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Title

Widespread Pressure Pain Sensitivity over Nerve Trunk Areas in Women with Frequent Episodic Tension Type Headache as a Sign of Central Sensitization

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Abstract

Objective: Previous studies reported the presence of widespread pressure pain sensitivity in patients with tension type headache. However, most of the studies assess pressure pain sensitivity over muscle tissue. Our aim was to investigate the difference in pressure pain sensitivity over musculoskeletal and nerve symptomatic and distant areas between women with frequent episodic tension type headache (FETTH) and healthy subjects.

Methods: Thirty-two women with FETTH and 32 matched healthy women participated. Pressure pain threshold (PPT) was bilaterally assessed over several nerve trunks (greater occipital, median, radial, ulnar, common peroneal, tibialis posterior) and musculoskeletal structures (temporalis muscle, C5/C6 joint, tibialis anterior) by an assessor blinded to the subject's condition. A 4-weeks headache diary was used to collect the intensity, frequency and duration of headache. The Hospital Anxiety and Depression Scale (HADS) was used to determine anxiety (HADS-A) and depressive (HADS-D) levels.

Results: The ANCOVA found lower widespread and bilateral PPTs over all nerve trunks and musculoskeletal structures in women with FETTH pain ($P<.001$). No significant effect of anxiety and depressive levels on PPTs were found (all $P>.222$). PPT over the temporalis muscle was significantly negatively correlated with headache intensity.

Conclusions: This study found widespread pressure pain hypersensitivity over both nerve trunks and musculoskeletal structures in women with FETTH suggesting the presence of central altered nociceptive processing is not just restricted to musculoskeletal areas, e.g., muscles, but also pain evoked from directly provoking the nerve trunks by pressure. It is also possible that nerve tissue treatment could lead to decrease of central sensitization and headache features.

Key words: Tension type headache, pressure pain, nerve trunks, sensitization.

Widespread Pressure Pain Sensitivity over Nerve Trunk Areas in Women with Frequent Episodic Tension Type Headache as a Sign of Central Sensitization

Introduction

Tension type headache (TTH) is probably the most common headache disorder seen by neurologists. In fact, headache has been found to be the second most prevalent pain condition in the world in the last Global Burden of Disease Study (1). Current evidence supports the presence of altered nociceptive pain processing in TTH (2). The most accepted theory is that the episodic form of the disease is more related to peripheral mechanisms whereas the chronic form is associated to central mechanisms, although both processes are present in both forms of headache (3). One of the main features of TTH is the presence of hypersensitivity to pressure pain, i.e., lower pressure pain thresholds, as compared to people without headache (4). This is supported by two reviews concluding that pressure pain thresholds, are consistently lower in people with TTH when compared with asymptomatic people being the trigemino-cervical region the most sensitive area to pressure pain (5,6). Additionally, other studies have also observed the presence of pressure hypersensitivity in distant pain-free areas (widespread) in people with TTH (7,8). Previous findings support that TTH is characterized by widespread mechanical pain hypersensitivity over deep somatic tissues; however, pain sensitivity has been mostly assessed over muscle tissue in previous studies. It is unclear if this generalised hypersensitivity is specific for muscle tissues or also manifested as hypersensitivity to pressure pain in other structures, e.g. nerve trunks.

Nerve mechano-sensitivity can be investigated by the application of non-noxious mechanical stimuli, e.g. manual palpation, or by assessment of pressure pain sensitivity (9). Generalized sensitisation of neural tissues is also a sign of hyper-excitability state of the central nervous system and it has been found in different chronic pain conditions, such as whiplash associated disorders (10), carpal tunnel syndrome (11), plantar heel pain (12), or lateral epicondylalgia (13). Few studies have investigated pressure pain sensitivity over nerve trunk areas in individuals with headache. Szikszay et al found that patients with unilateral head and neck pain exhibit pressure pain hypersensitivity of the greater occipital nerve when compared to controls (14); whereas Fernández-de-las-Peñas et al observed that patients with chronic TTH also showed sensitivity to pressure pain over the supra-orbital nerve (15). Both studies suggest that pressure stimulation of trigemino-cervical nerve trunks also exhibit sensitization in individuals with headache; however, these results can be related to both peripheral or central mechanisms. The only study investigating widespread pressure pain hyperalgesia over nerve trunks in patients with headache reported that patients with strictly unilateral migraine showed a bilateral increase on mechanical pain sensitivity at supra-orbital, median, radial and ulnar nerve trunks (16). No previous study has investigated widespread pressure pain sensitivity over nerve trunks in TTH. Additionally, no previous studies have controlled the role of depression and anxiety levels in pressure pain nerve sensitivity in this headache condition as depressive symptoms are associated with reduced pain thresholds (17).

