



## Heteronymous H reflex in temporal muscle as sign of hyperexcitability in ALS patients



Laura Libonati<sup>a</sup>, Tommaso Francesco Barone<sup>a</sup>, Marco Ceccanti<sup>a</sup>, Chiara Cambieri<sup>a</sup>, Giorgio Tartaglia<sup>a</sup>, Emanuela Onesti<sup>a</sup>, Antonio Petrucci<sup>b</sup>, Vittorio Frasca<sup>a</sup>, Maurizio Inghilleri<sup>a,\*</sup>

<sup>a</sup> Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

<sup>b</sup> Neuromuscular and Neurological Rare Diseases Center ASO San Camillo-Forlanini, Rome, Italy

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### HIGHLIGHTS

- Masseteric H reflex is used as an electrophysiological equivalent of mandibular jerk.
- Heteronymous H reflex is used as a sign of UMN involvement in suspected ALS patients.
- Heteronymous H reflex can be used to evaluate motor neuron pool excitability.

### ABSTRACT

**Objective:** The stimulation of the masseteric nerve elicits a homonymous and a heteronymous H reflex in the masseter muscle and in the temporalis one. The presence of the H reflex may be considered a sign of upper motor neuron (UMN) involvement in amyotrophic lateral sclerosis (ALS) patients. The aim of this study was to evaluate the presence of the heteronymous H reflex in patients with ALS and compare it with normal subjects.

**Methods:** We enrolled 36 ALS patients and 52 healthy subjects. We stimulated the masseteric nerve in the infratemporal fossa and recorded the muscle responses ipsilaterally to the stimulation.

**Results:** The heteronymous temporalis H reflex was elicitable in 88.9% of ALS patients and in none of the controls.

**Conclusion:** The heteronymous H reflex does not disappear when the stimulation intensity is increased. It can be used as sign of UMN involvement and may prove useful in patients with suspected MND/ALS with purely lower motor neurons (LMN) signs and no signs of UMN involvement.

**Significance:** The heteronymous H reflex is present far more often in ALS patients than in healthy people. It is a simple test that may be used to detect UMN involvement in patients in whom the only evident signs are LMN impairment, improving diagnosis of ALS.

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## 1. Introduction

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disorder with a fatal outcome and a mean survival time of 5 years (Qureshi et al., 2009). As ALS progresses, both the upper motor neurons (UMN) and the lower motor neurons (LMN) degen-

erate. There is no diagnostic test for ALS, and a confident diagnosis is mainly based on clinical assessments that rely on the detection of UMN and LMN signs in the limb and/or bulbar territories combined with a history of symptom progression (Onesti et al., 2016).

The mandibular reflex is a monosynaptic reflex analogous to the tendon jerk of the limbs (Fine and Lohr, 2003) and that was reported for the first time in 1885 (Boes, 2014). It is the only myotatic reflex in the cranio-bulbar district. This reflex is often imperceptible and is characterized by a small amplitude twitch. The occurrence of this reflex is reduced and its latency increased as

\* Corresponding author at: Department of Human Neurosciences, Sapienza University of Rome, viale dell'Università 30, 00185 Rome, Italy.

E-mail address: [maurizio.inghilleri@uniroma1.it](mailto:maurizio.inghilleri@uniroma1.it) (M. Inghilleri).

age progresses (Kossioni and Karkazis, 1998). When a lesion of the supranuclear trigeminal structures occurs, the mandibular reflex is brisk and exaggerated and may give rise to clonus (Beevor, 1886). Patients with an involvement of the corticonuclear tract above the mid brain (i.e. multiple sclerosis, bilateral corticobulbar infarction, ALS) may exhibit a brisk reflex.

The mandibular reflex can be evaluated electrophysiologically by recording the masseteric H reflex. An H response can be elicited in the masseter muscle by stimulating the masseteric nerve (Macaluso and De Laat, 1995). Besides eliciting a homonymous H reflex in the masseter muscle, stimulation of the masseteric nerve can also evoke a heteronymous H reflex in the temporalis muscle (Macaluso and De Laat, 1995). The heteronymous temporal H reflex acts differently from the homonymous masseteric H reflex. Indeed, by increasing stimulus intensities, it does not disappear, but persists and increases in amplitude (Macaluso et al., 1998). There are important connections between synergistic muscles in the masticatory system that are more complex than those associated with monosynaptic reflex organization. Different branches of the mandibular nerve innervate the masseteric and temporalis muscles in such a way as to prevent collision phenomena.

