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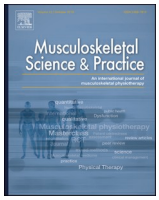

Migraine patients with and without neck pain: Differences in clinical characteristics, sensitization, musculoskeletal impairments, and psychological burden.

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ABSTRACT

Aims: This study aims to assess differences in clinical characteristics across healthy controls and migraine patients with (MNP) and without (MwoNP) neck pain.
Method: This study assessed: headache frequency; headache disability index (HDI); central sensitization inventory (CSI); Hospital Anxiety (HADS-A) and Depression (HADS-D) scale; active range of motion (AROM); flexion rotation test (FRT); activation pressure score (APS); number of active/latent myofascial trigger points (MTrPs) in head/neck muscles; number of positive cervical vertebral segments (C1/C2) who reproduce migraine pain; wind-up ratio (WUR); mechanical pain threshold (MPT) and static pressure pain threshold (sPPT) over the trigeminal area; sPPT and dynamic PPT (dPPT) over the cervical area; sPPTs and MPT over the hand.
Results: Compared to controls, MNP had: worse CSI, HADS-A, and HADS-D (all, $p < 0.002$); reduced AROM (flexion, extension, left lateral-flexion, and right-rotation), FRT, APS, and a higher number of MTrPs and positive cervical vertebral segments (all, $p < 0.020$); reduced trigeminal MPT and sPPT, cervical sPPT and dPPT, hand MPT and sPPT (all, $p < 0.006$).
Compared to controls, MwoNP had: worse CSI, and HADS-A (all, $p < 0.002$); reduced AROM (flexion, and left lateral-flexion), FRT, APS, and a higher number of MTrPs and positive cervical vertebral segments (all, $p < 0.017$); reduced trigeminal MPT and cervical dPPT (all, $p < 0.007$).
Compared to MwoNP, MNP had higher headache frequency, worse HDI and CSI (all, $p < 0.006$); reduced AROM (flexion, and right rotation) (all, $p < 0.037$); reduced cervical dPPT (all, $p < 0.002$).
Conclusion: MNP had worse headache characteristics, more pronounced cervical musculoskeletal impairments, enhanced signs and symptoms related to sensitization, and worse psychological burden compared to MwoNP.

1. Introduction

Migraine is a common neurovascular brain disorder characterized by cyclic activation of cortical and subcortical brain areas (Goadsby et al., 2017), affecting around 15% of the population. Migraine causes a significant social and economic impact (M. Ashina et al., 2021), being among the first cause of disability worldwide and the first cause of disability under the age of fifty (Steiner et al., 2018; Vos et al., 2017).

Although headache is the main one, a broader spectrum of concomitant symptoms occurs in patients with migraine, with neck pain being one of the most common (Calhoun et al., 2010). Neck pain has been estimated to be 12 times more likely to occur in migraine patients

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compared to healthy subjects (Al-Khazali et al., 2022).

As the higher the headache frequency and disability, the higher the prevalence of neck pain (Al-Khazali et al., 2022; S. Ashina et al., 2015; Calhoun et al., 2010; Carvalho et al., 2014; Florencio et al., 2014, 2021), neck pain and headache seem to share a common pathophysiological pathway in the migraine population. Specifically, increased sensitization of the trigeminocervical complex, where input from face and neck converges (Bartsch and Goadsby, 2003a, 2003b), could account for the relationship observed between headache and neck pain in the migraine population.

However, which link exists between migraine and neck pain is still a font of debate. On the one hand, neck pain could be considered a consequence of migraine itself, primarily driven by "central sensitization" mechanisms. Increased attack frequency could lead to an increased sensitization of the trigeminocervical complex and spinal neurons, leading to secondary hyperalgesia involving the neck receptive field and consequent neck pain (Liang et al., 2021, 2022a). On the other hand, neck pain could be considered comorbidity drove by "peripheral sensitization" mechanisms and could contribute to migraine pain. Peripheral alteration in the neck region, like cervical musculoskeletal impairments, could constitute a nociceptive input able to induce neck pain and further enhance sensitization of the trigeminocervical complex, increasing migraine frequency (Florencio et al., 2021; Hvedstrup et al., 2020a; Hvedstrup et al., 2020b)

Thus, this study aimed to assess the link existing between migraine and neck pain by two different approaches.

1) Investigating if migraine patients with neck pain (MNP) could be considered a different migraine phenotype compared to migraine patients without neck pain (MwoNP) by assessing differences in headache characteristics, cervical musculoskeletal impairments, signs and symptoms related to sensitization, and psychological burden across healthy controls (HC), MwoNP, and MNP.
2) Investigating which variables (general characteristics, headache characteristics, cervical musculoskeletal impairments, signs and symptoms related to sensitization, and psychological burden) could predict the presence of neck pain in migraine patients.

2. Method

2.1. Design

This multicenter, cross-sectional, observational study was conducted in the Headache Center of Parma and Genova (Italy) and approved by the Ligurian (244/2018) and "Area Vasta Emilia-Nord" (18305/2019) regional ethic committee. All subjects signed an informed consent form and were assessed between April 2019 and February 2022. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was chosen to conduct and report the study (von Elm et al., 2008).

2.2. Population

Patients on waiting lists to receive the first visit to the Headache Centers (Genova or Parma) were invited to participate in this study. Patients aged between 18 and 65 with the diagnosis of episodic migraine (EM) (with and without aura) and chronic migraine (CM) were included. EM were included if they were headache-free during the visit and did not have a headache within the 24 h before or after the visit (Sand et al., 2008; Uglem et al., 2017). CM patients were included if they were headache-free during the visit or had a background or interval headache (severity<6 on a scale 0–10) (Cosentino et al., 2014; Hsiao et al., 2021). Patients were excluded if they had: any other primary or secondary headache; less than 1 headache attack in four weeks; changes in headache characteristics or onset of a "new" headache after COVID-19 infection or vaccination; any other neurologic, psychiatric, rheumatologic, or systemic pathology with medical diagnosis; history of head/neck trauma in the previous year; received cervical/head surgery; received manual therapy in the cervical spine, cervical anesthetic block, or botulin injection in the last 6 months; changed migraine prophylactic treatment in the last 3 months; usage of acute pharmacologic treatment in the previous 24 h; were unable to speak and understand Italian;

Control participants were recruited specifically for this study. They were defined as healthy subjects with a maximum of two headache episodes per year that did not fulfill the criteria for migraine or any other primary headache type with no family history of migraine or other primary headaches. The exclusion criteria for the control subjects were the same as the criteria used for migraine patients.

