Brief Report

The Second Exteroceptive Suppression Period of the Temporalis Muscle Is Altered in Migraine Patients With Allodynia

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The Second Exteroceptive Suppression Period of the Temporalis Muscle Is Altered in Migraine Patients With Allodynia

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Abstract: Background/Objectives: The study of the second exteroceptive suppression period (ES2) of the temporalis muscle could provide information as to the brainstem neural circuits involved in migraine pathophysiology. Allodynia is known to be related to the sensitization of second/third order neurons in the trigeminal nucleus caudalis and sensory thalamus, respectively. The aim of this observational, pilot study was to investigate the ES2 of the temporalis muscle in the interictal period in female migraineurs, with and without allodynia, compared to controls. **Methods:** A total of 49 non-consecutive female patients fulfilling the diagnostic criteria for migraine (26 episodic and 23 chronic), naïve from any pharmacological prophylactic treatment, without relevant comorbidities and 19 healthy controls were enrolled. The exteroceptive suppression of the temporalis muscle activity was registered in the interictal period, according to international standards. The presence of allodynia was assessed by the Allodynia Symptom Checklist. **Results:** Twenty-four patients (50%) had allodynia and 16/24 (67%) were chronic migraineurs. The ES2 latency and duration between the groups were compared by the Student's t-test. There were no statistically significant differences in the ES2 latency or its duration between the migraine patients and controls. Conversely, the ES2 duration was significantly longer in allodynic migraineurs than in controls (p=0.04) and in allodynic than in non-allodynic migraineurs (p=0.04). **Conclusions:** This study suggests that the increased duration of ES2 observed in allodynic migraineurs may reflect an impaired activity of brainstem circuits. Indeed, we suppose that this alteration in ES2 may be a neurophysiological correlate of central sensitization in migraine patients with allodynia.

Keywords: migraine; exteroceptive suppression reflex; ES2; allodynia; clinical neurophysiology

1. Introduction

Migraine is a highly prevalent and disabling disorder. Indeed, migraine and its associated symptoms pose a significant physical, psychological and financial burden on patients and our health systems. Therefore, a better understanding of migraine pathophysiology is crucial as it may pave the way to novel treatment regimes.

Current literature has evidenced that migraine headache attacks are due to an abnormal activation and sensitization of trigeminal sensory pathways that innervate the pain-sensitive intracranial structures [1]. The chronic stimulation of peripheral trigeminal sensory afferents during repetitive migraine attacks would lead to the sensitization of central structures of the pain pathway, due to a reduction in the nociceptive threshold [2,3]. Moreover, it has been hypothesized that this "central" sensitization of the second-order "dural-responsive" neurons in the trigeminocervical complex (TCC), as well as that of the third-order neurons in the thalamic sensory nuclei, underpin respectively, cephalic allodynia (i.e., sensitivity of the scalp and tenderness to palpation of the

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pericranial and cervical muscles) and extracephalic allodynia (i.e., sensitivity of the skin or muscles in the limbs) during migraine attacks [1,4,5]. Central sensitization is also present in the interval phase, between migraine attacks, in patients with chronic migraine, where, along with allodynia, it could explain the low-grade interictal headache and other symptoms characteristic of this disorder [2].

It is known that the trigeminal caudal nucleus also receives input from higher antinociceptive centres that exert a descending modulation of nociceptive stimuli, including the periaqueductal grey (PAG), the raphe magnus nucleus and the lateral reticular nucleus [6–9] which, in turn, are under the control of higher subcortical and cortical centers, partly pertaining to the limbic system [7,10].

In subjects affected by chronic migraine, a complex dysfunction of both cortical [11] and subcortical structures, including the PAG [12], involved in pain modulation and antinociceptive function, has been described, which could predispose to the chronicization of pain.

Migraine pathophysiology may be investigated by electrophysiological techniques, mainly brainstem reflexes that can be elicited by the stimulation of the trigeminal afferents.

It is well known that electrical stimulation, delivered in the innervation territories of the second and third division of the trigeminus, elicits both an early and late suppression period (respectively, ES1 and ES2) of voluntary masseter and temporalis activity. ES1 and ES2 are produced by the activation of brainstem interneurons which inhibit the motoneurons in jaw-closing muscles, ES1 via an oligosynaptic neural network and ES2 via a polysynaptic circuit [7,13].

The nociceptive or non-nociceptive nature of ES reflex afferents remains controversial. It has been suggested that there is participation of both nociceptive (Aδ and possibly C) and non-nociceptive transmitting fibres, respectively, in the ES1 and ES2 [13].

