Sensitivity of transcranial magnetic stimulation of cortico-bulbar vs. cortico-spinal tract involvement in Amyotrophic Lateral Sclerosis (ALS)

Abstract Background An upper motor neuron (UMN) lesion in amyotrophic lateral sclerosis (ALS) is often difficult to identify because clinical signs may be discrete or masked by severe simultaneous lower motor neuron (LMN) lesions. We compared the diagnostic sensitivity of transcranial magnetic stimulation (TMS) to cranial muscles and limb muscles in the detection of UMN lesions.

Design We investigated corticobulbar and corticospinal tract function to the tongue/orofacial muscles and abductor digiti minimi/tibial anterior muscles with TMS in 51 patients with ALS to compare the diagnostic yield in the detection of UMN dysfunction. An UMN lesion was assumed when the following were found: the peripheral conduction time and amplitude of the M-wave were within the normal range, the response to cortical stimulation was absent, the TMS evoked/M-wave amplitude ratio was reduced, and the central motor conduction time or the interside difference was delayed (> mean+2.5 SD). Results On the basis of these criteria a UMN lesion to the orofacial muscles was identified in 24 patients (47%), to the tongue in 27 (53%), and to the upper and lower limbs in 13 (25%) and 22 patients (43%), respectively. Combined abnormalities from all sites increased the diagnostic yield to 39 patients (76%). TMS of the limb muscles confirmed a UMN lesion in only 15 (54%) of the 28 patients with clinically confirmed UMN involvement. This number increased to 23 patients (82%) if tongue and orofacial muscles were taken into account. Conclusion Our results indicate the early and in most cases subclinical corticobulbar tract involvement of the central motor pathways to the orofacial muscles and tongue in ALS. TMS of the tongue and orofacial muscles had a higher sensitivity in identifying UMN lesions than that of the upper and lower limbs.

Key words Amyotrophic lateral sclerosis · Cortico-bulbar tract · Hypoglossal nerve · Facial nerve · Cortico-spinal tract · Transcranial magnetic stimulation

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder involving both the upper and lower motor neurons [1]. The diagnosis of ALS is primarily based on clinical features, although electrodagnostic procedures are currently used to confirm the diagnosis and to evaluate progression of the disease. In addition to electromyography (EMG) performed to determine lower motor neuron involvement, the introduction of transcranial magnetic stimulation (TMS) of the motor cortex has allowed the assessment of central motor pathway function.

It has recently been shown by TMS that cortico-bulbar tract function to the orofacial [2], tongue [2], maseter [3] and trapezius muscles [4] is frequently impaired in the course of amyotrophic lateral sclerosis. In view of the finding that the cortico-bulbar and corticospinal tracts may be involved independently [5, 6], we investigated the sensitivity of TMS responses evoked in orofacial and tongue muscles as well as in the upper and lower limb muscles of ALS patients in different stages and with forms of clinical presentation.
Patients and methods

We studied 51 consecutive ALS patients with a mean age (± SD) of 60.2 ± 9.3 years (range: 31–77) and a mean duration of illness of 15 ± 13 months (range: 2–48) at the time of investigation. Compound muscle action potentials (CMAPs) were recorded bilaterally from the oro-facial muscles, tongue, hypothenar, and tibial anterior muscles.

The cortico-facial projections were investigated by TMS and recording of CMAPs of the buccinator muscles on either side of the face. We used pairs of Ag/AgCl-surface disc electrodes embedded at a distance of 18 mm in a specially designed fork-shaped methacrylate device, which was adapted to the oral cavity [7]. The electrodes were in contact with the inside of the cheeks. Slight contraction of the buccinator muscles was achieved by pursing the lips.

The cortico-lingual projections were examined by TMS and recording of CMAPs on each half of the tongue. Two pairs of Ag/AgCl-surface disc electrodes were mounted at an interelectrode distance of 18 mm on a spoon-shaped methacrylate device adapted to the oral cavity. The electrodes were placed above the lateral dorsum of the tongue. Slight contraction of the tongue muscles was achieved by gently pressing the dorsum of the tongue against the mouthpiece. This technique allows selective stimulation of either hemisphere and separate recording from each side of the tongue and the buccinator muscles, as shown in patients with middle cerebral artery infarction, unilateral hypoglossal nerve section, and unilateral facial palsies, respectively [8, 9].