2.3. Procedure

The first screening was conducted by telephone interview, and patients were excluded if they presented any signs of red flags (Do et al., 2019) or any exclusion criteria. Healthy controls were recruited from university students, hospital staff, university staff, and the general population. During the examination, two physiotherapists blinded to the subject's diagnosis, one for each recruitment center (S.D. and M.C.), performed the assessment, gave all patients four questionnaires to complete, explained how to fulfill a diary where they had to record headache characteristics for the following four weeks, and recorded the time from the last headache attack or the intensity of headache if present. The two physiotherapists had more than 10 years of experience in clinical practice, and their practice has been exclusively focused to the management of primary and secondary headaches, neck pain, and temporomandibular disorders for more than 5 years. Finally, a standardized questionnaire was performed to assess the presence of neck pain. After four weeks from the first evaluation, headache patients were visited by a neurologist who performed a diagnosis of headache according to the International Headache Classification Criteria(Olesen, 2018). The neurologist retrospectively assessed the diary and recorded the time between the first assessment and the following headache attack. Patients were included and divided into two subgroups according to the presence of neck pain.

- MwoNP: EM and CM without concomitant neck pain
- MNP: EM and CM with concomitant neck pain

2.4. Assessments

For each subject, general characteristics were assessed (Table 1). Migraine patients used a daily updated diary recording the presence of premonitory symptoms (premonitory symptoms were considered as

Table 1
General characteristic.

	Control (n = 54)	MwoNP (n = 44)	MNP (n = 63)
Age, mean (SD)	37.5(14.5)	36.2(11.7)	39.0 (10.9)
BMI, mean (SD)	22.10(2.8)	22.2(3.1)	23.4(4.2)
Gender, N (%)			
Female	40 (74%)	33(75%)	49(78%)
Male	14 (26%)	11(25%)	14(22%)
Menstrual cycle, N (%)			
No	24(44%)	18(41%)	27(43%)
Yes	30(56%)	26(59%)	36(57%)
Distance from last first day of menstrual cycle, mean days (SD)	16.8(2.7)	15.3(14.8)	17.3 (24.9)
Concomitant neck pain, N (%)			
No	48(89%)	44(100%)	0(0%)
Yes	6(11%)	0(0%)	63(100%)

BMI: body mass index; MwoNP: Migraine without neck pain; MNP: migraine with neck pain; N: number; SD: standard deviation.

present when they occurred in at least 50% of headache attacks (Schoonman et al., 2006), the total number of premonitory symptoms, the total use of symptomatic drugs, the frequency, intensity, and duration of headache attacks. Moreover, the headache side and total years lived with the headache were recorded (Table 2).

2.4.1. Presence of neck pain

A standardized questionnaire was conducted to identify the presence of neck pain. Migraine patients were asked to answer the following questions about neck pain, not referring to a migraine attack. Migraine patients and healthy controls were asked if they had neck pain of low, moderate, or high intensity or no neck pain or if they had neck pain during one of the following daily life activities: personal care, lifting, reading, driving, and recreation. Subjects with moderate or high neck pain or subjects with neck pain during at least two daily life activities were categorized as subjects with neck pain; if not, they were categorized as subjects without neck pain. This quality criterion was adopted to avoid an episode of not disabling low-intensity neck pain that could frequently occur in the general population (Di Antonio et al., 2022a; Hogg-Johnson et al., 2009).

2.4.2. Cervical musculoskeletal impairments (CMI)

Validated physical examination tests were used to assess the presence of CMIs (Di Antonio et al., 2022a; Luedtke et al., 2016)

- Active range of motion (AROM): cervical AROM (extension, flexion, left/right lateral flexion, left/right rotation) was recorded in degrees of movement with the cervical range of motion (CROM) device (Fletcher and Bandy, 2008; Jørgensen et al., 2014; Luedtke et al., 2018; Oliveira-Souza et al., 2020).
- Flexion rotation test (FRT): FRT (left, right) was used to record passive mobility of the upper cervical spine in degree using the CROM device (Hall et al., 2008; Luedtke et al., 2018; Ogince et al., 2007).
- Craniocervical flexion test (CCFT): CCFT was used to assess the function of deep cervical flexors muscles using a pressure biofeedback Unit 20–30 mmHg. Subjects performed craniocervical flexion in five incremental stages (one stage every 2 mmHg) in a supine position. The mmHg value held for 10 s without compensation (i.e., tremor, pain, discomfort, inability to hold the cranio-cervical flexion) was recorded as the activation pressure score (APS) (Jørgensen et al., 2014; G. Jull et al., 2007; G. A. Jull et al., 2008).
- Headache reproduction: the therapist applied sustained posterior-anterior (PA) pressure over C-0/C-1 and C-2/C-3 vertebral segments bilaterally. The vertebral segment was considered positive if PA pressure produced headache in control and typical migraine pain in patients. The total number of positive vertebral segments was calculated (0–4) (Luedtke et al., 2018; Watson and Drummond, 2012).
- Myofascial Trigger Points (MTrPs): The presence of MTrPs was assessed bilaterally in the temporal muscles, masseter muscle, sternocleidomastoid muscle, suboccipital muscles, splenius muscles, and in trapezius muscle. The total number of active and latent trigger points was recorded (Fernández-De-Las-Peñas et al., 2006; Fernández-de-las-Peñas & Dommerholt, 2018; Mayoral del Moral et al., 2018).