Our aim was to assess pressure sensitivity over symptomatic and distant pain-free nerve trunk areas between women with TTH and healthy controls, considering confounders like anxiety or depression. We hypothesized that women with TTH would exhibit widespread pressure hyperalgesia over nerve trunks and that pressure sensitivity would be associated with higher levels of depression and anxiety.

Methods

Participants

Consecutive women with a diagnosis of TTH by an experienced neurologist were recruited from a university centre in Cantabria (Spain) from February to December 2018. Diagnosis was conducted according to the third edition of the International Classification of Headache Disorders (18). To be included, patients had to describe all the typical features of TTH: bilateral location, pressing/tightening pain, mild/moderate intensity (≤6 on a 10 points numerical pain rate scale) and no aggravation of headache during physical activity (18). Only one, either photophobia or phonophobia was permitted in those patients with high frequency of attacks. Only individuals with frequent episodic tension-type headache (FETTH) were included in the study. Participants were excluded if presented any of the following criteria: 1, chronic headaches; 2, other primary/secondary headache including medication overuse headache; 3, history of head/neck trauma (i.e., whiplash); 4, cervical herniated disk or cervical osteoarthritis (medical records); 5, any systemic degenerative disease, e.g., rheumatoid arthritis, lupus erythematous; 6, diagnosis of fibromyalgia; 7, had received anaesthetic blocks or any physical treatment the previous 6 months; or, 8, pregnancy.

A control group without history of headache diagnosis and without reporting a headache pain attack the previous year, matched by age to the headache group, was also included. Exclusion criteria for the control group were the same as for headache group. The study was approved by the Cantabria human research ethics committee (2016/104). All subjects read and signed informed consent prior to their inclusion in the study.

Self-reported measures

Subjects completed a headache diary for 4 weeks to complement the diagnosis (19). An 11-point NPRS (20) (0: no pain to 10: maximum pain) was used to assess the

intensity of headache. The headache diary was used to registered the number of days with headache (days per week); the mean of intensity and duration of each headache attack (NPRS and hours per day, respectively).

The Hospital Anxiety and Depression Scale (HADS), a 14-items self-reported screening scale that assesses the presence of anxiety and depressive symptom, was also used (21). It consists of 7 items evaluating anxiety (HADS-A) and 7 evaluating depression (HADS-D). Each item is answered on a Likert-type scale (0-3). The sum of all answers is transformed into a global score (0-21) for each subscale, where higher score indicates more anxiety and depressive symptoms (22). The questionnaire has shown good validity and internal consistency in patients with headache (23).

Pressure pain sensitivity

Pressure pain Threshold (PPT), the minimal amount of pressure where a sensation of pressure first changes to pain (24), was assessed with an electronic algometer (Somedic AB©, Farsta, Sweden) in kPa. The pressure was applied approximately at a rate of 30 kPa/second. All participants were instructed to press switch when the sensation changed from pressure to pain. Three trials were performed on each point with a 30-second resting period between each measure. The mean of 3 trials was used for the main analysis. The PPT has exhibited high reliability (25).

Participants attended a preliminary session for familiarization with the pressure test procedure. Patients with FETTH were tested on headache-free day and they were also asked to avoid any analgesic or muscle relaxant 24 hours prior to the examination. PPT levels were bilaterally measured over the greater occipital, median, ulnar, radial, tibialis and common peroneal nerves; the temporalis and tibialis anterior muscles, and C5/C6 zygapophyseal joint by an assessor blinded to the subject' condition. The musculoskeletal

structures were assessed in the trigeminal symptomatic area (temporalis muscle), cervical symptomatic area (C5/C6 joint) and a distant pain-free non-related area (tibialis anterior).

