Title

Evaluation of Neurodynamic Responses in Women with Frequent Episodic Tension Type Headache

Abstract

Background: Current theories associated with the cause of tension type headache are mostly focused on muscle tissues. No study has investigated the presence of role of nerve tissues in this population.

Objective: Our aim was to examine the responses to different mechanical provocation tests of the nerve tissues in women with tension type headache when compared to healthy women.

Design: A case-control cross-sectional study.

Methods: Differences in range of motion and sensory responses (intensity and location) during the Passive Straight-Leg Raise Test (SLR), Long Sitting Slump test (LSS) and Seated Slump test (SLT) were assessed in 32 women with frequent episodic tension type headache (FETTH) and 32 age-matched healthy women.

Results: Women with FETTH demonstrated bilateral and significantly reduced range of motion in all tests ($P<0.001$) and also higher sensory responses in the LSS and SLT (both $P<0.001$), but not in the SLR (all $P>0.422$), compared to the healthy women. The location of sensory responses was also significantly different for the SLT ($P<0.05$).

Conclusion: The current study observed generalized lower mechanical pain thresholds to different provocation tests of the nerve tissues in women with FETTH supporting the presence of heightened nerve sensitivity to mechanical stimuli in this population. Future trials should investigate the efficacy of neurodynamic techniques in the clinical evolution of TTH.

Key words: Tension type headache, nerve tissues, neurodynamic, sensitization.

Evaluation of Neurodynamic Responses in Women with Frequent Episodic Tension Type Headache

Introduction

Tension type headache (TTH) is probably the most common headache disorder seen by neurologists with a global annual prevalence of 42% in the general population (Ferrante et al, 2013). In the last Global Burden of Disease Study, headache was found to be the second most prevalent pain condition in the world (Vos et al, 2017).

Although the pathophysiology of TTH is not completely understood, it appears to be associated with altered nociceptive pain processing (De Tommaso and Fernández-de-las-Peñas, 2016). It seems that continuous afferent bombardment to the central nervous system could lead to both peripheral and central mechanisms in TTH (De Tommaso and Fernández-de-las-Peñas, 2016). Several theories involving muscle tissues have been proposed for explaining TTH-related pain (Fernández-de-las-Peñas, 2015); however, most of these theories have excluded the role of nerve tissue. Identification of a potential role of nerve tissue could increase the current knowledge of underlying mechanisms of TTH and open new therapeutic strategies.

Nerve tissue may become irritated as a consequence of inflammatory processes and may sensitize C-fiber nociceptors producing ectopic discharges to the central nervous system (Bove and Light, 1997). Nerve sensitivity can be investigated by application of non-noxious mechanical stimuli (e.g. manual palpation), assessment of pressure pain sensitivity (i.e., pressure pain thresholds) or assessment of sensitivity to a mechanical stimulus (e.g., neural provocation tests) (Hall and Elvey, 1999). Sterling et al found generalized hyperalgesic responses to mechanical stimulation of neural tissues within the upper extremity in individuals with chronic whiplash associated disorders (Sterling et al, 2002). It would be interesting to determine if individuals with headaches also exhibit hyperalgesic responses to mechanical stimulation of nerve tissues.

The recommended neurodynamic tests in subjects with headaches mostly include the slump test and associated variations (Shacklock, 2005). The slump test is considered a general test influencing the entire longitudinal aspect of the nervous system (Shacklock, 2005). There are a small number of studies investigating the mechanical responses of nerve tissues in patients with headaches. Szikszay et al observed higher sensory responses during the long sitting slump test in adults with unilateral head/neck pain (Szikszay et al, 2018); whereas Von Piekartz et al reported similar results in children with cervicogenic or migraine headache (Von Piekartz et al, 2007). On the contrary, Zito et al did not find differences in neural tissue sensitivity between patients with cervicogenic or migraine headache and a control group (Zito et al, 2006). No study has previously investigated the responses to clinical tests of mechanical provocation of nerve tissue in patients with TTH. Therefore, the aim of our study was to investigate the response to several mechanical provocation tests of nerve tissues in women with TTH compared to healthy asymptomatic women. We hypothesized that women with TTH would exhibit higher sensory responses during mechanical provocation tests of the nerve tissue than healthy women.