Current evidence indicates that inhibitory interneurons mediating ES1 are located in the dorsal-medial pons and extend rostrally to the area of the main trigeminal and masticatory nuclei [14]. Although the location of the interneurons responsible for ES2 is less certain, it has been proposed that they belong to the bulbar reticular formation, in close proximity to the trigeminal nucleus caudalis [13,14]. This area not only receives afferents from the periphery, but also from limbic structures, the orbito-frontal cortex, the nucleus raphe magnus and the periaqueductal grey matter, which are relevant structures interposed in antinociceptive circuits [10]. Therefore, as the interneurons responsible for ES2 receive afferents from the anti-nociceptive system, studying the exteroceptive suppression of temporalis muscle activity may provide information on the functional status of the brainstem circuits involved in migraine pathophysiology, particularly in the central sensitization processes underlying allodynia.

This observational, retrospective, pilot study investigated this reflex of exteroceptive suppression of temporalis muscle activity during the interictal period in a sample of female migraineurs to identify the presence of any differences in ES2 parameters (latency and/or duration) of the temporalis muscle in the study group, with and without allodynia, compared to healthy controls.

2. Materials and Methods

This pilot observational, retrospective study investigated into the exteroceptive suppression reflex of temporalis muscle activity in a sample of female migraine patients who referred to our Headache Centre, situated within a community hospital at Novi Ligure, Alessandria Province, Italy, for a first examination, from 2020 to 2023. Written informed consent was obtained from all the subjects.

Our Centre performs the exteroceptive suppression reflex of temporalis muscle activity in a selected number of migraine subjects, i.e., when deemed useful by the physician.

The inclusion criteria were: a diagnosis of migraine (episodic or chronic, with or without aura), according to the 3rd edition of the International Classification of Headache Disorders, volume 3 (ICHD3) [15]; an age between 18 and 65 years; no ongoing pharmacological prophylactic treatment; a time interval of at least 72 hours from the last migraine attack and/or intake of painkillers. The exclusion criteria were: any internistic, neurological or psychiatric comorbidities; the presence of a

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temporomandibular dysfunction or a myofascial syndrome and/or declination of written informed consent.

Exteroceptive suppression of the temporalis muscle activity was registered according to the standards recommended by the European Headache Federation [16]. A standard bipolar stimulatory electrode was placed at the left labial commissure. Eight single stimuli were applied with a 20mA intensity and a 0.2 ms duration, maintaining a minimum interval of 30s between the stimuli. The EMG was recorded via two channels from the left temporalis muscle. A disposable surface-active electrode was placed over the anterior belly of the temporalis muscle, just in front of the temporal hair line, with the reference electrode in front of the tragus, as previously described [7]. The patients were asked to clench their teeth as hard as they could during the stimulatory pulse application. The amplifier sensitivity was 200μV per division and the frequency band was 20-3000Hz. The same investigator, blinded as to diagnostic category, measured the off-line recordings, after full-wave rectification. Suppression was defined as an EMG amplitude reduction of at least 50%.

The presence of cutaneous mechanical allodynia was assessed by the Allodynia Symptom Checklist (ASC-12) [17]. Indeed, every patient attending our Headache Centre is given a routine complete neurological and cranial/cervical musculoskeletal examination, a psychological assessment for allodynia and psychiatric comorbidities.

The number of headache days per month was recorded by the patient in a day-by-day diary.

A descriptive statistical analysis was carried out. The clinical variables (age and monthly headache frequency) and data on the temporalis ES1, ES2 latency and duration, were compared by the paired Student's t-test. The level of statistical significance was set at 0.05.

3. Results

Forty-nine non-consecutive Italian female patients and 19 healthy female volunteers, were retrospectively enrolled into the study.

The main clinical and neurophysiological features, i.e., ES1, ES2, latency and duration of the total sample, of allodynic, non-allodynic patients and controls are reported in Table 1.

No significant difference was observed among the four groups as to the average age.

Table 1. The main clinical and neurophysiological features (ES1, ES2, latency and duration) of migraine patients, allodynic and non-allodynic migraineurs and healthy controls; comparison (using the Student's t-test) between migraine patients and controls, allodynic and non-allodynic migraineurs, allodynic migraineurs and controls.