All the nerves were identified by manual palpation and marked with a pencil. The greater occipital nerve was located at an average distance of 4 cm (range 1.5–7.5) lateral to a horizontal line through the occipital protuberance (14). For the upper extremity, the median nerve (C5) was located over the cubital fossa medial to and immediately adjacent to the tendon of biceps; the radial (C6) nerve was marked where it passes through the lateral intermuscular septum between the medial and lateral heads of triceps to enter the mid to lower third of the humerus; and the ulnar nerve (C7) was located in the groove between the medial epicondyle and the olecranon (10-12). For the lower extremity, the common peroneal nerve was marked where it passes behind the head of the fibula as it winds forwards around its neck whereas the tibial nerve was marked where it bisects the popliteal fossa, lateral to the popliteal artery (12). The reliability of PPT assessment over these nerve trunks was moderate to high (26,27). There is no minimal detectable change data published for PPTs in individuals with headache. Walton et al found that the minimal detectable change for PPT over the cervical spine was 47.2 kPa and 98 kPa for the tibialis anterior muscle in patients with acute neck pain (28), whereas Ylinen et al considered that between-groups differences over 20% can be considered as a real difference (29).

Sample size calculation

Sample size determination and calculations were based on detecting a moderate-large effect size of 0.75 between TTH and healthy control groups, a 2-tailed test, with an alpha level (α) of 0.05, and a desired power (β) of 90%. This generated a sample size of at least 30 participants per group.

Statistical analysis

Data were analysed with the SPSS statistical package (21.0 Version). Results are expressed as mean, standard deviation (SD) or 95% confidence interval (95%CI). The Kolmogorov-Smirnov test was used to determine the normal distribution of the data ($P>0.05$). Quantitative data without a normal distribution (i.e. pain history, headache intensity, frequency or duration) were analysed with non-parametric tests, and data with a normal distribution (PPTs) were analysed with parametric tests. A multivariate mixed-model ANCOVA test was used to investigate the differences in PPT assessed over each point (temporalis muscle, C5/C6 joint, second metacarpal, tibialis anterior muscle, greater occipital, median, ulnar, radial, tibialis posterior and common peroneal nerves) with side (right or left) as within-subjects factor, group (FETTH or controls) as between-subjects factor, and depression/anxiety as covariates. Post-hoc comparisons were conducted with a Bonferroni test. Finally, the Spearman's rho (rs) test was used to analyse the association between PPTs (mean data of both sides) with clinical variables related to headache and depression and anxiety levels. In general, the statistical analysis was conducted at a 95% confidence level and a P-value less than 0.05 was considered statistically significant; but for multiple comparisons (ANCOVA), a Bonferroni-corrected alpha level of 0.025 (2 independent-samples t tests) was considered significant.

Results

Demographic and Clinical Data of the Sample

Fifty-seven consecutive women who presented with headache were screened for eligibility criteria. Twenty-five subjects were excluded: migraine (n=12), chronic tension type-headache (n=7), and previous whiplash (n=6). Finally, a total of 32 women, aged 18 and 25 years (mean age: 22±3 years) satisfied all criteria, agreed to participate, and signed the informed consent. The patients presented 2.9 (95%CI 2.1-3.6) years of headache history, 7.7 (95%CI 6.5-8.9) days per month with headache, 1.4 (95%IC 1.1-1.7) hours per day with headache, and 5.4 (95%IC 5.0-5.8) points of headache intensity per attack. No significant association between headache intensity, frequency, or duration was found (all, P>0.6). The HADS-A score was 6.3 (95%CI 5.6-7.0) whereas the HADS-D score was 3.0 (95%CI 2.3, 3.7).

In addition, 32 matched women without headache history, aged 18 to 21 years (mean age: 22±1 years) was recruited as a control group. The HADS-A score within the control group was 4.6 (95%CI 4.0-5.2) whereas the HADS-D score was 1.3 (95%CI 0.8, 1.8).

Pressure Pain Sensitivity over Trigeminal Nerve Trunk

The ANCOVA revealed significant differences between groups, but not between sides, for PPTs over the greater occipital nerve (group: F=9.965, P=.002; side: F=0.303, P=.621) without any significant effect for anxiety (F=1.014; P=.316) or depressive levels (F=0.759; P=.385): women with FETTH showed bilateral lower PPT over the greater occipital nerve than controls. **Table 1** summarizes PPTs over the greater occipital nerve for both sides within each group.