Several physiological and pathological mechanisms may affect the excitability of motor neurons (Crucchi et al., 2001), which are assessed on a widespread basis by means of the H reflex (Pierrot-Deseilligny and Mazevet, 2000). In case of corticonuclear tract involvement, as occurs in ALS patients, tendon reflexes are brisk and the mandibular one, and the H reflex can be recorded more easily.

Although the H reflex may be considered as a sign of UMN involvement and supports a diagnosis of ALS in patients with motor neuron diseases and predominant LMN signs, few studies have assessed this reflex in such patients. The majority of these studies have been conducted on the soleus muscle and have shown that the H reflex is a good means of evaluating the excitability of the motor neuron pool (Mazzini et al., 1997) (Misra and Kalita, 1998).

The temporalis H reflex in healthy subjects can only be evoked by means of a voluntary contraction, such as teeth clenching (Macaluso and De Laat, 1995), whereas in the limb muscle the H reflex can be elicited at rest without pre-excitation (Schieppati, 1987). The influence of the H reflex on the excitability of the trigeminal motoneuron was evaluated in only a few studies. The reason is mainly twofold: (1) the threshold for eliciting the H-reflex in the masticatory motor neurons is much higher than in calf muscles, so the H reflex can only be evaluated in the presence of voluntary contraction; (2) the onset latencies of the H-reflex and the direct motor response are very close to each other (about 2 and 6 ms respectively), making measurements more difficult.

The aim of this study was to assess the presence of the heteronymous temporalis H reflex in patients with ALS by comparing it with that in normal subjects and considering it as a sign of hyperexcitability of alpha motor neuron and a sign of UMN (Schieppati, 1987) involvement in the bulbar district. In all patients we evaluated the presence or the absence of mandibular reflex and we compared it with the presence or absence of heteronymous H reflex. We further evaluated if there were any differences in the presence of heteronymous H reflex among patient with prevalent involvement of upper or lower motor neuron.

The presence of mandibular reflex, and the heteronymous H reflex in temporalis muscle be considered as sign of involvement of the UMN rostral to other signs of damage of the LMN and confirm the diagnosis of ALS.

## 2. Methods

The study was conducted at the Rare Neuromuscular Diseases Center of Umberto I Hospital in Rome. The study was conducted according to the declaration of Helsinki and was approved by the

institutional ethics committee. Informed consent was obtained from all the subjects.

### 2.1. Patients

We enrolled 36 patients (mean age  $62.19 \pm 12.22$  years) with a definite or probable diagnosis of ALS, according to the revised El Escorial criteria (Brooks et al., 2000). All patients took Riluzole 50 mg BID. The data collected were compared with those from a control group with similar demographic characteristics (Table 1). We enrolled 52 subjects with a similar age of patients (mean age  $58.58 \pm 11.44$  years) without any evidence neurological disease (i.e. previous stroke, multiple sclerosis, polyneuropathy...) or using any drugs that might bias the test results as a control group.

### 2.2. Clinical assessments

The clinical presence/absence of the mandibular reflex was recorded in every subject. The mandibular reflex was assessed with the patient sitting in a comfortable armchair with a slightly reclined head rest, with the mouth slightly open. The operator holds the patient's chin between his thumb and his index and gives a sharp blow with the hammer on his own index. The reflex was considered present if an elevation of the jaw was visually observed.

For each patient we further recorded the presence of Babinski's sign, and the tendon reflexes (hyper or hypo elicitable/absents). We considered patient with positive Babinski's sign and with hyper elicitable reflexes in the group of patients with prevalent involvement of upper motor neuron and those without Babinski's sign and hypo elicitable/absent reflexes in the group with prevalent involvement of lower motoneuron.

### 2.3. Neurophysiological assessments

The patients were set in a comfortable armchair with a slightly reclined head rest without clenching their teeth, in a bright room. During the examination, the experimenter talked to patients to maintain high the awareness. The subjects remained completely relaxed monitored with audiovisual feedback.

The electrophysiological study of the H reflex and M response was performed by stimulating the masseteric nerve, a branch of the trigeminal nerve, in the infratemporal fossa and by recording the muscle response from masseteric and temporalis muscles, ipsilaterally to the stimulation. The nerve conduction was performed using a Micromed Myoquick 1400 EMG machine (Micromed S.p.A., Treviso, Italy). A stainless steel, teflon-coated needle (length 25 mm, diameter 0.36 mm; Model 902-DMF25-TP, TECA, Care

**Table 1**

Main characteristics of ALS patients and healthy subjects. Values are reported as mean  $\pm$  standard deviation or percentage.