The proximal peripheral facial and hypoglossal nerves were stimulated magnetically in the extra-axial intracranial segments. The circular coil was located ipsilaterally in the parieto-occipital region, which is appropriate for measuring the peripheral motor conduction time (PMCT) [7, 10]. For stimulation of the left (right) peripheral nerve, side “B” (“A”) was viewed from outside. The distal nerves were also stimulated electrically. All responses were recorded at least twice to assure reproducibility. A detailed description of the recording technique has been published elsewhere [7, 11–14].

In control subjects the cortico-lingual fibres have been shown to project bilaterally from each hemisphere to the hypoglossal nuclei [8]. Thus, involvement of the ipsi- and contralateral connections can be evaluated separately. Cortico-orofacial fibres projected to the contralateral facial subnuclei in 100% and to the ipsilateral subnuclei in only 58 to 67% of the control subjects. Thus, only the contralateral connections can be used reliably for evaluating the central pathways [11].

The cortico-spinal projections were tested by activating the abductor digiti minimi (ADM) and tibialis anterior (TA) muscles using TMS and recording CMAPs via surface electrodes placed on the belly-tendon position. The peripheral conduction time was determined by magnetic stimulation of the respective spinal nerve roots with the coil placed over the cervical and lumbar spine. Central motor conduction time (CMCT) was calculated as the difference between the shortest onset latency (total motor conduction time, TMCT) of the cortically evoked response and the PMCT. The peripheral nerves were stimulated electrically to determine M-wave amplitudes and to calculate the TMS evoked/M-wave amplitude ratio [15].

Filter settings for CMAP-recordings were 20–2,000 Hz. A Magstim 200S (Novametrix, Whitland, Dyfed, U.K.) and a circular coil (mean diameter 9 cm) with a peak magnetic field of 2.0 tesla were used for TMS recordings. The centre of the coil was positioned tangentially, 4–6 cm (tongue), and 1–2 cm (buccinator muscle) lateral of C2, at C2 (upper limbs) and at T2 (lower limbs), respectively. Side “A” (“B”) was viewed from above on stimulation of the left (right) hemisphere. Stimulation strength was increased stepwise during slight preinnervation until stable latencies were achieved. The shortest latency and largest amplitude (peak-to-peak) obtained for four responses were measured.

An UMN-lesion was assumed when 1) the cortical evoked response was absent, or 2) the TMS evoked/M-wave amplitude ratio was reduced (<15% at the ADM and ≤ 10 at the TA), or 3) the CMCT, or 4) the CMCT-difference between the hands and legs were delayed (> mean +2.5 SD) with the PMCT, while the absolute amplitude of the M-wave was within normal limits. Stimulation intensity was increased to 100% of the maximum output of the stimulator before a response was considered to be absent. Absence of a potential was defined as no reproducible response for 4 consecutive trials at a gain of 200 µV (16). Normative data obtained by our laboratory have previously been reported for all target muscles investigated in the present study [7, 8, 14, 17]. All patients gave their informed consent to participate in the study, which was approved by the local ethics committee (Landesarztekammer Rheinland-Pfalz).

Results

The diagnosis of ALS was established in all 51 patients from the clinical findings observed in the course of the disease. However, the majority of the patients were electrophysiologically investigated early in their disease. Initial manifestations of the disease included a bulbar syndrome in 18 patients, involvement of the upper and lower limbs in 18 and 14 patients respectively, and respiratory muscle weakness in one patient.

At the time of TMS, clinical examination demonstrated bulbar signs (tongue atrophy and/or fibrillations, dysarthria) in 26 patients. Three patients showed isolated pseudobulbar signs such as reduced tongue motility with spastic dysarthria and dysphagia, hyperactive jaw reflexes, but no tongue atrophy or fibrillations. Unequivocal signs of an UMN lesion to the limbs (exaggerated deep tendon reflexes, sustained clonus, extensor plantar responses, spasticity) were observed in 28 patients. Generalized LMN involvement was observed clinically (atrophy, fasciculations) and/or electromyographically in 44 patients. On TMS, the diagnosis of ALS according to revised El Escorial criteria (1, Airlie House Conference 1998) was clinically definite in 19, clinically probable in 12, and clinically possible in 20 patients.

TMS of the orofacial muscles

TMS demonstrated abnormalities of the cortico-facial projections on at least one side in 24 out of 51 patients (47%). Peripheral conduction abnormalities were not observed. TMS responses were absent in 21 sides (14 patients) and delayed in 17 sides (10 patients). Clinically, 8 patients showed slight to moderate bilateral facial paresis, which was not definitely identified as being of either nuclear or supranuclear origin.

TMS of the tongue

Because of the observation that magnetic stimulation of the peripheral hypoglossal nerve does not consistently elicit a CMAP in healthy subjects, LMN involvement was...