Pressure Pain Sensitivity over Extra-trigeminal Nerve Trunk Structures

The ANCOVA found significant differences between groups (median: F=10.182, P<.001; radial: F=1.563, P=.033; ulnar: F=2.636, P=.007; tibialis posterior: F=2.671, P=.006; common peroneal: F=5.196, P=.024) but not between sides (median: F=1.043, P=.309; radial: F=0.011, P=.915; ulnar: F=0.202, P=.654; tibialis posterior: F=0.005, P=.941; common peroneal: F=0.045, P=.832) for PPTs over extra-trigeminal nerve trunk areas: women with FETTH exhibited bilateral lower PPTs in all peripheral nerve trunks than controls. Neither anxiety nor depressive symptoms showed a significant effect for the median (HADS-A: F=0.015, P=.902; HADS-D: F=1.507, P=.222), radial (HADS-A: F=0.986, P=.323; HADS-D: F=0.793, P=.375); ulnar (HADS-A: F=0.036, P=.851; HADS-D: F=0.536, P=.465); tibialis posterior (HADS-A: F=1.160, P=.284; HADS-D: F=0.421, P=.518), or common peroneal (HADS-A: F=0.191, P=.663; HADS-D: F=0.797, P=.374) nerves. **Table 1** details PPT over the peripheral nerves for both sides within each group.

Pressure Pain Sensitivity over Musculoskeletal Structures

The ANCOVA exhibited significant differences between groups, but not between sides, for PPTs over all musculoskeletal areas: temporalis muscle (group: F=5.470, P=.021; side: F=0.145, P=.704), C5/C6 joint (group: F=6.353, P=.013; side: F=0.054, P=.817), and tibialis anterior muscle (group: F=10.285, P=.002; side: F=0.016, P=.900): again, women with FETTH showed bilateral widespread lower PPTs than controls (**table 1**). Again, no significant effects for anxiety or depressive levels showed a significant effect for temporalis (HADS-A: F=0.878, P=.351; HADS-D: F=1.218, P=.272), C5/C6 joint (HADS-A: F=1.050, P=.308; HADS-D: F=0.328, P=.568) or tibialis anterior muscle (HADS-A: F=1.119, P=.292; HADS-D: F=0.416, P=.520).

Pressure sensitivity and clinical features in women with FETTH

A significant negative association between headache frequency and PPTs over the temporalis muscle (rs: -0.420; P=.013) was found: the higher the frequency of headache attacks, the lower the PPTs (i.e., higher sensitivity to pressure pain) over the temporalis muscles. No other significant association was observed (all, P>.4).

Discussion

The current study found widespread pressure hypersensitivity when pressure pain thresholds were assessed over nerve trunks (with no stimulation of other musculoskeletal structures) in women with FETTH. The study furthermore supported previous studies showing widespread pressure hypersensitivity in musculoskeletal structures. This suggest altered central nociceptive processing is not just restricted to musculoskeletal structures. Depression and anxiety levels were not associated with widespread pressure hyperalgesia.

In this study, PPT was significantly decreased bilaterally over local (trigeminal), related segment (cervical spine) and distant pain-free (tibialis anterior) points, supporting the presence of widespread pressure pain hyperalgesia over musculoskeletal structures in women with FETTH. The between-groups PPT differences observed in our study ranged from 30kPa (C5/C6 joint) to 115kPa (tibialis anterior). These values are superior to those determined for the tibialis anterior, but lower than for the cervical spine, in people with acute neck pain (28). The presence of widespread pressure pain hyperalgesia over these musculoskeletal areas in patients with FETTH agree with the results previously reported by Palacios-Ceña et al (8); however, differences in our study were small since this study included individuals with FETTH with higher frequency of headaches (8). It is possible that a higher frequency of headaches would lead to higher pressure pain hypersensitivity as previously suggested by Buchgreitz et al (30). It could be hypothesized that widespread

pressure hyperalgesia could be developed with time in parallel with an increase in the frequency of headaches.