	Migraine patients (total, 49)	**Allodynic (24)**	**Non-allodynic (25)**	**Controls (19)**	**Migraine patients vs Controls**	**Allodynic vs Non-allodynic**	**Allodynic vs Controls**
Age (mean, years)	40	38	43	42	n.s	n.s.	n.s.
Headache monthly frequency	14	16	12	-	n.s	n.s.	n.s.
ES1 latency (mean, msec)	12.8	13.1	12.6	13.9	n.s.	n.s.	n.s.
ES1 duration (mean, msec)	14.4	14.9	13.8	14.8	n.s.	n.s.	n.s.
ES2 latency (mean, msec)	61.5	62.1	60.1	56.3	n.s.	n.s.	n.s.
ES2 duration (mean, msec)	28.2	31.8	26.5	26.9	n.s	p: 0.04	p: 0.04

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A total of 13/49 (26.5%) had migraine with aura; 26 (53%) had episodic migraine and 23 (47%) had a chronic migraine pattern.

Twenty-four patients (49%) had allodynia; 16/24 (67%) were chronic migraineurs, based on the mean headache frequency in the previous three months; the average attack frequency in the allodynic group was 16 days per month.

There were 25 (51%) non allodynic patients and 4/25 (16%) were chronic; in the non-allodynic migraineurs group, the average monthly headache frequency was 12 days.

There were no differences in the ES1 parameters or the ES2 latency between the migraine patients and controls or allodynic versus non-allodynic migraineurs.

Conversely, the ES2 duration was significantly longer in allodynic migraineurs than in controls ($p=0.04$), as was the case in allodynic migraineurs compared to non-allodynic migraineurs ($p=0.04$).

4. Discussion

The main finding of this pilot study is that chronic migraineurs with cutaneous mechanical allodynia, i.e., the perception of pain in response to non-noxious skin stimulation, have an increased duration of the second exteroceptive suppression period (ES2) of the temporalis muscle, compared to controls and non-allodynic migraineurs, in the interictal period.

In our hypothesis, this may reflect an impaired activity of brainstem circuits, notably of the second-order neurons in the trigeminal nucleus caudalis and/or of the inhibitory control from superior antinociceptive systems. Therefore, we may reasonably suppose that this alteration in ES2 may be a neurophysiological correlate of central sensitization in migraine patients with allodynia.

Indeed, allodynia has been considered the clinical epiphenomenon of central sensitization in migraineurs and has been linked to a higher likelihood of developing a chronic form, as it is more common in patients with frequent attacks and/or long-lasting disease [18]. Although the mechanisms underlying cutaneous allodynia in migraine have not yet been completely understood, it is likely that they include a sensitization phenomenon at different levels of the trigemino-vascular system and ascending projection, along with a dysfunction of the various brainstem and cortical areas that modulate thalamocortical inputs [18].

Although this novel neurophysiological finding of altered ES2 in allodynic migraneurs does require confirmation on larger patient samples, it is intriguing. Indeed, there is evidence that in migraine the sensitization of peripheral trigeminal sensory afferents could lead to the sensitization of 2nd and 3rd order neurons in the trigeminal cervical complex and sensory thalamus. This could account for cephalic and extracephalic allodynia, respectively, during migraine attacks [1] as well as for the interictal low-grade headache and allodynia [3].

The interneurons responsible for the masseter and temporalis ES2 are most likely located in the lateral tegmental field, close to the trigeminal nucleus caudalis/cervical complex [13,14], an area which not only receives afferents from the periphery, but also from limbic structures, the orbito-frontal cortex, the nucleus raphe magnus and the periaqueductal grey matter, which play a key role in the endogenous control of pain. Therefore, ES2 latency and duration may reflect, at least to a certain extent, the functionality of the brainstem circuits.

Previous studies have assessed the exteroceptive suppression of the masseter and temporalis muscle activity in primary headaches, including tension-type headache and migraine, as well as in chronic pain. It has been observed that ES2 was abolished or shortened in patients with chronic tension-type headache [19], although contrasting results as to the ES2 duration and latency have been reported in various studies in primary headaches, this probably depends both on the differences in the methods applied and the patient samples studied [20]. For example, the ES2 latency and duration may be affected by the phase of migraine cycle, considering that trigeminal pain processing differs if it is done during or outside the attack [20].

In migraine, the ES2 of masseter or temporalis muscle activity was either reported as normal [21] or as having a tendency to protract in latency both in adults [7] and juvenile migraineurs [20].

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The interictal ES2 protraction in juvenile migraineurs was interpreted by the authors as a sign of overactivity of the interneurons of the reflex loop, due to impaired inhibitory control from superior antinociceptive systems [20].

