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Increase pain sensitivity during the four phases of the migraine cycle in patients with episodic migraine

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Migraine is a complex disorder characterized by recurrent attacks of unilateral, pulsating, moderate to severe headache, with nausea, vomiting, photo-phobia and/or phono-phobia, that are associated with cyclic changes in the excitability of cortical, subcortical, and brainstem areas[1]. Quantitative sensory testing (QST) have been used to assess sensitization in patients with episodic migraine (EM) and highlight cyclic changes in the pain thresholds in trigeminal, cervical, and pain-free areas during the attacks. It is still uncertain if signs of trigeminal, cervical, and widespread sensitizations are also present in the interictal phase of the migraine cycle[2]. The aims of our study were (1) to assess pain thresholds in trigeminal, cervical, and distal pain-free areas with different QST methods in subjects with EM, (2) compare the pain thresholds of patients with EM during the four phases of the migraine cycle to healthy controls (3) correlate the presence of signs of sensitization with the interval from the last and the next headache attack and with the attack clinical characteristics and headache-related disability. The study was approved by ethics committees in the Ligurian Region (244/2018) and Area Vasta Emilia-Nord (18305/2019). The study has in full been published[3]. The present work is focused on the analysis of the variations in relation to the trend of the attacks. All patients signed an informed consent form. We recruited patients on the waiting list to receive their first visit to the Headache Centers of Genova and Parma (Italy), both men and women, aged between 18 and 65 with EM (with and without aura). Diagnosis of EM was done according the International Classification of Headache Disorders Criteria. Controls were healthy subjects with a maximum of two headache episodes per year that did not fulfil the criteria for migraine or any other primary headache and with no family history of migraine or other primary headaches. For each subject, general and headache-related characteristics were assessed. Patients used a daily updated diary recording the number of symptomatic drugs and the frequency, intensity, and duration of headache attacks. The Headache Disability Index (emotional HDI-E and physical HCI-P) was used to assess the headache-related disability. QST were assessed during the 4 migraine phases in patients with EM and compared to controls. Static pressure pain threshold (sPPT), mechanical pinprick pain threshold (MPT) and temporal summation of mechanical pinprick (Wind-up ratio, WUR) were assessed from the trigeminal area, sPPT and dynamic PPT (dPPT) from the cervical area, and sPPT and MPT over the hand. The examiner was kept blinded to the presence of headache for as long as possible. A linear regression models was used to compare QST results of patients at specific migraine phases to controls while adjusting for possible confounders. A total of 135 patients and 46 controls were included.

Comparison between EM and controls. The data showed[3] the following results when comparing EM and controls. WUR was facilitated in ictal EM (EM versus controls: mean+SD 2.7+2.0 versus 1.4+1.8; p=0.004); trigeminal sPPT and MPT were reduced in interictal (sPPT: 198.5+79.3 kPa; p=0.021; MPT: 12.6+15.7 g; p=0.001), preictal (sPPT: 200.6+71.6 kPa; p=0.033; MPT: 10.7+12.4 g; p<0.001), ictal (sPPT: 171.4+95.9 kPa; p<0.001; MPT: 7.3+ 12.0 g; p<0.001), and postictal EM (sPPT: 182.2+76.3 kPa; p=0.006; MPT: 10.1+14.9 g; p=0.001), compared to controls (sPPT: 238.3+73.8 kPa; MPT: 21.9+17.3) g). Cervical sPPTs and dPPT were reduced in interictal (sPPT cervical spine: 420.5+176.7 kPa; p=0.031; dPPT: 4826.5+ (2698.0 g; p<0.001), preictal (sPPT cervical spine: 389.3+ 133.4 kPa; p=0.006; dPPT: 4184.2+ 2628.3 g; p<0.001), ictal (sPPT cervical spine: 379.9+ 205.6 kPa p=0.003; dPPT: 3838.3+2638.7 g; p<0.001), and postictal EM (sPPT cervical spine: 385.5+131.6 kPa; p=0.020; dPPT: 4679.6+2894.9 g; p=0.001), compared to controls (sPPT cervical spine: 494.9+171.5 kPa; dPPT: 7693.9 +2896.8 g). Preictal EM had reduced hand sPPT and MPT (sPPT: 248.8+96.6 kPa versus 319.8+112.3) kPa; p=0.006; MPT: 23.6+12.2 g versus 32.5+14.4 g; p=0.035), while EM in the other phases showed reduction in hand MPT (interictal: 22.3+15.6 g versus 32.5+14.4 g; p=0.002; ictal: 22.4+17.0 g versus 32.5+14.4 g; p=0.004; postictal: 24.2+18.8 g versus 32.5+14.4 g; p=0.003) without significant reduction in hand sPPT.

Correlations with the last/next migraine attack. We found[3] a significant positive correlation between time from next headache attack and MPT over temporalis (r = 0.45; p = 0.005), sPPT over the upper cervical spine (r = 0.36; p = 0.029) and sPPT over the lower cervical spine (r = 0.35; p = 0.031), in preictal EM. A

significant positive correlation was found between time from next headache attack and sPPT over the upper cervical spine (r = 0.34; p = 0.048) and hand sPPT (r = 0.35; p = 0.042) in interictal EM.

