REVISTA NEUROCIÊNCIAS

Transcranial magnetic stimulation for ALS: an integrative review

Estimulação magnética transcraniana para ELA: uma revisão integrativa

Estimulación magnética transcraneal para la ELA: una revisión integradora

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Resumo

Introdução. A Esclerose Lateral Amiotrófica (ELA) é uma doença neurológica progressiva rara que afeta os neurônios responsáveis pelos movimentos voluntários e os sintomas pioram com o tempo. Uma das ferramentas de avaliação e tratamento é a estimulação magnética transcraniana (EMT), que é uma alternativa não invasiva para a estimulação elétrica do tecido neural, com esta estimulação alguns neurorreceptores específicos podem ser excitados. A literatura atual mostra vários benefícios da EMT como terapia e diagnóstico para pacientes com ELA. **Objetivo**. Investigar a aplicabilidade da EMT para o diagnóstico e tratamento da ELA. **Método.** Foi realizada revisão integrativa na qual foram identificados artigos relevantes por meio de busca nas seguintes bases de dados: SCiELO, PubMed, PEDro, Scopus de abril de 2020 a setembro de 2020. Os autores selecionaram os artigos relevantes de acordo com os critérios pré-estabelecidos. **Resultados**. A busca nas bases de dados encontrou 26.602 artigos, 4 foram incluídos por atenderem aos critérios de inclusão. Dentre os artigos selecionados, 2 referem-se a propostas diagnósticas, enquanto os demais apresentam a EMT como ferramenta de tratamento. Estudos têm mostrado resultados promissores em relação ao efeito da EMT na avaliação e tratamento da ELA. **Conclusões.** Nossos resultados mostram um progresso significativo da EMT como terapia e diagnóstico inovador e eficaz da ELA.
Unitermos. Esclerose lateral amiotrófica; estimulação magnética transcraniana; estimulação elétrica; diagnóstico; tratamento

Abstract

Introduction. Amyotrophic Lateral Sclerosis (ALS) is a rare progressive neurological disease that affects neurons responsible for voluntary movements and the symptoms get worse over time. One of the assessment and treatment tools is transcranial magnetic stimulation (TMS), which is a non-invasive alternative for the electric stimulation of neural tissue, with this stimulation some specific neuro-receptors can be excited. Current literature shows several benefits of TMS as therapy and diagnosis for patients with ALS. **Objective**. To investigate the applicability of TMS for diagnosing and treating ALS. **Method.** An integrative review was carried out in which relevant articles were identified by searching the following databases: SCiELO, PubMed, PEDro, and Scopus from April 2020 to September 2020. The authors selected the relevant articles according to the pre-established criteria. **Results**. Database search found 26,602 articles, 4 were included due to meeting the inclusion criteria. Among the selected articles, 2 refer to diagnostic proposals, while the others present TMS as a tool for treatment. Studies have shown promising results regarding the effect of TMS on the assessment and treatment of ALS. **Conclusions**. Our results show a significant progress of TMS as an innovative and effective therapy and diagnosis of ALS.
Keywords. Amyotrophic lateral sclerosis; transcranial magnetic stimulation; electric stimulation; diagnosis; treatment