The presence of widespread pressure pain hypersensitivity is a manifestation of an altered central pain processing as structures away from the site of pain were assumed non-symptomatic and considered normal. There is clear evidence supporting the presence of sensitivity to pressure pain in musculoskeletal areas in patients with TTH; however, previous studies have mostly investigated muscle tissues (3). The novelty of our study is that we assessed widespread mechanical pain sensitivity over nerve trunks which was not analyzed in previous studies. In fact, our study observed that women with FETTH also exhibited widespread pressure pain hyperalgesia over nerve trunks, similarly than over other musculoskeletal structures. Nevertheless, it should be noted that between-groups differences in PPTs over nerve trunk areas ranged from 40kPa (median nerve) to 70kPa (common peroneal nerve), which could suggest lower sensitization over neural tissues as compared to other musculoskeletal areas. The hyperalgesia observed over neural tissue could be evoked by the centralization of the central nervous system as result of increased responsiveness of nociceptive neurons to different stimuli (31). The fact that widespread pressure pain hyperalgesia over nerve trunk areas was not associated with anxiety or depressive levels would support that hyperalgesia to pressure pain over musculoskeletal and neural tissues is a consistent finding in TTH.

It has been proposed that sensitization of central pathways is associated to long-lasting nociceptive inputs from peripheral tissues. Some theories mainly involving muscle tissues have been proposed for explaining TTH-related pain (32); however, most of these theories excluded the role of nerve tissues. It is also possible that nociception from nerve tissues, and not just those from the muscles, can be also involved in direct sensitization processes in this population. For example, peripheral sensitization of neural structures

could also represent a nociceptive barrage to the central nervous system by changing the neurotransmitters and altering inhibitory pain mechanisms (9). It has been suggested that excessive peripheral afferent stimulation found in people with nerve tissue involvement will drive central adaptations potentially leading to chronic pain which may be like the pathophysiology occurring in FETTH (33). Furthermore, it has been reported that nerve endings located within the nervi nervorum (the small nerves innervating the nerve trunk) may be stimulated by lower thresholds of stimuli resulting in neurogenic inflammation (9). These sensitized nociceptors may possibly result in a barrage of impulses resulting in ectopic activity in the dorsal root ganglion which may result in central hyperexcitability (34). This hypothesis is partially supported by a randomized clinical trial showing that the inclusion of neural mobilization techniques targeting the trigeminal nerve trunk into a multimodal treatment approach was effective for decreasing headache pain and pressure pain hypersensitivity in subjects with TTH (35). It is important to note that the presence of widespread pressure pain sensitivity over nerve trunk areas found in our study seems to be mostly related to central sensitization since all nerve trunks were asymptomatic. To confirm a potential peripheral sensitization role of nerve tissue in TTH, the association between pressure pain sensitivity over terminal branches of the trigeminal nerve (since it innervates the main symptomatic area in TTH) with clinical features of headache should be conducted. Preliminary evidence suggests the presence of pressure pain hyperalgesia over the greater occipital (14) and supra-orbital (15) nerves in patients with TTH; but its role in the clinical manifestation is still unknown.

Finally, some limitations of the current study should be also considered. First, the cross-sectional design does not permit to determine any cause and effect relationship between nerve trunk sensitivity and TTH related-pain. Second, we only included women with FETTH. It is well known that women exhibit higher sensitivity to pressure stimuli

than men (36). Greater population-based studies examining the sensitivity of neural trunks in men with FETTH, and also in those with the chronic form, will assist with increasing the generalizability of the results. Third, depression and anxiety levels in our sample were low. This may be related to the fact that we included women with FETTH with lower frequency of headaches. There is evidence supporting that depressive levels are related to headache frequency and, therefore, more prevalent in the chronic form of the disease (37). Therefore, the role of these factors in pressure pain hypersensitivity over nerve trunk areas in women with FETTH should be considered with caution at this stage. Finally, we did not also collect measure of kinesiophobia levels which often accompanies chronic diseases and may result in a heightened central nervous system. A recent study observed that the presence of kinesiophobia was associated with cutaneous allodynia, a clinical manifestation of central sensitization, in individuals with migraine (38). No study has investigated the presence of kinesiophobia in tension type headache.

Conclusion

In the current sample, women with FETTH exhibited widespread hyperalgesia to pressure pain over nerve trunks and likewise over musculoskeletal structures suggesting that the presence of a altered central nociceptive processing is not just restricted to musculoskeletal structures. These findings also suggest the presence of nerve tissue sensitization which may further drive the process of central sensitization leading to the symptoms often found in people with FETTH. Futures studies should examine the effects of treating the identified peripheral sensitization in this population.