2.4.3. Quantitative sensory testing (QST)

QST was performed from distal pain-free areas first, then the cervical area, and finally the trigeminal area (symptomatic side in patients with unilateral migraine; dominant side in patients with side/shift or bilateral migraine and in controls) to assess signs related to sensitization. The examiner was kept blinded to the presence of headache for as long as possible (Di Antonio et al., 2022b).

- Static pressure pain threshold (sPPT): Pressure pain thresholds to hand-held algometry (Somedic AB, Sweden), probe area 1 cm^2, 30 kPa/s force increase) (Barón et al., 2017; Fernández-De-Las-Peñas et al., 2009; Geber et al., 2011) were assessed over the: trigeminal area (temporalis muscle), upper cervical spine (left and right), lower cervical spine (left and right); distal pain-free areas (second metacarpophalangeal joint of the dominant hand; tibialis anterior muscle of the dominant leg).
- Dynamic pressure pain threshold (dPPT): dPPT was assessed to evaluate the pressure pain threshold to a dynamic algometry (constant force spring controlled from 550 g to 5300 g) (Finocchietti et al., 2015; Guerrero-Peral et al., 2018; Palacios-Ceña et al., 2017) over the posterior aspect of the neck (left and right sides).
- Mechanical pain threshold (MPT): MPT was used to assess the mechanical pain threshold to pinprick stimulation (from 0.80g to 50.1g nylon filaments) (Geber et al., 2011; Lo Vecchio et al., 2014) over the following areas: trigeminal area (temporalis muscle); distal pain-free areas (thenar eminence of the dominant hand).

For sPPT, dPPT, and MPT, the lower the threshold, the more sensitization.

- Wind-up ratio (WUR): WUR was assessed over the temporalis muscle and used to assess mechanical pinprick pain's temporal summation (50.1 g). The patient was instructed to give a pain rating (11-point Numeric Rating Scale) for the first and last stimulus of 10 stimuli. The difference between the pain rating of the last of a ten stimuli series and the first stimulus was calculated (Geber et al., 2011; Matos et al., 2011). A positive WUR was a sign of increased temporal summation, and the higher WUR, the more sensitization.

2.4.4. Questionnaires

Headache-related disability was assessed using the headache

Table 2
Headache characteristics.

	MwoNP (n = 45)	MNP (n = 63)	Difference between groups p-value
Headache type, N (%) [c]			**0.027***
EM	40(91%)	47(75%)	
CM	4(9%)	16(25%)	
Headache side, N (%) [c]			0.913
Bilateral or side shift	31(70%)	45(71%)	
Unilateral (Left or right)	13(30%)	8(29%)	
Years with headache, mean years (SD) [b]	16.4(13.3)	17.3 (12.6)	0.639
Frequency, mean day/four weeks (SD) [b]	6.3(4.3)	10.7(7.4)	**0.001***
Duration, mean hours/day (SD) [b]	7.4(5.3)	8.8(5.6)	0.158
Intensity, mean NPRS 0–10 (SD) [b]	5.6(1.8)	5.5(1.6)	0.850
Drugs, mean number/four weeks (SD) [b]	4.1(3.2)	6.8(6.0)	**0.027***
Presence of premonitory symptoms, N (%) [c]			**0.006***
Yes	10(23%)	31(49%)	
No	34(77%)	32(51%)	
Number of premonitory symptoms, mean (SD)[b]	0.5(1.1)	1.3(1.9)	**0.005***
HDI total, mean (SD) [a]	35.0(18.0)	47.7 (19.9)	**0.001***

CM: chronic migraine; EM: episodic migraine; HDI: headache disability index; HDI-E: headache disability index emotional; HDI-P: headache disability index physical; MwoNP = migraine without neck pain; MNP = migraine with neck pain, N: number; NPRS: numeric pain rating scale; SD: standard deviation.
*significant at $p < 0.05$.
[a] *t*-test.
[b] Mann-Whitney.
[c] Chi-quadro.

disability index (HDI). The higher the score, the higher the disability (0–100) (Di Antonio et al., 2021; Seng and Holroyd, 2012). The central sensitization inventory (CSI) questionnaire was used to assess symptoms related to sensitization. The higher the score more symptoms related to central sensitization are present (0–100). A cut-off value of 40 was normally used in the literature (Aguila et al., 2015; Chiarotto et al., 2018; Di Antonio et al., 2021). The Hospital Anxiety and Depression Scale was used to assess the impact of anxiety (HADS-A) and depressive (HADS-D) symptoms. A higher score indicates a higher level of anxiety and depression (HADS: 0–21; HADS-D: 0–21) (Barón et al., 2017; Costantini et al., 1999; Di Antonio et al., 2021).

Details of the assessment were previously presented(Di Antonio et al., 2022a; Di Antonio et al., 2022b; Di Antonio et al., 2021).

2.5. Statistical analysis

The sample size was calculated using G*Power 3.1., and 141 subjects were required for the Generalized linear model (GLM) and 96 for regression models to achieve a moderate/large effect size (f: 0.35; f2:0.25) (Fernández-De-Las-Peñas et al., 2019; Hall et al., 2010) with a power of 90% and an alpha level of 0.05 using 3 covariate and 3 groups in GLM and 11 predictors in the multiple regression model.

Data were presented as mean (standard deviation) or number (%) according to the variable type. For subjects included between April 2019 and August 2021, this was a secondary analysis of these data and previous results were reported elsewhere (Di Antonio et al., 2022a; Di Antonio et al., 2022b; Di Antonio et al., 2021; Finocchi et al., 2022). Differences in headache characteristics between MwoNP and MNP were assessed using the T-test, Mann-Whitney, or Chi-square test according to variable type and distribution. Differences in CMI, QST, CSI, and HADS questionnaires among HC, MwoNP, and MNP were investigated by transforming non-normal distributed variables to fulfill the normality assumption. Linear and Poisson regression models were performed, accounting for potential confounders, including age, gender, and body mass index as a covariate in the models. A Bonferroni-adjusted post-hoc analysis was performed to make single groups comparisons.