Resumen
Introducción. La esclerosis lateral amiotrófica (ELA) es una rara enfermedad neurológica progresiva que afecta a las neuronas responsables de los movimientos voluntarios y los síntomas empeoran con el tiempo. Una de las herramientas de evaluación y tratamiento es la estimulación magnética transcraneal (EMT), la cual es una alternativa no invasiva para la estimulación eléctrica del tejido neural, con esta estimulación se pueden excitar algunos neurorreceptores específicos. La literatura actual muestra varios beneficios de la EMT como terapia y diagnóstico para pacientes con ELA. **Objetivo**. Investigar la aplicabilidad de la EMT para el diagnóstico y tratamiento de la ELA. **Método.** Se realizó una revisión integradora en la que se identificaron artículos relevantes mediante búsqueda en las siguientes bases de datos: SCiELO, PubMed, PEDro, Scopus desde abril de 2020 hasta septiembre de 2020. Los autores seleccionaron los artículos relevantes según los criterios preestablecidos. **Resultados**. La búsqueda en bases de datos encontró 26.602 artículos, 4 fueron incluidos por cumplir con los criterios de inclusión. Entre los artículos seleccionados, 2 hacen referencia a propuestas diagnósticas, mientras que los demás presentan la EMT como herramienta de tratamiento. Los estudios han mostrado resultados prometedores con respecto al efecto de la EMT en la evaluación y el tratamiento de la ELA. **Conclusiones**. Nuestros resultados muestran un avance significativo de la EMT como terapia y diagnóstico innovador y eficaz de la ELA.
Palabras clave. Esclerosis lateral amiotrófica; estimulación magnética transcraneal; estimulación eléctrica; diagnóstico; tratamiento

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease characterized by deterioration of both upper motor neurons (UMN) and LMN. Those affected experience muscle weakness differently making everyday tasks difficult, making it hard to get a diagnosis that is based on predominantly clinical examination[1]. Further exams may help in the diagnosis of ALS, such as a magnetic resonance image (MRI) through the MTC/ST1 technique that is effective in the identification of cortico-spinal dysfunction related to the UMN, to exclude diagnosis of other diseases. On the other hand, needle electromyography (nEMG) can detect

denervation in LMN which is not observed in clinical examination[2,3].

For this reason, different electrophysiological techniques have been applied to measure the progressive loss of motor units, through nEMG[4]. Furthermore, its diagnosis is supported by Awaji[1], Amyotrophic Lateral ScleA format osis Functional Rating Scale (ALSFRS-R)[5], MRI[6], and biochemical indicators that identify a combination of signs of injury in the UMN and LMN, to identify the appropriate therapeutic tools[1,7].

Studies have shown strategies proposed to support diagnosis and treatment and to favor a better quality of life for these patients with the assistance of a multidisciplinary team[8]. From this point of view, transcranial magnetic stimulation (TMS)[2,8,9] has supported the development of diagnostic and prognostic biomarkers of neurodegenerative diseases[8]. Regarding neurophysiological investigation, its main advantages are the temporal resolution of the integrity of the brain pathways and the possibility of directly interfering with physiological mechanisms in the central nervous system[2,8,9].

This technique uses a transient magnetic field generated by a coil placed over the individual's head, to induce an electrical current in specific regions of the cortex[3]. Its application must be performed at regular intervals allowing maximum pulse frequencies of up to 60Hz. Therefore, when frequencies above 1Hz are applied, high-frequency repetitive TMS (rTMS) is considered, which

promotes the temporary increase of excitability of the motor cortex through the activation of corticospinal axons, generating direct waves (D). In turn, when lower frequencies are used, it is called low-frequency rTMS, which generates interactions between excitatory and inhibitory cortical neurons, resulting in indirect waves (I)[3,10]. Excitation is mediated mainly by the interaction of receptors glutamate/NMDA, while inhibition is facilitated by γ-aminobutyric acid (GABA)/GABAA/B receptor action[10].

The main application of TMS techniques has been in the investigation of neuronal networks in the primary motor cortex (M1), which is influenced by both inhibition and excitatory mechanisms. It is, therefore, an excellent biomarker for tracking and monitoring lower motor neurons (LMN) dysfunctions in patients with ALS[10], since changes after TMS show cortical hyperexcitability by reducing short-range intracortical inhibition and increasing evoked motor potential amplitude, which are considered early features of neurodegeneration in ALS patients[8].

From this perspective, in the present study, we aim to investigate the effect of TMS on the diagnosis and treatment of ALS. It is expected that this knowledge may support further therapies and research on new tools of diagnosis and therapeutics to improve the quality of life of ALS patients.