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 (ICHD-III, 2018). In all subjects, headache features, temporal profile and family history were collected through the clinical history. To be included, patients had to describe the typical features of TTH: bilateral location, pressing/tightening pain, mild/moderate intensity (≤6 on a 10 points numerical pain rate scale, NPRS) and no aggravation of headache during physical activity (ICHD-III, 2018). Only photophobia or phonophobia was permitted in those individuals with a high frequency of attacks. Only individuals with frequent episodic tension-type headache (FETTH) were included in the current study. Exclusion criteria included: 1, any chronic headache; 2, other primary or secondary headaches including medication overuse headache (ICHD-III, 2018); 3, history of head or neck trauma (i.e., whiplash); 4, cervical herniated disk or cervical osteoarthritis based on medical records; 5, any systemic degenerative disease, e.g., rheumatoid arthritis, lupus erythematous; 6, diagnosis of fibromyalgia; 7, had received anaesthetic blocks or physical treatment the previous 6 months; 8, higher levels of anxiety or depressive symptoms; or, 9, pregnancy.

A control group without history of a headache diagnosis and without reporting a headache pain attack over the previous year, matched by age to the headache group, was recruited from the general population by local announcements. 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 participation in the study.

Self-reported measures

Subjects completed a headache diary for 4 weeks to complement the diagnosis of TTH and to record headache clinical features (Phillip et al, 2007). An 11-point numerical pain rate scale (NPRS, 0: no pain-10: maximum pain) was used to determine headache intensity in the diary (Jensen et al, 1999). The headache diary was used to registered the number of days with headache (days per week); the mean of intensity (NPRS) and the duration (hours per day) of the headache.

The burden of headache was measured with the headache Disability Inventory (HDI) (Jacobson et al, 1995). It consists of 25 items for evaluating the impact of headache in both emotional functioning and daily life activities. Each item includes YES (4 points), SOMETIMES (2 points) and NO (0 points) responses. The emotional burden (HDI-E maximum score 52) is assessed with 13 items, whereas the physical burden (HDI-P, maximum score: 48) is assessed with the remaining 12 items. A greater score on each domain suggests a greater burden of headache. This questionnaire has good stability at short and long-term (Jacobson et al, 1995).

The Beck Depression Inventory (BDI-II) is a 21-item self-reported screening scale evaluating the affective, cognitive and somatic symptoms of depression (Beck et al, 1996; Beck et al, 1988). Participants were asked to choose from a group of sentences that best described how they had been feeling in the preceding 2 weeks. All items are rated on a 4-points scale ranging from 0 to 3 based on severity of each item (absent, mild, moderate, and severe). Subjects are classified with no depression with scores less than 13, mild depression if the score ranges from 14 to 19, moderate if ranges from 20 to 28, and severe depression if ranges from 29 to 63 (Beck et al, 1988). This questionnaire has shown good internal consistency.

Passive Straight-Leg Raise Test

The passive SLR test examines the sensitivity of the lumbo-sacral nerve roots (**Fig. 1**). Subjects were placed in a supine position with their legs straight. A gravitational inclinometer (Bi-Level Inclinometer, US Neurologicals©) was fixed just distal to the tibial tuberosity. The examiner passively lifted the tested leg into hip flexion with the knee fixed in full extension. A positioning splint (Orliman©) was used to maintain a fixed ankle position in either plantar flexion (30º) or in neutral (0º) dorsiflexion (Boyd et al, 2009). The passive SLR performed with neutral position of the ankle (0º) as the reference test and plantar flexion of the ankle (30º) was considered the sensitized test (Boyd, 2012). The hip flexion range of motion in either neutral and plantar flexion of the ankle was measured when participants felt discomfort or pain sensation (ONSET 1) and maximum tolerable pain sensation during 5sec (ONSET 2). The assessor explained carefully to the participants the difference between discomfort/pain or tolerance level in a familiarization session. The mean of 3 trials on each position with each leg was calculated with a 30-s resting period between each measure. Boyd et al (2009) found excellent reliability of hip flexion measurements at the onset of symptoms (ONSET 1) on the same day (ICC 0.78 to 0.96) and the minimal detectable change (MDC) for hip flexion range of motion ranged from 1.5º to 3.4º in healthy individuals (Boyd, 2012). Additionally, the intensity of pain elicited during the passive SLR test at both first pain sensation and maximum tolerable pain sensation was also recorded. The order of leg assessment (right, left) was randomized between subjects.