A univariate binary logistic regression model was performed in migraine patients to determine risk factors associated with the presence of neck pain. Then, variables resulting in a p-value$<$0.05 in the univariate analysis were included as predictors in a multivariate Stepwise logistic regression model using forward and backward methods.

Subjects with any missing data were excluded from the analysis. The threshold accepted for the statistical significance of the results was $p < 0.05$, and tests of statistical significance were two-tailed. Statistical analyses were performed using the SPSS software (version 24).

3. Results

After 777 subjects were initially recruited, 161 were included (Fig. 1). Four patients were excluded because did not fulfill the questionnaire and it was not possible to categorize them as having or not having neck pain. General characteristics of all subjects were reported in Table 1.

3.1. Differences in headache characteristics between MNP and MwoNP

Compared to MwoNP, MNP had higher headache frequency (mean (SD): 10.7(7.4) vs 6.3(4.3), $p = 0.001$), total use of symptomatic drugs (6.8(6.0) vs 4.1(3.2), $p = 0.027$), number of premonitory symptoms (1.3 (1.9) vs 0.5(1.1), $p = 0.005$), and HDI (47.7(19.9) vs 35.0(18.0), $p = 0.001$). MNP had a higher proportion of patients with chronic migraine (25% vs 9%, $p = 0.027$) and with premonitory symptoms (49% vs 23%, $p = 0.006$) (Table 2).

3.1.1. Differences across groups in CMI, QST, questionnaires

FRT and APS were reduced while the total number of MTrPs and positive vertebral segments were increased in MwoNP compared to controls ($p < 0.001$) with no differences between the two migraine patient groups.

Compared to controls, MwoNP had reduced AROM in flexion ($p = 0.017$) and left lateral flexion ($p = 0.012$) while MNP in flexion, extension, left lateral flexion ($p < 0.001$), and in right rotation ($p = 0.020$). Compared to MwoNP, MNP had reduced AROM in flexion ($p = 0.028$) and right rotation ($p = 0.037$).

Compared to controls, MwoNP had reduced trigeminal MPT ($p < 0.001$) and cervical dPPT ($p < 0.007$), while MNP had reduced trigeminal MPT ($p < 0.001$) and sPPT ($p = 0.003$), cervical sPPT (Upper cervical spine: $p = 0.005$; Lower Cervical spine: $p = 0.001$) and dPPT ($p < 0.007$), and hand sPPT ($p = 0.001$), and MPT ($p = 0.002$). Compared to MwoNP, MNP had reduced cervical dPPT ($p = 0.002$). No differences across groups were observed in trigeminal WUR and sPPT over tibialis muscles.

Compared to controls, MwoNP scored higher to CSI ($p < 0.001$) and HADS-A ($p = 0.002$) questionnaires, while MNP scores higher to CSI ($p < 0.001$), HADS-A ($p < 0.001$), and HADS-D ($p = 0.002$) questionnaires.

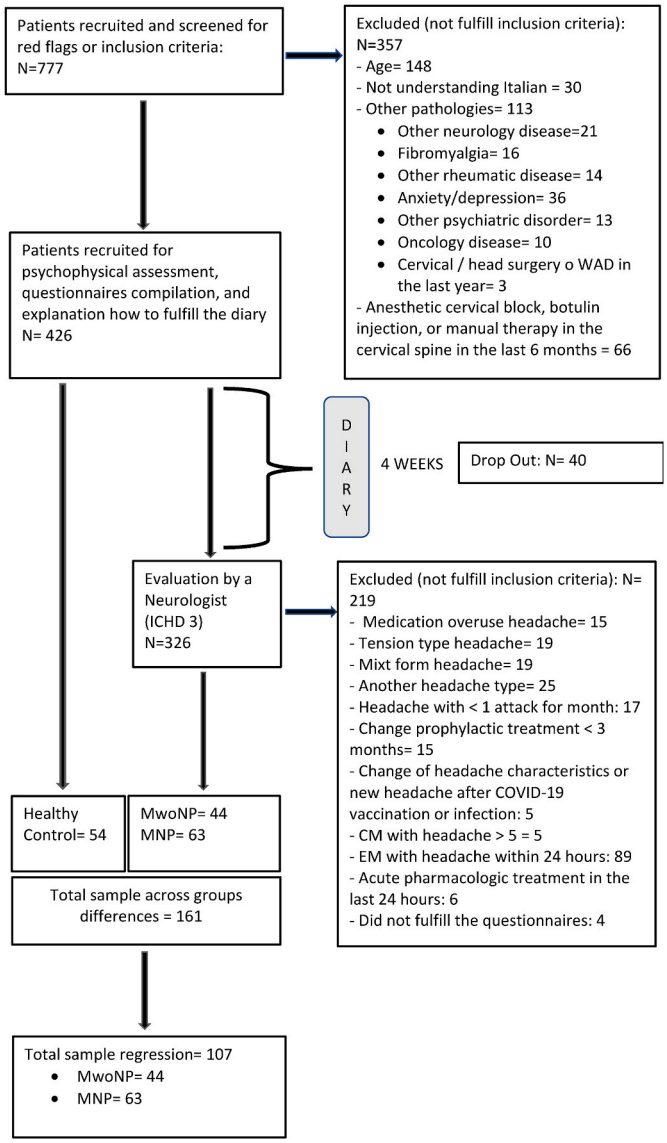

Fig. 1. Flow chart
CM: chronic migraine; EM: episodic migraine; ICHD: international classification headache disorder; MwoNP: migraine without neck pain; MwNP: migraine with neck pain; N: number.

MNP scores higher in CSI compared to MwoNP ($p < 0.001$) (Table 3, Fig. 2).

3.1.2. Variables associated with the presence of neck pain

The stepwise backward logistic regression model included as predictors only significant ($p < 0.05$) variables in the univariate analysis indicated that at an alpha level of $p < 0.05$ for five variables (frequency, presence of premonitory symptoms, AROM in extension, cervical dPPT, and CSI). These variables could significantly predict the presence of neck pain (Chi2 (5) = 47.456; $p < 0.001$, $R^2 = 0.36$). The stepwise forward multiple regression confirms the effect of these five predictors on the presence of neck pain (Table 4).