Key Findings

1. This study observed similar widespread hyperalgesia to pressure pain over nerve trunks and other musculoskeletal structures in women with frequent episodic tension type headache.
2. Widespread pressure pain sensitivity was associated not associated with anxiety and depressive levels.
3. Current results suggest the presence of nerve tissue sensitization in tension type headache may further drive the process of central sensitization.

References

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1545-602
2. Yu S, Han X. Update of chronic tension-type headache. Curr Pain Headache Rep 2015; 19: 469
3. de Tommaso M, Fernández-de-las-Peñas C. Tension type headache. Curr Rheumatol Rev 2016; 12: 1-13.
4. Abboud J, Marchand A, Sorra K, Descarreaux M. Musculoskeletal physical outcome measures in individuals with tension-type headache: a scoping review. Cephalalgia 2013; 33: 1319-36.
5. Andersen S, Petersen MW, Svendsen AS, Gazerani P. Pressure pain thresholds assessed over temporalis, masseter, and frontalis muscles in healthy individuals, patients with tension-type headache, and those with migraine: a systematic review. Pain 2015; 156: 1409-23.
6. Castien RF, van der Wouden J, De Hertogh W. Pressure pain thresholds over the cranio-cervical region in headache: a systematic review and meta-analysis. J Headache Pain 2018; 19: 9.
7. Ashina S, Bendtsen L, Ashina M, Magerl W, Jensen R. Generalized hyperalgesia in patients with chronic tension type headache. Cephalalgia 2006; 26: 940-8
8. Palacios-Ceña M, Castaldo M, Wang K, Torelli P, Pillastrini P, Fernández-de-las-Peñas C, Arendt-Nielsen L. Widespread pressure pain hypersensitivity is similar

438 in women with frequent episodic and chronic tension-type headache: A blinded
439 case-control study. Headache 2017; 57: 217-225
440 9. Hall TM, Elvey RL. Nerve trunk pain: physical diagnosis and treatment. Man
441 Ther 1999: 4: 63-73
442 10. Sterling M, Treleaven J, Edwards S, Jull G. Pressure pain thresholds in chronic
443 whiplash associated disorder: further evidence of altered central pain processing.
444 J Musculoskelet Pain 2002; 10 (3): 69-81
445 11. Fernández-de-las-Peñas C, de la Llave-Rincón AI, Fernández-Carnero J,
446 Cuadrado ML, Arendt-Nielsen L, Pareja JA. Bilateral widespread mechanical
447 pain sensitivity in carpal tunnel syndrome: evidence of central processing in
448 unilateral neuropathy. Brain. 2009; 132: 1472-9.
449 12. Plaza-Manzano G, Ríos-León M, Martín-Casas P, Arendt-Nielsen L, Fernández-
450 de-las-Peñas C, Ortega-Santiago R. Widespread pressure pain hypersensitivity in
451 musculo-skeletal and nerve trunk areas as a sign of altered nociceptive processing
452 in unilateral plantar heel pain. J Pain 2019; 20: 60-67
453 13. Fernández-de-las-Peñas C, Ortega-Santiago R, Ambite-Quesada S, Jiménez-
454 Garcí A R, Arroyo-Morales M, Cleland JA. Specific mechanical pain hyper-
455 sensitivity over peripheral nerve trunks in women with either unilateral
456 epicondylalgia or carpal tunnel syndrome. J Orthop Sports Phys Ther 2010; 40:
457 751-60.
458 14. Szikszay TM, Luedtke K, Harry von P. Increased mechanosensivity of the greater
459 occipital nerve in subjects with side-dominant head and neck pain: a diagnostic
460 case-control study. J Man Manip Ther 2018; 26: 237-248.