Correlations with headache history and characteristics. In ictal EM, a significant positive correlation was found between cervical dPPT and years with headache (r = 0.42; p = 0.024) and between WUR and HDI-P (r=0.38; p=0.040) and HDI-E questionnaires (r=0.53; p=0.003. A significant negative correlation was found between pain intensity during the current headache attack and sPPT in the metacarpophalangeal joint of the dominant hand (r = −0.37; p = 0.050) and MPT on the thenar eminence (r = −0.49; p = 0.007). In interictal, preictal, and postictal EM pooled, a significant negative correlation was found between WUR over temporalis and headache frequency (r = −0.23; p = 0.022), headache intensity (r = −0.21; p = 0.040), HDI-P (r = −0.29; p = 0.003), and HDI-E score (r = −0.34; p = 0.001), and a significant negative correlation between MPT over the thenar eminence and years lived with migraine (r = −0.25; p = 0.011) and monthly usage of symptomatic drugs (r = −0.31; p = 0.002)[3].

The main findings of the study are summarized in Table 1

This study shows that patients with EM have signs of sensitization not only in the ictal phase, as already known, but also in the interictal phase, even if the sensitization increases as the attack approaches, and somehow correlates with the frequency of the attacks In addition, signs of widespread sensitization are evident in the preictal period and characteristic of patients with the longest disease duration, greater number of symptomatic drugs and higher pain intensity during the current migraine attack.
In the ictal phase, the lower pain thresholds in the trigeminal and cervical area could represent a sensitization of the trigeminocervical complex in the brainstem while the widespread hyperalgesia in distal pain-free areas occurring in a subgroup of subjects may be a sign of the diffusion of activity-dependent sensitization to spinal cord neurons and/or higher cortical/subcortical brain areas.
The enhanced sensitization observed interictally in the trigeminal and cervical areas (and widespread in some subjects) could be seen as the phenotypic manifestation of the "late-onset transcription-dependent central sensitization" of second-order neurons in the trigeminocervical complex.
However, in the interictal, unlike the ictal phase, we found a negative correlation between facilitation of the trigeminal WUR and headache-related disability. Between the attacks those migraine patients with a higher level of disability present a less pronounced sensitization of second-order neurons in the spinal trigeminal nucleus. This could be explained as an adaptive response of the trigeminal nociception pathway or as expression of a neuronal damage after higher repeated episodes.

In conclusion, patients with EM signs of increased sensitization in the trigeminocervical area, are present interictally with further enhanced sensitization approaching the headache attack. During the ictal phase, the headache-related disability increases with a more facilitated trigeminal WUR. Signs of enhanced widespread sensitization were more evident in preictal phase and in patients with the longest disease duration, the greater number of symptomatic drugs and the higher pain intensity during the current migraine attack.

I certify that there is no actual or potential conflict of interest in relation to this article

"Ethical standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study

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Table 1: comparison between healthy controls and EM patients during the four phases of the migraine cycle.

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	Controls(N=46)	EM interictal(N=37)	EM preictal (N=41)	EM ictal(N=30)	EM postictal(N=27)
WUR temporalis, mean (SD)	1.4(1.8)	1.7(1.6) B=0.042 p=0.371	1.8(2.5) B=0.59 p=0.218	2.7(2.0) **p=0.004***	1.7(2.6) p=0.196
MPT temporalis†, mean g (SD)	21.9(17.3)	12.6(15.7) **p=0.001***	10.7(12.4) **p<0.001***	7.3(12.0) **p<0.001***	10.1(14.9) **p=0.001***
sPPT temporalis†, mean kPa (SD)	238.3(73.8)	198.5(79.3) **p=0.021***	200.6(71.6) **p=0.033***	171.4(95.9) **p<0.001***	182.2(76.3) **p=0.006***
sPPT UCS total†, mean kPa (SD)	494.9(171.5)	420.5 (176.7) **p=0.031***	389.3(133.4) **p=0.006***	379.9(205.6) **p=0.003***	385.5 (131.6) **p=0.020***
sPPT LCS total†, mean kPa (SD)	586.9(210.8)	458.6(207.3) **p=0.002***	450.8(174.3) **p=0.005***	436.3(271.1) **p=0.001***	413.0(150.3) **p=0.002***
dPPT total† mean g (SD)	7693.9(2896.8)	4826.5(2698.0) **p<0.001***	4184.2(2628.3) **p<0.001***	3838.3(2638.7) **p<0.001***	4679.6(2894.9) **p<0.001***
sPPT second MCP†, mean kPa (SD)	319.8(112.3)	278.0(110.6) p=0.089	248.8(96.6) **p=0.006***	280.0(118.5) p=0.159	299.3(125.8) p=0.519
MPT thenar eminence†, mean g (SD)	32.5(14.4)	22.3(15.6) **p=0.002***	23.6(12.2) **p=0.035***	22.4(17.0) **p=0.004***	24.2(18.8) **p=0.003***
sPPT tibialis muscle†, mean kPa (SD)	407.8(183.0)	391.2(191.6) p=0.737	366.6(140.4) p=0.767	358.7(200.1) p=0.381	356.9(166.4) p=0.447

dPPT: Dynamic pressure pain threshold; EM: Episodic migraine; g: grams; LCS: lower cervical spine; MPT: Mechanical pain threshold; MCP: Metacarpophalangeal; PPT: Static pressure pain threshold; UCS: upper cervical spine; kPa: kilopascal; WUR: wind up ratio *: significant at p<0.05 vs. Control; †= data were log-transformed for statistical analysis. The table has in full been published (3)