4. Discussion

Migraine patients with neck pain had worse headache characteristics, more impaired cervical active range of motion, enhanced signs and symptoms related to sensitization, and worse psychological burdens compared to migraine patients without neck pain. Different variables could predict the presence of neck pain in migraine patients, such as increased headache frequency, the presence of premonitory symptoms, reduced cervical mobility, and higher signs and symptoms related to sensitization.

4.1. Difference between migraine patients with and without neck pain

Neck pain was present in 58% of the migraine sample. These results were lower than the overall prevalence of neck pain in migraine (Al-Khazali et al., 2022) but similar to the estimated prevalence of neck pain unrelated to a migraine attack (Hvedstrup et al., 2020a; Liang et al., 2022b; Yu et al., 2019). MNP showed higher headache frequency and worse disability due to migraine compared to MwoNP, confirming that

Table 3
A Generalized Linear Models (GLM) including age, gender, and BMI as a covariate in the models was performed to assess differences across groups. Bonferroni-adjusted post-hoc analyses was performed to make single groups comparisons.

	Control N = 54	MwoNP N = 44	MNP N = 63	Between groups adjusted p-value	MwoNP vs Control	MNP vs Control	MwoNP vs MNP
CERVICAL MUSCULOSKELETEAL IMPAIRMENTS							
AROM total, mean ° (SD)	359.9(41.5)	339.9(50.6)	315.3(50.8)	**<0.001***	**0.026***	**<0.001***	0.110
Flexion, mean ° (SD) [b]	63.0(9.7)	57.4(11.0)	51.0(12.3)	**<0.001***	**0.017***	**<0.001***	**0.028***
Extension, mean ° (SD)	73.2(15.7)	67.7(15.2)	59.9(13.9)	**<0.001***	0.095	**<0.001***	0.098
Right lateral flexion, mean ° (SD)	39.6(9.4)	37.6(7.6)	36.7(10.9)	0.283	0.509	0.518	1.000
Left lateral flexion, mean ° (SD)	46.0(9.6)	41.0(9.8)	38.8(11.3)	**<0.001***	**0.012***	**<0.001***	1.0000
Right rotation, mean ° (SD)	68.5(8.7)	68.6(8.5)	62.9(11.5)	**0.009***	1.000	**0.020***	**0.037***
Left rotation, mean ° (SD)	69.6(8.6)	67.6(9.9)	65.9(11.3)	0.289	0.763	0.389	1.000
FRT, mean ° (SD)	102.9(10.7)	84.4(20.4)	81.7(19.7)	**<0.001***	**<0.001***	**<0.001***	1.0000
FRT left, mean° (SD)	50.1(5.8)	40.9(10.9)	39.9(10.5)	**<0.001***	**<0.001***	**<0.001***	1.0000
FRT right, mean° (SD)	52.8(7.4)	43.5(11.5)	41.8(12.0)	**<0.001***	**<0.001***	**<0.001***	1.0000
Total TrPs, mean number (SD)	3.9(3.6)	7.6(3.2)	8.6(3.1)	**<0.001***	**<0.001***	**<0.001***	0.220
Total positive vertebral segments, mean number (SD) [c]	0.9(1.4)	2.9(1.4)	3(1.3)	**<0.001***	**<0.001***	**<0.001***	1.0000
QUANTITATVIE SENSORY TESTING							
WUR temporalis, mean (SD) [a]	1.4(2.1)	1.7(2.1)	1.9(2.1)	0.606	1.000	05.978	1.000
MPT temporalis, mean g (SD) [a]	21.2(17.8)	11.1(14.7)	11.5(13.5)	**<0.001***	**0.001***	**0.001***	1.000
sPPT temporalis, mean kPa (SD) [a]	249.3(99.5)	209.5(78.6)	198.5(82.7)	**0.003***	0.118	**0.003***	0.837
sPPT Upper cervical spine total, mean kPa (SD)[a]	512.8(235.3)	436.3(187.4)	404.2(167.1)	**0.005***	0.230	**0.003***	0.569
sPPT Upper cervical spine left, mean kPa (SD)[a]	254.5(117.4)	216.0(95.3)	197.4(80.6)	**0.005***	0.272	**0.003***	0.493
sPPT Upper cervical spine right, mean kPa (SD)[a]	258.3(121.8)	220.3(96.6)	206.8(89.1)	**0.008***	0.223	**0.006***	0.762
sPPT Lower cervical spine total, mean kPa (SD)[a]	602.8(267.7)	496.1(212.5)	461.6(204.9)	**0.001***	0.084	**0.001***	0.574
sPPT Lower cervical spine left, mean kPa (SD)†	294.5(120.1)	240.9(100.6)	225.0(99.5)	**0.001***	0.061	**<0.001***	0.558
sPPT Lower cervical spine right, mean kPa (SD)[a]	308.3(151.8)	255.2(116.6)	236.6(110.5)	**0.002***	0.132	**0.002***	0.631
dPPT total mean g (SD) [a]	7804.6 (2721.9)	5962.1 (3044.1)	4344.2 (2785.4)	**<0.001***	**0.007***	**<0.001***	**0.002***
dPPT left mean g (SD) [a]	3896.3 (1396.3)	2921.14 (1563.2)	2212.7 (1461.1)	**<0.001***	**0.006***	**<0.001***	**0.010***
dPPT right mean g (SD) [a]	3908.3 (1481.0)	3040.9 (1602.6)	2131.4 (1457.6)	**<0.001***	**0.026***	**<0.001***	**0.001***
sPPT second MCP, mean kPa (SD)[a]	333.4(135.4)	296.4(120.3)	260.4(107.4)	**0.002***	0.372	**0.001***	0.204
MPT thenar eminence, mean g (SD)[a]	31.6(15.3)	25.6(16.3)	21.7(14.9)	**0.003***	0.072	**0.002***	1.000
sPPT tibialis muscle, mean kPa (SD)[a]	437.0(210.2)	391.5(160.8)	426.3(191.6)	0.577	1.000	1.000	1.000
QUESTIONNAIRES							
CSI, mean (SD)	17.2(11.2)	29.1(13.1)	40.3(12.1)	**<0.001***	**<0.001***	**<0.001***	**<0.001***
HADS-A, mean (SD)[b]	4.2(3.3)	6.5(4.9)	7.7(3.6)	**<0.001***	**0.002***	**<0.001***	0.209
HADS-D, mean (SD)[b]	2.6(2.5)	3.5(3.5)	4.7(3.3)	**0.002***	0.630	**0.002***	0.120