461 15. Fernández-de-las-Peñas C, Coppieters MW, Cuadrado ML, Pareja JA. Patients
462 with chronic tension-type headache demonstrate increased mechano-sensitivity of
463 the supra-orbital nerve. Headache 2008; 48: 570-7
464 16. Fernández-de-las-Peñas C, Arendt-Nielsen L, Cuadrado ML, Pareja JA.
465 Generalized mechanical pain sensitivity over nerve tissues in patients with
466 strictly unilateral migraine. Clin J Pain 2009; 25: 401-6.
467 **17.** Engstrøm M, Hagen K, Bjørk M, Stovner LJ, Stjern M, Sand T. Sleep quality,
468 arousal and pain thresholds in tension-type headache: a blinded controlled
469 polysomnographic study. Cephalalgia 2014; 34: 455-63.
470 18. ICHD-III Headache Classification Subcommittee of the International Headache
471 Society: The International Classification of Headache Disorders, 3 edition.
472 Cephalalgia 2018; 38: 1-211
473 19. Phillip D, Lyngberg AC, Jensen R. Assessment of headache diagnosis: a
474 comparative population study of a clinical interview with a diagnostic headache
475 diary. Cephalalgia 2007; 27: 1-8.
476 20. Jensen MP, Turner JA, Romano JM, Fisher L. Comparative reliability and validity
477 of chronic pain intensity measures. Pain 1999; 83: 157-162.
478 21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta
479 Psychiatr Scand 1983; 67: 361-70.
480 22. Herrmann-Lingen C, Buss U, Snaith RP. Hospital Anxiety and Depression Scale–
481 Deutsche Version (HADS-D) Verlag Hans Huber, Bern; 2011.
482 23. Juang KD, Wang SJ, Lin CH, Fuh JL. Use of the Hospital Anxiety and Depression
483 Scale as a screening tool for patients with headache. Zhonghua Yi Xue Za Zhi
484 (Taipei) 1999; 62: 749–55.

485 24. Fischer AA. Application of pressure algometry in manual medicine. J Man Med
486 1990; 5: 145-150.
487 25. Chesterson LS, Sim J, Wright CC, et al. Inter-rater reliability of algometry in
488 measuring pressure pain thresholds in healthy humans, using multiple raters. Clin
489 J Pain 2007; 23: 760-766.
490 26. Fingleton C, Dempsey L, Smart K, Doody CM. Intra-examiner and inter-examiner
491 reliability of manual palpation and pressure algometry of the lower limb nerves
492 in asymptomatic subjects. J Manipulative Physiol Ther 2014; 37: 97-104.
493 27. Pedersini P, Negrini S, Cantero-Tellez R, Bishop MD, Villafañe JH. Pressure
494 algometry and palpation of the upper limb peripheral nervous system in subjects
495 with hand osteoarthritis are repeatable and suggest central changes. J Hand Ther.
496 2019 Jan 21. pii: S0894-1130(17)30424-6.
497 28. Walton DM, Macdermid JC, Nielson W, Teasell RW, Chiasson M, Brown L:
498 Reliability, standard error, and minimum detectable change of clinical pressure
499 pain threshold testing in people with and without acute neck pain. J Orthop Sports
500 Phys Ther 2011; 41: 644-50
501 29. Ylinen J, Nykänen M, Kautiainen H, Häkkinen A. Evaluation of repeatability of
502 pressure algometry on the neck muscles for clinical use. Man Ther 2007; 12: 192-
503 7
504 30. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is
505 related to sensitization: A population study. Pain 2006; 123: 19-27.
506 31. Woolf CJ. Central sensitization: uncovering the relation between pain and
507 plasticity. Anesthesiology 2007; 106: 864-867.

32. Fernández-de-las-Peñas C. Myofascial Head Pain. Curr Pain Headache Rep 2015; 19: 28

33. Schmid AB, Hailey L, Tampin B. Entrapment neuropathies: Challenging common beliefs with novel evidence. J Orthop Sports Phys Ther 2018; 48: 58-62.

34. Hansson P. Difficulties in stratifying neuropathic pain by mechanisms. Eur J Pain 2003; 7: 353-7.

35. Ferragut-Garcías A, Plaza-Manzano G, Rodríguez-Blanco C, Velasco-Roldán O, Pecos -Martín D, Oliva-Pascual-Vaca J, Llabrés-Bennasar B, Oliva-Pascual-Vaca A. Effectiveness of a treatment involving soft tissue techniques and/or neural mobilization techniques in the management of tension-type headache: A Randomized Controlled Trial. Arch Phys Med Rehabil 2017; 98: 211-219

36. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10 years of research on sex/gender and experimental pain perception - part 1: are there really differences between women and men? Pain 2012; 153: 602-1

37. Zwart JA, Dyb G, Hagen K et al. Depression and anxiety disorder associated with headache frequency: The Nord-Trøndelag Health Study. Eur J Neurol 2003; 10: 147-52.

38. Benatto MT, Bevilaqua-Grossi D, Carvalho GF et al. Kinesiophobia is sssociated with migraine. Pain Med 2019; 20: 846-851.