METHOD

Protocol design

An integrative review has been designed to provide a comprehensive understanding that will contribute with new evidence for health practices, based on the analysis of experimental and non-experimental studies, considering that the TMS may be a non-invasive tool for its diagnosis and treatment[11].

Literature search

To conduct a comprehensive search, it is recommended to search several literature sources, including electronic databases. From this perspective, the following databases were searched: SCiELO, PubMed, PEDro, and Scopus from April 2020 to September 2020. To ensure the most accurate keywords in different concepts related to this review were searched Medical Subjects Headings - MeSH (Table 1; Appendix 1). Besides, the reference list of all included studies has been manually checked to search for additional relevant studies.

Table 1. Main concepts and matching related keywords used in the literature search.

Concepts	Matching keywords
Synonyms for ALS	Amyotrophic Lateral Sclerosis, Progressive Muscular Atrophy, Adult Onset Spinal Muscular Atrophy, Hereditary Motor Neuronopathy, Progressive Myelopathic Muscular Atrophy, Bulbospinal Neuronopathies, Central motor conduction time, Charcot disease, Guam disease, Lou Gehrig Disease, Motor Neuron Disease, Thenar Complex Muscles, Lower Motorneuron.
Synonyms for TMS	Transcranial Magnetic Stimulation, Magnetic Stimulation, Transcranial Stimulation, Repetitive Transcranial Magnetic Stimulation.

Study selection

The authors selected the relevant articles according to the following pre-established criteria based on the PICOS (Population, Intervention, Comparison, Outcomes, and Study) strategy[12].

- Types of participants:

We selected studies in which TMS was used as a tool for diagnosis or treatment in patients with ALS regardless of severity. Participants must be over 18 years of age. We excluded studies that included people with other associated neurological diseases or who use some invasive stimulation technique.

- Types of interventions:

This review included studies that investigated the use of TMS for diagnosis and treatment and used quantitative or qualitative instruments for evaluation.

- Types of comparators:

We inserted studies comparing the following comparison possibilities: (1) active TMS versus no therapy, (2) active TMS versus sham TMS, (3) active TMS versus sham TMS versus another resource considered the gold standard either in the diagnosis or treatment of ALS, (4) only TMS.

- Types of outcomes:

The Primary outcomes will be the clinical effectiveness of TMS applied to the diagnosis and treatment of people with ALS.

The Secondary outcomes will be adverse effects, TMS parameters to evaluate and treat this disease, and tools that have been also used for assessment associated with the TMS.

- Types of studies:

We will include full-text studies and experimental study designs, including randomized controlled trials (RCTs) to investigate the effect of TMS. In the absence of RCTs, non-RCTs, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies will be included to identify the use of TMS as a tool for assessment.

Screening Process

Screening process has been conducted including the inclusion and exclusion criteria within a random sample of 10% of the retrieved cases. Once the final set of criteria was performed, the titles abstracts, and/or previews were simultaneously examined to search the relevant studies. For this, the authors independently applied the inclusion criteria on all retrieved citations, and the full-text of the included articles was analyzed in the second phase for the final inclusion decision. Besides, the references of the included articles were analyzed, considering the same steps mentioned above. Disagreements have been resolved by consensus, through team discussion.

Collating, Summarizing, and Reporting The Results

The extracted data have been inserted in a table in which rows represent the included articles, and columns represent the collected variables, such as study design, patient characteristics, outcome measures, intervention, and findings.

RESULTS

The literature search undertaken yielded 26,602 records, of which initially, the titles and abstracts were read, and excluded the duplicate articles. In addition, review articles and not full text were excluded, resulting in 194 articles. Thus, after careful analysis, four articles were included in the full-text review. Then, only three studies were inserted for using TMS as a treatment or diagnosis strategy in people with ALS, and, later, it was possible to insert one more article through the grey literature, totalizing four articles. Figure 1 shows the PRISMA flowchart[13] of the results from the literature search.