AROM: active range of motion; BMI: body mass index; CSI: central sensitization inventory dPPT: dynamic pressure pain threshold; FRT: flexion rotation test; g: grams; HADS-A: The Hospital Anxiety and Depression Scale – Anxiety; HADS-D: The Hospital Anxiety and Depression Scale – Depression kPa: kilopascal; MCP: metacarpophalangeal; MPT: mechanical pain threshold; MTrPs: myofascial trigger points; SD: standard deviation; sPPT: static pressure pain threshold; WUR: wind-up ratio.
*Significant at $p < 0.05$.
[a] = data were log-transformed for statistical analysis (ANCOVA).
[b] data were square-root transformed for statistical analysis (ANCOVA).
[c] = data were treated as counting variable in a Poisson regression model.

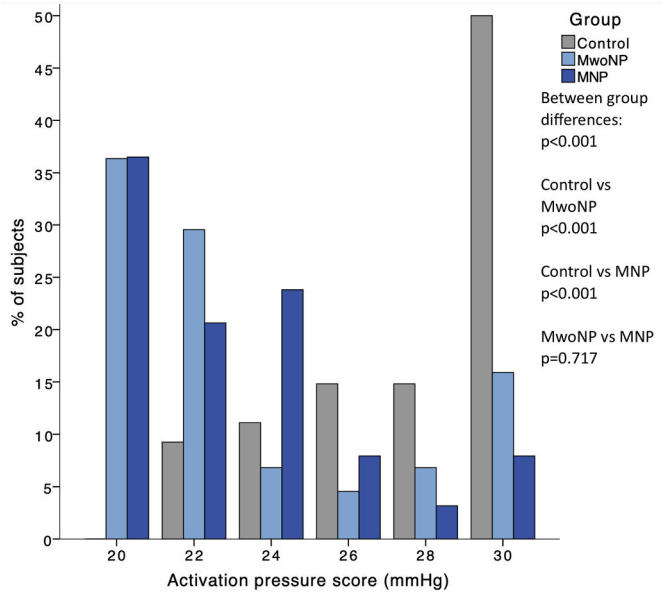

Fig. 2. Activation pressure score
MwoNP: migraine without neck pain; MwNP: migraine with neck pain
A Poisson regression model including age, gender, and BMI as a covariate in the models was performed to assess differences across groups in activation pressure score. Bonferroni-adjusted post-hoc analyse was performed to make single groups comparisons.

this subgroup of patients could be considered a migraine phenotype worse affected by the condition (Al-Khazali et al., 2022; S. Ashina et al., 2015; Calhoun et al., 2010; Carvalho et al., 2014; Florencio et al., 2014, 2021).

The presence of premonitory symptoms was more frequent in MNP patients compared to MwoNP. Moreover, NP patients had a higher number of premonitory symptoms. As it is likely that migraine patients with interictal neck pain also have ictal and peritcal neck pain (Liang et al., 2022b), neck pain could have also occurred as a premonitory symptom in MNP patients (Giffin et al., 2003; Wang et al., 2021), explaining these findings. These results outline the difficulty in differentiating neck pain related or not related to a headache attack in the migraine population. This difficulty further increased in MNP. As these patients had a higher headache frequency, the lower interval between headache attacks would make differentiating preictal and interictal symptoms even more challenging. Future studies assessing neck pain in migraine patients should use a diary to avoid this limitation. The use of a diary could allow researchers to control the temporal relationship between neck pain and a headache attack, understanding if neck pain could be considered a premonitory symptom, an interictal symptom, or an ictal symptom (Liang et al., 2022b).

4.1.1. Cervical musculoskeletal impairments

MNP and MwoNP had a reduction in the functionality of deep neck flexors muscles (Rodrigues et al., 2021), reduced passive mobility of the cervical spine (Bragatto et al., 2019), a higher number of positive vertebral segments and MTrPs compared to controls, with no differences between migraine subgroups. If no difference in deep neck flexors muscles functionality between MNP and MwoNP is in line with a previous study (Rodrigues et al., 2021), other authors found differences between MNP and MwoNP in cervical passive mobility (Bragatto et al., 2019). Thus, future studies should assess differences in FRT between MNP and MwoNP before firm conclusions can be reached (Bragatto et al., 2019).

Our study's results suggest that CMI and neck pain are not mutually related (Liang et al., 2021), with CMI occurring also in MwoNP (Di Antonio et al., 2022a). However, the cervical active range of motion was

Table 4
Univariate binary logistic regression models to determine risk factors associated with presence of neck pain. Multivariate Stepwise logistic regression model using forward and backward method including as predictors only variables resulting with a p-value<0.05 in the univariate analysis.