Moreover, other neurophysiological methods, mainly the blink reflex, have been used to assess the trigeminal pathways in migraine. For example, the increase in R2 recovery observed in a study on both episodic and chronic migraine patients suggested an impairment of the central inhibitory mechanisms during the interictal period in migraineurs [22].

Furthermore, another study where a prepulse stimulation of the median nerve was applied at the wrist [23], identified a deficit of blink reflex sensory gating, in association with cutaneous allodynia. These findings probably support the hypothesis that cutaneous allodynia may be partly mediated and maintained by an abnormal sensory modulation of nociceptive afferents at the brainstem level [24,25].

The aforementioned evidence is in agreement with our results, suggesting that the ES2 increased duration detected in this study interictally in allodynic migraineurs may be underpinned by the sensitization of second-order neurons in the trigeminal cervical complex, likely related to an impaired inhibition by the suprasegmental antinociceptive structures, including the PAG [12].

Serotonin (5-HT) mediates the PAG suppression of the jaw opening reflex [20]. Drugs that increase the 5-HT level reduce the ES2 duration, whilst the 5-HT receptor antagonist methysergide prolongs ES2 duration [26]. Although 5-HT plasma levels are lower interictally, they increase during attacks [27]. Even if the underlying mechanisms involved in these changes have not yet been clarified, the findings as to the roles 5-HT in ES play in migraine suggest that low plasma 5-HT between migraine attacks corresponds to a prolonged ES2 duration, as demonstrated both in previous studies [20] and ours.

Moreover, a significant decrease in ES2 latency and duration in the temporalis ES2 was reported in a small sample of migraineurs during erenumab treatment, indicating that ES2 is a neurophysiological marker of the effects that monoclonal antibody may exert at the brainstem circuits involved in migraine pathophysiology [28].

A possible role of peripheral sensitization in affecting ES2 in our study may be reasonably ruled out by the fact that the patients were investigated in the interictal period. Indeed, temporary sensitization of central trigeminal neurons during acute migraine attacks has been demonstrated by a neurophysiological study using a “nociception-specific” blink reflex, which revealed a shortening of R2 onset latencies [29].

However, we are aware that this study does have some limitations, such as the small number of cases and our having studied only female migraineurs.

It is common knowledge that the neurophysiological investigation of the masseteric and temporalis exteroceptive suppression reflex poses numerous technical challenges. Despite this, we did our best to minimize the technical factors responsible for the variability reported in literature as to normal values for ES2 duration, which was, at times, attributable to subtle differences in methods [20]. Moreover, the interpretation of some ES2 suppression periods may be uncertain, as such response is mediated by a multisynaptic circuit and may be influenced by both the patient’s cooperation and mandibular function [14].

As we registered the exteroceptive suppression period of the temporalis muscle only on the left, it cannot be ruled out that had we investigated on the side of the prevalent pain location, the results may have differed.

Lastly, although ES2 may vary due to this hormonal factor, the phase of the menstrual cycle was not taken into account when the ES2 registration was carried out [20].

However, despite these drawbacks, our data showed a statistically significant difference in the temporalis ES2 duration in allodynic migraineurs versus non allodynic ones and controls, which may well be related to sensitized brainstem trigeminal nuclei and/or impaired suprasegmental inhibitory neural circuits involved in migraine pathophysiology.

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Although neurophysiological techniques are extremely useful in the investigation of the pathophysiological basis of migraine, mainly migraine with aura [30], further studies are warranted to confirm this intriguing hypothesis.

5. Conclusions

In thus study, the modification of the temporalis ES2 duration in allodynic migraine patients versus non allodynic and controls seems to be an indication that ES2 plays some kind of role as a neurophysiological marker of central sensitization associated with allodynia during the inteval period in chronic migraineurs. Indeed, such an interictal ES2 protraction suggests an overactivity of the interneurons of the reflex loop due to sensitized second-order neurons in the trigeminal nucleus caudalis and/or to impaired inhibitory control from superior antinociceptive systems.

Although further studies on larger cohorts are required to confirm these preliminary findings on such an intriguing hypothesis, the data herein reported indicate that the study of ES2 would be a useful tool to investigate the functionality of brainstem circuits in migraine.

Conflicts of interest: the authors declare no competing interests.

Authors' contribution: E.R. conceived the study; E.R., A.M., M.A., E.G., M.G.S. collected the data; P.I. performed the statistical analysis; E.R. wrote the manuscript and tables; all authors revised the manuscript and tables. All authors read and approved the manuscript and all data were generated in-house and that no paper mill was used.

Ethics approval: The Local Authorities approved the study

Consent to participate: all patients gave informed consent to participate in the study and to having their data published.

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