Further, Table 2 describes the following information on the articles inserted: study design, patients' demography (e.g. age, number of participants, and disease duration), outcome measures (i.e. tools used in evaluation), intervention (e.g. frequency, duration, description, and adverse effects), and findings of each article included in this review.

Figure 1. Prisma flowchart of the results from the literature search.

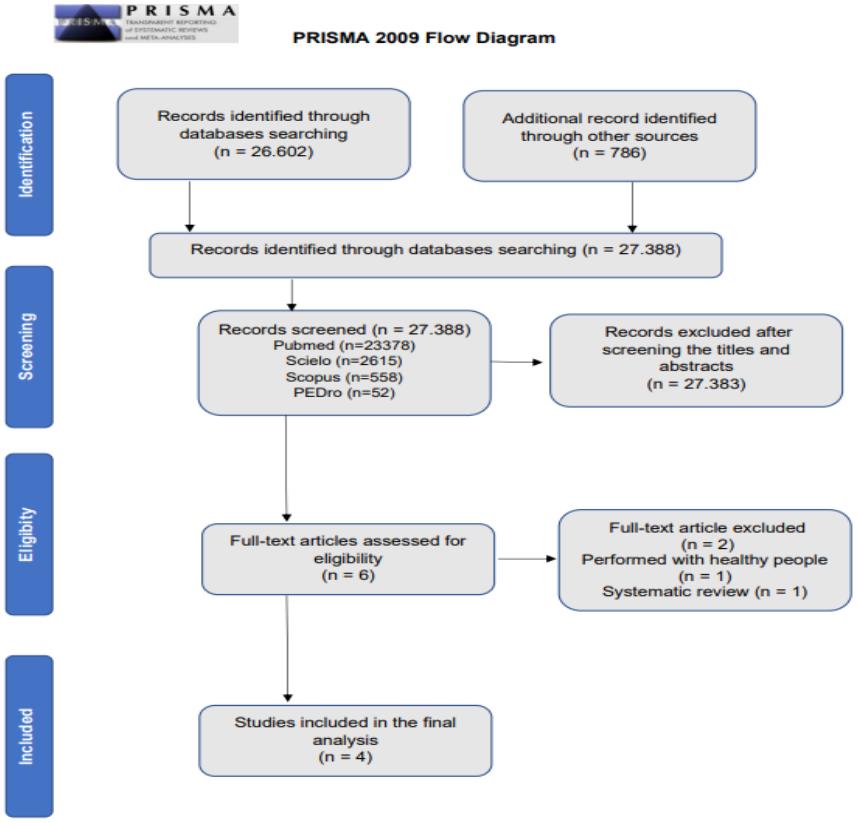

Table 2. Effect of TMS for diagnosis and treatment on ALS.

Author(s)	Study design	Patients characteristics	Outcome measures	Intervention	Findings
Di Lazzaro *et al* 2006[1]	Double-blind, placebo-controlled trial	**Sham** Age=61.2±10.7 yo. N=8 (5M, 3W). Disease duration= 14.5±8.3 months. **Active** Age=60.6±13 yo. N=7 (5M, 2W). Disease duration = 13.9±8.8 months.	Patients were evaluated at the beginning of the treatment and every month until the end of the 6 months, through the following outcomes: MMT. MVIC-hand. ALSFRS-R.	rTMS was applied over hand motor area for 5 consecutive days every month for 6 consecutive months. Active = rTMS was performed using the cTBS pattern in which 3 pulses of stimulation were given at 50 Hz, and repeated every 200 ms for a total of 600 pulses, and stimulation intensity was 80% AMT tested on contralateral first interosseous muscle. Sham = no stimulating effect on the cortex but produces similar auditory and tactile sensations as the active coil.	Significant slowing in activation of the motor cortex through cTBS of ALS patients as evaluated with ALSFRS-R and with MMT. No significant difference between active and sham patients for MVIC-hand. Authors do not provide information on whether or not adverse events occurred during the research.