	Univariate		Multivariate	
	OR [95% CI] Neck pain vs no neck pain	p-value	OR [95% CI] Neck pain vs no neck pain	p-value
GENERAL CHARACTERISTICS				
Age	1.023 [0.988–1.059]	0.208		
Gender				
Female	1.167 [0.472–2.883]	0.738		
Male	–	–		
BMI	1.099 [0.982–1.230]	0.102		
HEADACHE CHARACTERISTICS				
Headache type				
EM	**0.294 [0.091–0.950]**	**0.041***		
CM				
Headache side				
Bilateral or side/shift	1.048 [0.449–2.447]	0.913		
One side (Left or right)				
Years with headache	1.005 [0.975–1.036]	0.738		
Frequency	**1.137 [1.048–1.234]**	**0.002***	**1.143 [1.021–1.280]**	**0.020***
Duration	1.048 [0.974–1.129]	0.211		
Intensity	0.967 [0.765–1.222]	0.777		
Drugs	**1.138 [1.029–1.259]**	**0.012***		
Presence of premonitory symptoms				
yes	**3.294 [1.393–7.790]**	**0.007***	**3.830 [1.326–11.060]**	**0.013***
no				
Number of premonitory symptoms	**1.540 [1.084–2.188]**	**0.016***		
HDI	**1.036 [1.013–1.060]**	**0.002***		
MUSCULOSKELETEAL IMPAIRMENTS				
AROM				
Flexion	**0.954 [0.921–0.988]**	**0.009***		
Extension	**0.962 [0.934–0.991]**	**0.011***	**0.954 [0.918–0.991]**	**0.015***
Right lateral flexion	0.990 [0.951–1.031]	0.624		
Left lateral flexion	0.981 [0.946–1.018]	0.309		
Right rotation	**0.946 [0.908–0.986]**	**0.008***		
Left rotation	0.985 [0.950–1.022]	0.422		
FRT total				
Negative	0.595 [0.240–1.478]	0.264		
Positive				
APS	0.966 [0.860–1.084]	0.555		
MTrPs	1.108 [0.979–1.254]	0.104		
Positive vertebral segments	1.020 [0.766–1.359]	0.890		

(*continued on next page*)

Table 4 (*continued*)

	Univariate		Multivariate	
	OR [95% CI] Neck pain vs no neck pain	p-value	OR [95% CI] Neck pain vs no neck pain	p-value
QUANTITATIVE SENSORY TESTING				
sPPT temporalis	0.998 [0.994–1.003]	0.486		
MPT temporalis	1.003 [0.975–1.031]	0.859		
WUR temporalis	1.053 [0.873–1.269]	0.591		
sPPT Upper cervical spine	0.999 [0.997–1.001]	0.352		
sPPT Lower cervical spine	0.999 [0.997–1.001]	0.397		
dPPT cervical, total	**0.999 [0.999–1.000]**	**0.007***	**0.999 [0.999–1.000]**	**0.005***
MPT hand	0.984 [0.960–1.009]	0.200		
sPPT second MCP	0.997 [0.994–1.001]	0.112		
sPPT tibialis muscle	1.001 [0.999–1.003]	0.324		
QUESTIONNAIRES				
CSI	**1.080 [1.041–1.120]**	**<0.001***	**1.064 [1.021–1.109]**	**0.003***
HADS-A	1.095 [0.983–1.219]	0.099		
HADS-D	1.126 [0.993–1.277]	0.064		

AROM: active range of motion; APS: activation pressure score; BMI: body mass index; CI: confidence interval; CSI: central sensitization inventory dPPT: dynamic pressure pain threshold; FRT: flexion rotation test; HDI: headache disability index: HADS-A: The Hospital Anxiety and Depression Scale – Anxiety; HADS-D: The Hospital Anxiety and Depression Scale – Depression; MCP: metacarpophalangeal; MPT: mechanical pain threshold; MTrPs: myofascial trigger points; OR: odd ratio; sPPT: static pressure pain threshold; WUR: wind-up ratio; *Significant at $p < 0.05$.

more impaired in MNP, suggesting this subgroup could be considered a migraine phenotype with more impaired cervical mechanical behavior (Bragatto et al., 2019; Florencio et al., 2021). The link between Increased sensitization and poorer musculoskeletal function may explain reduced cervical active mobility observed in MNP (Arendt-Nielsen et al., 2008; Jorge et al., 2021).

In a recent paper, our research group observed that during the ictal phase, the period in which the sensitization of the trigeminocervical complex reaches its peak (Burstein et al., 2000a; Di Antonio et al., 2022b), a reduction in the cervical active range of motion was present despite the presence of neck pain (Di Antonio et al., 2022a). The reduction in the cervical active range of motion was not observed in other headache phases when the sensitization of the trigeminocervical complex was restored to the baseline level. Thus, a transitory increase in trigeminocervical sensitization (the migraine attack) could have a short-term effect on cervical motor functionality. The current paper's results showed that, interictally, a subgroup of patients with higher sensitization had worse cervical AROM, strengthening the hypothesis that a relationship between increased sensitization and worse cervical motor functionality exists in migraine patients (Di Antonio et al., 2022a). In this context, neck pain can be seen as a proxy to identify migraine patients with worse interictal sensitization and more impaired cervical motor functionality.

4.1.2. Signs and symptoms related to sensitization

No differences in trigeminal WUR across groups were observed, suggesting that increased trigeminal temporal summation of pain is a feature limited to the ictal phase that seems not to occur interictally in migraine patients (Di Antonio et al., 2022b).

Migraine patients with and without neck pain had reduced trigeminal MPT, with no differences between the two subgroups (Yu et al., 2019). Moreover, a reduction in cervical dPPT was observed in MNP and MwoNP compared to controls, with MNP having a more enhanced reduction in cervical dPPT. To the author's knowledge, this study was the first to assess dPPT in the cervical spine in migraine patients with and without neck pain.

A reduction in trigeminal and cervical sPPT and hand sPPT and MPT were observed only in MNP compared to controls. The higher sensitization in trigeminal and cervical areas is in line with previous studies (S. Ashina et al., 2015; Yu et al., 2019), while the higher sensitization over the hand was not (S. Ashina et al., 2015). Heterogeneity in the population examined could account for these differences. In our paper, neck pain was asked referring to the period in which the examination occurred. On the other hand, Ashina and colleagues (S. Ashina et al., 2015) investigated the presence of neck pain in the previous year, probably including subjects less impaired by neck pain with lower sensitization. Finally, this study provides the first line of evidence that MNP and MwoNP had higher symptomatology related to sensitization, with MNP even worse than MwoNP.