	ALS patients	Healthy subjects	P value
Total	36	52	
Sex n (%)			
Male	23 (63.8%)	30 (57.7%)	
Female	13 (36.2%)	22 (42.3%)	
Age (years)	$62.19 \pm 12.22$	$58.58 \pm 11.44$	ns
Prevalent involvement of UMN	16 (44%)		
Prevalent involvement of LMN	20 (56%)		
H reflex			
Absent	4 (11.1%)	52 (100%)	
Present	32 (88.9%)	0 (0%)	
Latency (ms)	$5.43 \pm 0.38$	–	
Amplitude (mV)	$0.64 \pm 0.31$	–	
Masseteric cMAP			
Latency (ms)	$1.74 \pm 0.35$	$1.66 \pm 0.36$	ns
Amplitude (mV)	$5.75 \pm 2.41$	$6.51 \pm 2.28$	ns

Fusion, 97,204 Hoechberg, Germany) was used as the cathode and a surface electrode ( $15 \times 20$  mm, model DENIS15026, Neuro Dart, Spes Medica, Genoa, Italy) as the anode to stimulate the masseteric nerve. The needle was introduced to a depth of 2.5 cm between the condyle and the coronoid process of mandibular bone, just below the zygomatic arch. The surface electrode was placed at approximately 1 cm from the needle in order to selectively stimulate the masseteric nerve. For the stimulation of masseteric nerve we used the same technique described by Godaux and Desmedt (1975). The masseteric cMAP and H reflex were simultaneously recorded by means of surface electrodes ( $15 \times 20$  mm, model DENIS15026, Neuro Dart, Spes Medica, Genoa, Italy). The active electrode was placed on the ipsilateral masseter muscle belly while the reference electrode was placed 4 cm under the mandibular angle, on the neck. To record temporalis activity, the active electrode was placed on the ipsilateral temporalis muscle belly while the reference electrode was placed on the forehead at approximately 4 cm along the line connecting the coronoid insertion of the muscle and the electrode on the muscular belly. An electrode placed in the center of the tragus was used as ground (Fig. 1). We delivered a single square stimulus with a duration of 100  $\mu$ s by means of a constant current stimulator. The intensity of the stimulus was steadily increased until the best motor response (M) was elicited. The best motor response was considered the M response with the shortest latency and the largest amplitude. We performed a random stimulation at a rate of approximately 0.2 Hz to avoid the effects of a previous stimulus on a subsequent response. If no response was recorded the patient was invited to clench his teeth, as facilitation maneuver, and then another registration of H reflex was performed. We recorded the amplitude and latency of each response, the most useful parameters in the evaluation of H reflex (Fisher, 1992; Burke, 2016; Huynh et al., 2016).

The H reflex was considered absent if: (1) the amplitudes were not reproducible or were less than 100  $\mu$ V (2) the latency of H response was less than 4 ms (3) it appears after facilitation maneuver in healthy subjects (clenching of teeth).

#### 2.4. Statistical analysis

IBM SPSS statistics Data version 23 software was used to analyze the data. Levene's test was performed before using the t test

for independent samples to evaluate any differences in the masseteric cMAP in the two groups (ALS patients and controls). Pearson's chi-square test was used to compare the clinical presence/absence of the mandibular reflex with the presence/absence of the H reflex.

Pearson's chi-square test was used also to compare the presence/absence of the H reflex among the groups of patients with prevalent involvement of upper or lower motoneuron. A value of  $p < 0.05$  was considered statistically significant for all the tests.