Table 2 (cont.). Effect of TMS for diagnosis and treatment on ALS.

Author(s)	Study design	Patients characteristics	Outcome measures	Intervention	Findings
Zanette *et al* 2008[14]	Pilot controlled study documented in a double-blind study	**Sham** Age= 60.2±8.7 yo. N=5 (3M, 2W). Disease Duration= 12.2±4.0 months. **Active** Age= 59.4±9.2 yo. N=5 (4M, 1W). Disease Duration= 11.4±3.0 months.	Patients were examined before rTMS treatment (T0), the day after the end of rTMS treatment (T1) and two weeks after the end of rTMS (T2). ALSFRS-R. SF-36. MRC (e.g. UL - biceps, triceps, extensor carpi radialis, first dorsal interosseus; and LL - quadriceps, tibialis anterior, gastrocnemius, extensor hallucis longus). MVIC from UL (bilateral elbow flexion and extension) and LL (bilateral knee flexion and extension) ROM. FSS.	rTMS was delivered for 5 consecutive days per week for two weeks to stimulate UL and LL (tibialis anterior muscles) cortical areas on both sides. Active = 20 trains of 15 stimuli, 60 s interval between trains; 110% resting motor threshold. Sham = rTMS was performed using the same stimulator connected to a specific sham coil that has no stimulating effect on the cortex but produces similar auditory and scalp sensations as the active coil.	Isometric MVIC and isokinetic AP were significantly better in the active rTMS group. For ROM, only a trend towards better improvement to active rTMS was found. MVIC represents a robust motor outcome measure that has been used to assess weakness and fatigue in ALS. We could not find any change in ALSFRSr and MRC. A significant difference was identified in QoL. No adverse effects have been reported.
Menon *et al* 2015[15]	Prospective study.	N= 333 (206 M, 127 M). Age= 57.6±14.6 yo. 9 patients with probable ALS had been diagnosed with the disease before recruitment, with evidence of disease progression during a follow-up period of 6 months from initial assessment; or a neuromuscular disorder mimicking ALS, defined as muscle weakness and wasting for at least 6 months.	All patients have been evaluated by: ALSFRS-R. TMS (MEP and SICI), according to the Awaji diagnostic criteria. The following muscle groups were assessed bilaterally from MRC score: shoulder abduction, elbow flexion and extension, wrist dorsiflexion, finger and thumb abduction, hip flexion, knee extension, and ankle dorsiflexion.	It used the TMS with a 90 mm circular coil. MEP amplitude and measured changes were fixed in the test stimulus intensity needed to generate a target response of 0·2 mV (with a 20% allowance above and below) when preceded by a subthreshold conditioning stimulus. Recorded MEP response over the right abductor pollicis brevis muscle. Defined resting motor threshold as the stimulus intensity needed to maintain this target MEP response. It did paired-pulse threshold tracking to establish SICI and intracortical facilitation, whereas used single-pulse TMS to establish the MEP amplitude (mV), cortical silent period duration (ms), and central motor conduction time, according to a previously reported technique.	The findings show that threshold tracking TMS reliably distinguishes ALS from non-ALS mimic disorders. Reduction of averaged SICI seemed to be the most robust diagnostic biomarker and, when combined with motor cortex inexcitability, showed high sensitivity and specificity, with the number needed to test with TMS to diagnose one extra case of ALS being only 1·8. Diagnostic utility of threshold tracking TMS was similar between Awaji diagnostic categories and patients with bulbar-onset and limb-onset ALS. Threshold tracking TMS technique as an aid to the diagnosis of ALS, irrespective of the site of disease onset, providing an objective biomarker of UMN dysfunction and potentially permitting earlier diagnosis by an average of 15·8 months when combined with clinical and conventional neurophysiological measurements compared with these techniques used without TMS. However, A potential limitation might occur in patients with ALS who have severe hand wasting, which might preclude TMS testing. TMS abnormalities were evident in about 70% of patients with ALS classified as Awaji possible or not meeting criteria. Assessment of cortical excitability from lower limb muscles or intrinsic hand muscles less affected by LMN loss than the abductor pollicis brevis muscle might increase the diagnostic yield of threshold tracking TMS. Any adverse events from the performance of the index test have been reported.

