthy muscles (Brooks, 1994).

However, with the further revision of the revised El-Escorial criteria (Brooks et al., 2000) in 2006 to the Awaji criteria, detection of fasciculations has become an important step in the diagnosis of ALS (Hardiman et al., 2011). Fasciculations are similar to PSWs and fibrillations if they occur in muscles showing neurogenic changes (De Carvalho et al., 2008). This modification increases the sensitivity of diagnosis without increasing the false-positive rate (de Carvalho and Swash, 2009; Boekestein et al., 2010). A meta-analysis showed that the use of the Awaji criteria increased the number of patients diagnosed with probable or definitive ALS by up to 23%, without a decrease in specificity, compared with that diagnosed using the revised El-Escorial criteria (Costa et al., 2012) that emphasizes on the importance of refined electrodiagnostic studies. However, in daily clinical routine, EMG is invasive, painful, and time consuming (Mills, 2011).

In recent years, muscle ultrasonography (MUS) has become a promising tool for diagnosing neuromuscular disorders (Pillen et al., 2008; Boon et al., 2012; Mayans et al., 2012; Grimm et al., 2013).

In this study, we employed both MUS and EMG to diagnose ALS and other neuromuscular disorders (ALS-mimicking disorders). Healthy controls underwent only MUS. The primary end points were detection of spontaneous activity on MUS in one hand and evaluation of muscle structure on the other.

The aim was to determine whether MUS was more sensitive than EMG for the detection of fasciculations, as demonstrated previously (Walker et al., 1990; Reimers et al., 1996a; Scheel and Reimers, 2004; Misawa et al., 2011), and whether fibrillations could also be detected using MUS, as suggested by some studies (Dengler, 2009; Pillen et al., 2009a; Pillen and van Alfen, 2011; van Alfen et al., 2011), which would enhance the role of MUS in the diagnosis of neuromuscular disorders and facilitate the diagnosis of ALS. The study also intended to evaluate whether MUS would determine fasciculations as the leading symptom of ALS in clinically and/or electrophysiologically unaffected muscles.

To determine the degradation of muscle structure, we focused on echo intensity (EI) as a diagnostic parameter because several studies have shown that affected muscles show structural changes in different aspects of myosonography compared to healthy muscles and clinically unaffected muscles having normal strength (Pillen et al., 2007, 2008; Walker et al., 2004; Arts et al., 2008, 2010, 2011a, 2012). Muscle atrophy, fatty infiltration, and intramuscular fibrosis can be detected using ultrasonography (Pillen et al., 2009b). The differences between patients with ALS, patients with other neuromuscular disorders, and healthy controls were analyzed.

The second end point of the study was to determine whether the sensitivity and specificity of the combination of EMG and MUS (included in a reasonable clinical program) was equivalent to that of EMG alone.

2. Materials and methods

2.1. Subjects

In all, 80 patients with suspected ALS who were aged 18–90 years and who visited our hospital or the ALS special unit between October 2011 and March 2013 were included in this observational study. Patients underwent clinical examination, EMG, and MUS. The study also included 30 healthy age-matched controls who underwent the same MUS protocol as the patients. The study was registered with the German Clinical Trials Register (DRKS-ID: DRKS00004322) and was approved by the local ethics committee (No. 3519-07/12). Informed consent was obtained from all patients and controls before their inclusion in the study.

2.2. Ultrasonography

MUS was performed using real-time linear array scanner (Siemens Acuson, Erlangen, Germany) with a 9–13-MHz probe. Initial settings (such as contrast) were kept constant for all examinations, except depth, which was changed for each examination to observe the complete muscle, e.g., rectus femoris (RF).

Different muscles of the upper (cervical) and lower limbs (lumbar), muscles of the trunk (thoracic), and bulbar muscles were examined bilaterally (biceps brachii muscle [BB], extensor [ER] muscles of the forearm, rectus femoris [RF] muscle, tibialis anterior muscle [TA], rectus abdominis muscles [RA], and the tongue).

Four anatomical regions were defined (bulbar = tongue, cervical = BB and ER, thoracic = RA, and lumbar = RF and TA). Patients were examined in the supine position, with arms and legs extended and muscles relaxed as recommended (Reimers and Kellner, 1996b; Scholten et al., 2003; Arts et al., 2010). Muscles were scanned in the axial and longitudinal planes, and each muscle was measured at the standardized anatomical points; in detail: BB and RF at the midline between the origin and insertion, ER at the first third of the distance between the elbow and processus styloideus radii, TA at the first third of the distance between the knee and malleolus lateralis, and RA periumbilical at 2 cm laterally to the midline. The tongue was examined from the submandibular direction, and patients were asked to stop swallowing and breathing for 10 s.

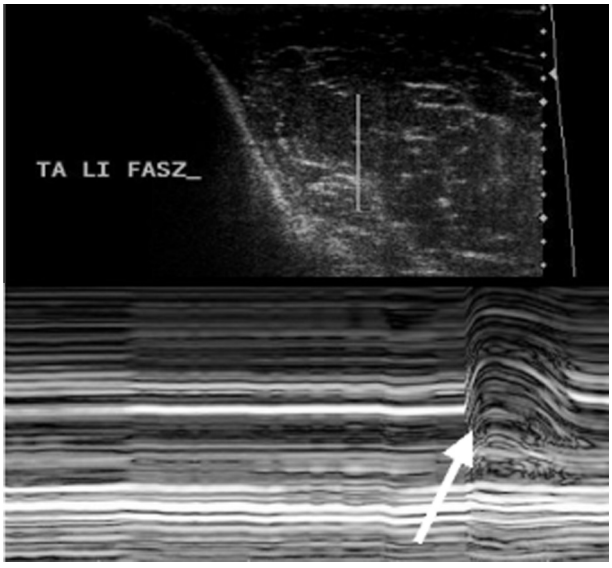

Fig. 1. Ultrasonic cross sections through the left tibialis anterior muscle (TA) showing a fasciculation using M-mode.