### 3. Results

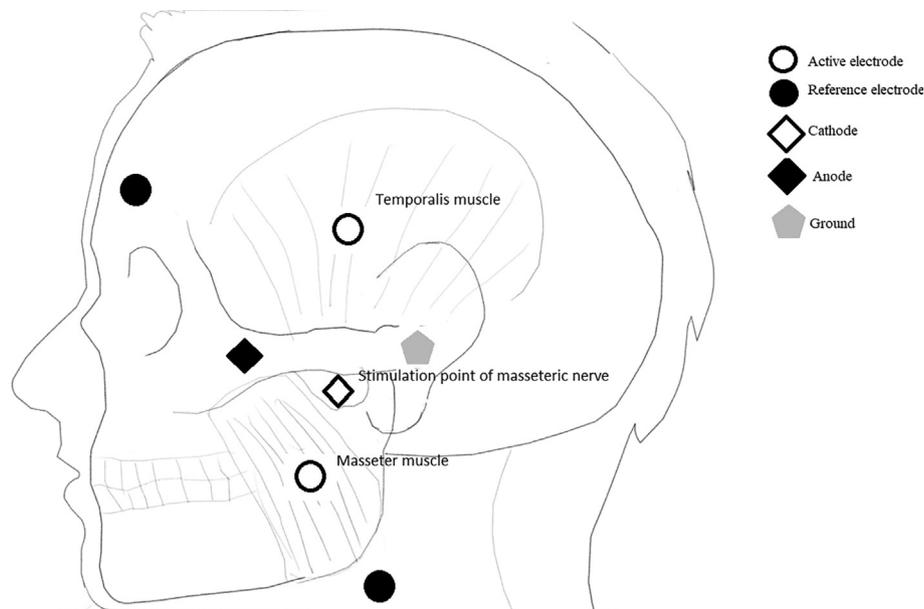
Thirty-six patients ( $62.19 \pm 12.22$  years) with a definite or probable diagnosis of ALS according to the revised El Escorial criteria (Brooks et al., 2000) and 52 normal control subjects ( $58.58 \pm 11.44$  years) were enrolled. Table 1 shows the subjects' clinical and demographic characteristics.

### 4. Electrophysiological evaluation

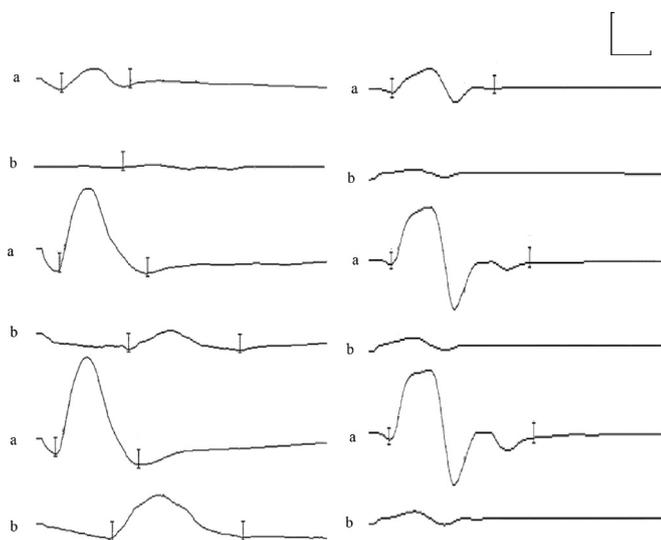
The heteronymous temporalis H reflex was elicitable in 88.9% of the ALS patients (mean latency  $5.43 \pm 0.38$  ms, mean amplitude  $0.64 \pm 0.31$  mV) and in none of the control subjects (Fig. 2). In six control subjects, the H reflex was recorded only after a facilitation maneuver. We did not observe any differences in electrophysiological characteristics of the masseteric cMAP (mean latency  $1.74 \pm 0.35$  ms for ALS patients and  $1.66 \pm 0.36$  ms for healthy subjects, mean amplitude  $5.75 \pm 2.41$  mV for ALS patients and  $6.51 \pm 2.28$  mV for healthy people) between the two groups of subjects ( $p = 0.277$  and  $p = 0.101$  respectively) (Table 1). We did not observe any differences in the presence/absence of the H reflex in the patients with prevalent involvement of upper or lower motoneuron ( $p > 0.05$ ).

### 5. Clinical evaluation

When we clinically evaluated the presence of the mandibular jerk, we found that this reflex was absent in 86.4% of patients in whom we detected the H reflex. We used Pearson's chi-square test to compare the clinical presence/absence of the mandibular reflex with the presence/absence of the H reflex and we found no differ-



**Fig. 1.** The figure shows the position of the electrodes for stimulation and registration of the homonymous and heteronymous H reflex after stimulating of the masseteric nerve in the masseter and temporal muscles. For the localization of the electrodes, see the text. (Modified from Ulkatan et al. (2017).)



**Fig. 2.** Recording of masseteric cMAP (a line) and temporalis H reflex (b line) from ALS patient (left panel) and normal subject (right panel). The intensity of the stimulus was steadily increased until the best response was elicited. Sweep 3 ms/division, gain 1 mV/division.

**Table 2**

Relation between the presence of electrophysiological H reflex and the clinical presence of mandibular reflex.

		Mandibular reflex	
		Present	Absent
H reflex	Present	14	19
	Absent	0	3

ences ( $p = 0.546$ ) (Table 2). None of the patients, in whom the H reflex was not recorded, had the mandibular reflex.