Table 2 (cont.). Effect of TMS for diagnosis and treatment on ALS.

Author(s)	Study design	Patients characteristics	Outcome measures	Intervention	Findings
Geevasinga *et al* 2014[16]	Prospective and cohort study	N= 82 (52 men and 30 women). Mean age= 60 yo. Median disease duration at the time of TMS testing from symptom onset was 11 months.	TMS, according to the Awaji criteria by utilizing the following parameters: SICI, ICF, RMT, CMCT, MEP amplitude (% CMAP response) and CSP duration. ALSFRS-R. MRC score: shoulder abduction; elbow flexion and extension; wrist dorsiflexion; finger abduction; thumb abduction; hip flexion; knee extension; ankle dorsiflexion. nEMG from a concentric electrode in the cranial, cervical, and lumbosacral regions. Nerve conduction was assessed by stimulating the median nerve.	-	SICI was significantly reduced in patients with ALS (P<0.0001) with a comparable reduction evident in the Awaji groups (SICI AWAJI POSSIBLE 1.3%; SICI AWAJI PROBABLE / DEFINED 1.4% - 1.7%). CMCT was significantly prolonged: CMCT (P <0.001), MEP amplitude (P <0.05) and ICF (P <0.05) were increased. 88% of Awaji possible patients could be reclassified as Awaji probable/definite if TMS abnormalities, including prolonged CMCT, inexcitable motor cortex, or reduced SICI. Any comments about adverse effects were mentioned.

ALS:Amyotrophic Lateral Sclerosis; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; AMT: Active Motor Threshold; CMCT: Central Motor Conduction Time; CMAP: Compound Muscle Action Potential; CMCT: Central Motor Conduction Time; CSP: Cortical Silent Period; cTBS: Continuous Theta-Burst Stimulation; FSS: Fatigue Severity Scale; ICF: Intracortical Facilitation; LL: Lower Limb; MMT: Manual Muscle Test ; MRC: Medical Research Council; MVIC: Maximal Voluntary Isometric Contraction; NI: Neurophysiological Index; QoL: Quality of Life; RMT: Resting Motor Threshold; ROM: Range of Motion; rTMS: Repetitive Transcranial Magnetic Stimulation; SICI: Short Intracortical Inhibition; MEP: Motor Evoked Potentials.

DISCUSSION

Our integrative review has been conducted to investigate the effect of TMS as a tool to evaluate and treat symptoms of ALS. Our results suggest that TMS is a non-invasive method that may support the diagnosis and therapy of ALS without causing adverse events and bring benefits by relieving symptoms and improving the diagnosis. From this review, it is possible to identify its adverse effects, parameters, and tools applied for assessment associated with the TMS to base and guide the use of this technique in people with ALS from all the benefits that it can provide.

Of the four articles inserted, two refer to the use of TMS for diagnosis whilst the others show it as an alternative to treatment. It is known that the diagnosis of ALS is initially made through clinical analysis and physical examination by a multidisciplinary team given the importance of TMS can be associated with the most common tests, for instance, biochemical exams, MRI or CT of the cervical spine, and motor and respiratory evaluation to describe the greatest therapeutics resources[8,10].