Overall, this study's results suggest that, even if a subtle increase in trigeminal and cervical sensitization could occur in MwoNP, MNP had more pronounced trigeminal, cervical, and widespread sensitization and more increased symptomatology related to sensitization. As different QST modalities are designed to test distinct peripheral nerve afferents (Walk et al., 2009) it is likely that "peripheral sensitization" mechanisms could underlie the increased sensitization limited to one stimulus modality and area observed in MwoNP. On the other hand, "central sensitization mechanisms" could underlie the increased sensitization to multiple stimuli and areas observed in MNP. Increasing cortical/subcortical, and spinal sensitization mechanisms could have occurred in MNP. The reduced trigeminal and cervical pain threshold for different stimuli could be seen as an indirect sign of increased sensitization of second-order spinal neurons in the trigeminocervical complex or cervical spine. On the other hand, the reduced hand pain threshold for different stimuli is a sign of increased sensitization of second-order cervical spinal neurons or higher-order cortical/subcortical neurons. Finally, the reduced leg pain threshold could be seen as an indirect sign of increased sensitization of second-order lumbar spinal neurons or higher-order cortical/subcortical neurons (Burstein et al., 2000a; Di Antonio et al., 2022b). As increased sensitization in MNP was present for different stimuli from the trigeminal and cervical areas and from the hand but not from the leg, it is questionable if the spreading of sensitization in cervical spinal neurons more than cortical/subcortical sensitization mechanisms could explain the widespread sensitization we observed in migraine patients with neck pain (Burstein, 2001; Burstein et al., 2000b; Graven-Nielsen and Arendt-Nielsen, 2010). Future studies should assess cervical spinal sensitization using appropriate assessment modalities.

4.1.3. Psychological burden

Both MNP and MwoNP had a higher level of depression than healthy control, supporting the high prevalence of this disorder in the migraine population and the strong link between these two medical conditions (Di Antonio et al., 2021; Fernández-De-Las-peñas et al., 2010; Yang et al., 2016). However, MNP showed worse depression and anxiety, suggesting that this migraine phenotype had a worse psychological burden. Differences in genetic biomarkers could underlie worse disability, higher signs of sensitization, and worse psychological burden in migraine patients (Fernández-De-Las-Peñas et al., 2019). As all these characteristics were present in migraine patients with neck pain, future studies should assess if genetic factors could identify a migraine phenotype with neck pain.

4.2. Mechanisms underlying the presence of neck pain in the migraine population

Overall, this study's results suggested that neck pain in the migraine population could be predicted both by "centrally mediated mechanisms" as higher headache frequency, higher presence of premonitory symptoms, and worse CSI, and by "peripherally mediated mechanisms," as lower AROM in extension, and lower dPPT over the cervical area.

The fact that neck pain could be predicted by migraine characteristics, supports the hypothesis that neck pain could be a consequence of migraine and could be considered among its symptoms (Liang et al., 2021, 2022a).

On the other hand, the fact that neck pain could be predicted by reduced AROM in extension, and increased cervical hyperalgesia, supports the hypothesis that peripheral nociceptive input from the cervical spine could play a role in inducing neck pain (Hvedstrup et al., 2020a; Hvedstrup et al., 2020b). In this scenario, neck pain could be seen as a comorbidity driven by peripheral sensitization mechanisms.

It remains unanswered if different phenotypes of MNP pain exist or if multiple mechanisms could account for the presence of neck pain in the migraine population. On the one hand, different MNP phenotypes could exist, one in which "centrally mediated mechanisms" prevails and another in which "peripherally mediated mechanisms" prevails. On the other hand, both "centrally and peripherally mediated mechanisms" could account for the presence of neck pain in each migraine patient. The migraine attack could be seen as nociceptive input inducing short-lasting enhanced "central sensitization" of the trigeminocervical complex, where input from the face and neck converges, causing ictal neck pain (Bartsch and Goadsby, 2003b; Kaube et al., 2002). In a subgroup of migraine patients with higher premonitory symptoms and worse CSI, increased headache frequency could induce long-lasting enhanced "central sensitization" of the trigeminocervical complex, leading to interictal neck pain. As the headache attack has been shown to affect cervical mechanical behavior (Di Antonio et al., 2022a), the increased headache frequency could also lead to peripheral alterations in the neck region (Florencio et al., 2015; Tolentino et al., 2018). The resulting peripheral nociceptive input from the cervical spine could further enhance and maintain neck pain.

4.3. Limitation

The population was recruited from a specialized headache center, and over half of the patients were excluded for age, concomitant pathologies, and the presence of other headache types. Thus, the external validity of these results should be interpreted with caution.

As no gold standard exist to evaluate the presence of neck pain in the migraine population, we used a structured interview (Di Antonio et al., 2022a). The percentage of migraine patients and controls with neck pain unrelated to a migraine attack was similar to previous studies (Hvedstrup et al., 2020a; Liang et al., 2022b; Yu et al., 2019), supporting the method's validity.

Moreover, the blindness of the assessor was not maintained for the entire evaluation of every patient. To reduce the assessment duration, we decided to evaluate the trigeminal pain threshold only on one side, incurring the possibility that, for those patients with a unilateral headache on the non-dominant side, blindness could be lost. Our decision was supported by the fact that the assessor would be blinded regarding the presence of neck pain.

5. Conclusion

Migraine patients, independently of neck pain, presented a reduction in the functionality of deep neck flexors muscles, reduced passive and active mobility of the cervical spine, increased number of myofascial and cervical segments able to reproduce referred pain, increased trigeminal and cervical sensitization, higher symptoms of sensitization, and worse psychological burden compared to healthy subjects. However, migraine patients with neck pain could be considered a migraine phenotype worse affected by the disease, with worse headache characteristics, more pronounced cervical musculoskeletal impairments, enhanced signs, and symptoms related to sensitization, and worse psychological burden. Multiple characteristics seem to predict the presence of neck pain in migraine patients, including higher headache frequency, higher prevalence of premonitory symptoms, lower cervical active movement in extension, lower dynamic pressure pain threshold over the cervical area, and worse symptomatology due to sensitization.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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