## 6. Discussion

In the present study, the temporalis H reflex proved to be significantly more elicitable in ALS patients than in healthy subjects, thus suggesting that it may be used to detect corticonuclear tract involvement. It may be possible to use the heteronymous H reflex as a tool for investigating bulbar motor neuron pool excitability. No differences were found in the masseteric cMAP between the two groups. The masseter motor neurons are less often lost in ALS (Finsterer et al., 1998).

The identification of both cortical and spinal (upper and lower) motor neuron signs in multiple body regions is essential to be able to diagnose ALS. The heterogeneous clinical presentation of ALS is due to a variable mix of UMN and LMN signs (Sabatelli et al., 2011). Although UMN signs, such as hyperreflexia with reflex spread, spasticity and Babinski sign (Brooks et al., 2000), are essential for a diagnosis of ALS, they are initially absent in 7–10% of patients (Rocha and Maia Junior, 2012). While more sensitive means of assessing LMN involvement are available thanks to the Awaji criteria, the assessment of UMN involvement to make a diagnosis of ALS is essentially clinically based (de Carvalho et al., 2008). Conventional MRI can play but a marginal role in identifying UMN involvements in ALS patients (Rocha and Maia Junior, 2012).

The presence of a masseteric jerk may be considered as a sign of hyperexcitability, as occurs when there is corticonuclear tract involvement. Its presence, especially if it is brisk, in a patient with signs of involvement of LMNs in other parts of body can suggest a diagnosis of ALS (Beevor, 1886). For a diagnosis of probable ALS is

essential that a sign of UMN involvement is rostral to LMN (Brooks et al., 2000), and so evaluating the presence of this reflex, during neurological examination is very important.

The presence of an H reflex in a weak muscle may be considered an easier means of detecting a UMN dysfunction (Pierrot-Deseilligny and Burke, 2012). Macaluso and colleagues (Macaluso et al., 1998) demonstrated that it is also possible to record an H reflex in the temporalis muscle when the masseteric nerve is stimulated. This heteronymous reflex possesses the important characteristic of not disappearing when subjected to a higher stimulation intensity (Macaluso et al., 1998).

The H reflex is a non-expensive test that can easily be performed in any EMG laboratory. This reflex can even be recorded in the cranial district, in both the homonymous and heteronymous muscles. The H reflex can normally only be elicited by using background activation of the muscle (Macaluso and De Laat, 1995) or a state of hyperexcitability. Afferent sensory impulses, intracortical inhibition/facilitation and motoneuron excitability can modulate the H reflex. These ones can be influenced, not only by cortico-nuclear degeneration, but also by medical therapy and awareness (Alvarez et al., 2004). A previous trial demonstrated the reduction of cortical excitability induced by chronic Riluzole treatment (Ceccanti et al., 2018). Thus, the presence of H-reflex in our patients cannot be interpreted as a consequence of medical therapy but an epiphenomenon of the disease itself (Theiss et al., 2011).

## 7. Conclusion

ALS is a fatal neurodegenerative disease. The diagnosis is primarily based on clinical examination. Electrophysiological studies can identify lower motor neuron involvement but there is a lack of tools to evaluate upper motor neuron involvement. Needle EMG findings will reflect the evolution of disease by identifying features of fibrillation potentials, neurogenic fasciculation potentials, large complex unstable motor unit potentials, and reduced recruitment, throughout non-contiguous regions of the body. Early in the disease course, however, these abnormalities can only be identified in the affected regions (Sorenson, 2012; Inghilleri and Iacovelli, 2011). In ALS-population-based studies, there is currently a delay of approximately one year from the onset of symptoms to diagnosis (Zoccollella et al., 2006). The masseter reflex is a monosynaptic reflex and it is the only myotatic reflex in the cranial district. This reflex is often imperceptible and is characterized by a small amplitude but when a lesion of the supranuclear trigeminal structures occurs, as ALS patients, the masseter reflex is brisk and exaggerated and may give rise to clonus (Beevor, 1886). Thus, is very important assessing this reflex during neurological examination, particularly in patient with limb weakness because it can suggest a diagnosis of ALS.

The H reflex is a simple, non-expensive test that may be used as a rostral sign of UMN involvement in ALS patients. It may prove useful in patients with suspected MND/ALS who have purely LMN signs and few, or no, signs of UMN involvement. Furthermore, the heteronymous H reflex can be recorded even when the mandibular reflex is absent owing to ALS.

As this reflex is present in a considerably larger proportion of ALS patients than healthy subjects, despite the assumption of Riluzole, it may help to make a diagnosis ALS in patients with motor neuron diseases who have no evident signs other than LMN impairment.

## Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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