Geevasinga *et al*.[16] found SICI has been significantly decreased in ALS given a reduction evident in the Awaji groups ($SICI_{AWAJI\ POSSIBLE}$ 1.3%±1.3%; $SICI_{AWAJI\ PROBABLE/DEFINITE}$ 1.4%±1.7%), and CMCT has been significantly prolonged while the ME amplitude and FIC have been increased. Nevertheless, cortical excitability may facilitate an earlier diagnosis of 88% of Awaji possible patients to Awaji probable/definite when associated with clinical and traditional neurophysiological findings. Furthermore, Menon *et al*.[15] underscore the combinations of these outcomes may reduce the diagnosis time to 15.8 months. Regardless, a potential limitation might occur in patients with ALS who have severe hand wasting.

Studies revealed benefits of TMS suggesting its use might be useful for treatment of ALS. Di Lazzaro[1] observed decrease of the motor cortex excitability, which could antagonize glutamate excitotoxicity in ALS by reducing the response of corticospinal cells, associated with the slower deterioration rate in the active group identified[1,16]. Besides,

MVIC-hand and MRC scores in active and sham patients with no statistical difference[15]. Furthermore showed that a 5-Hz rTMS may be able to improve on QoL, MVIC, and isokinetic average power with statistically significant differences in the active group[1,15,17,18]. did not report any adverse event. Nonetheless, there are other kinds of therapies for ALS, such as Riluzol and Edaravone. Despite their benefits, may provoke any adverse effects, for example, Riluzol may cause tachycardia, headache, dizziness, oral paraesthesia, drowsiness, diarrhea, abdominal pain, vomiting, nausea, fatigue, and risk of liver enzyme alterations. In addition, Edaravone has the possibility of causing dysphagia, nasopharyngitis, constipation, and gait disturbance. It is noteworthy that there are also therapies based on genetic targets that are involved in the disease, many of which are still under investigation. These adverse events interfere with the quality of life of patients with ALS, when associated with the symptoms of the disease, this is aggravated[18,19].

Moreover, researchershave been able to suggest that TMS may be used to evaluate neural mechanisms of ALS[14,17]. Menon *et al*.[15] and Geevasing *et al*.[16] have used assessment tools such as ALSFRS-R and MRC score to assess the health condition of people with ALS associated with TMS, according to the Awaji diagnostic criteria. Both of these studies have used the MEP fixed amplitude (mV) over the right abductor pollicis brevis muscle and measured changes to generate a target response of 0-2 mV preceded by a subthreshold conditioning stimulus. SICI and ICF were established by

paired-pulse threshold tracking. Thus, Menon *et al*.[15] suggest that this threshold TMS reliably distinguishes ALS from non-ALS people. In addition, Geevasing *et al*.[16] showed further techniques to improve the diagnosis of ALS as an nEMG and nerve conduction study. From them, 61% were classified as 'possible' whereas 39% were 'probable/definite' ALS based on the Awaji criteria. CMAP amplitude, averaged and peak SICI, CSP, duration, and RMT and NI were significantly reduced whit MEP amplitude was increased and CMCT prolonged in ALS.

CONCLUSION

The present results indicate that TMS might work as an efficacy tool for diagnosis and therapy in ALS whether associated with other resources favoring early diagnoses. Taking into consideration that there is still no cure for ALS and its debilitating symptoms. From this point of view, it is important to start treatment early to try to provide a quality of life for these patients.

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Appendix 1: Databases Search Scripts in PubMed without filters.

Search Scripts
(Amyotrophic Lateral Sclerosis OR Progressive Muscular Atrophy OR Adult Onset Spinal Muscular Atrophy OR Hereditary Motor Neuronopathy OR Progressive Myelopathic Muscular Atrophy OR Bulbospinal Neuronopathies OR Central motor conduction time OR Charcot disease OR Guam disease OR Lou Gehrig Disease OR Motor Neuron Disease OR Thenar Complex Muscles OR Lower Motorneuron) AND (Transcranial Magnetic Stimulation OR Magnetic Stimulation OR Transcranial Stimulation OR Repetitive Transcranial Magnetic Stimulation)