Long Sitting Slump test (LSS)

This test is a modification of standard slump test. In the current study, we followed the same procedure as described by Von Piekartz et al (Von Piekartz et al, 2007) in children with cervicogenic headache (**Fig. 2**). Both legs of subjects were placed straight against the table with dorsal flexion of the ankle. A restraining belt was placed 10cm above the base of the patella to ensure that the posterior aspect of the knee contacted the table. In this position, the subject was asked to perform the greatest possible spinal flexion position. The spinal flexion range of motion, in relation to the lumbo-sacral region, was collected with a hand inclinometer. The position had to be maintained for 5 secs. Starting from this position, maximum active cervical flexion was performed next. The degrees of active cervical flexion range were measured with a Cervical Range of Motion (CROM®) SP-5060 and the intensity was assessed. The mean degrees of three trials was calculated with a 30-s resting period between each measure. The reliability of this procedure has been found to be high (ICC 0.89 to 099) and the MDC has been reported to be 7.9º (Von Piekartz et al, 2007).

In the current study, we evaluated the spinal flexion, cervical flexion range of motion, the intensity of the sensory response (NPRS, 0-10) and location of the sensory response (lower extremity, lumbar, thoracic, or cervical spine, head or none) as previously described (Von Piekartz et al, 2007).

Seated Slump test (SLT)

The SLT assesses the mechanical sensitivity of the nervous tissue (Johnson and Chiarello, 1997). Subjects were asked to sit on the edge of the table with their knees together and popliteal crease at the edge of the table. The sequence of movements was as follows where subjects were asked to: 1, place their hands behind their back; 2, slump as much as possible at the mid- and lower back, while the examiner placed the hand at the cervicothoracic junction to monitor neck position; 3, conduct a cranio-cervical flexion, with the instruction to bring the chin close to the breastbone, as much as possible. In this position, the therapist fixed the cervical spine position; 4, dorsally flexed the ankle as far as possible, position that the therapist maintained; and 5, perform a knee extension as far as possible (**Fig. 3**). In the current study, the knee extension range of motion (degrees), pain intensity (NPRS, 0-10) and the location of the sensory response (legs, low back, thoracic, cervical, head or none) was recorded. The mean of three trials in each leg was calculated with a 30-s resting period between each measure. This test has shown a sensitivity of 0.91 and specificity of 0.70 to identify neuropathic pain in the lower extremity (Urban and MacNeil, 2015). Additionally, the SLT has excellent intra- and inter- explorer reliability with correlation coefficients of 0.95 and 0.92, respectively (Gabbe et al, 2004). The order of leg assessment (right, left) was randomized between individuals. All outcomes were evaluated by an assessor blinded to the subject's condition

Statistical analysis

Data were analyzed with the SPSS statistical package (21.0 version). Descriptive data was collected on all patients. Results are expressed as mean ± SD. The Kolmogorov-Smirnov test revealed that all data showed a normal distribution ($P>0.05$); therefore, parametric tests were used in the analysis. Differences in the cervical range of motion and sacrum position (LSS test) between groups were assessed with the unpaired Student t test. A mixed-model analysis of variance (ANOVA) test was used to evaluate the differences of range of motion in each test (PSLRT: ONSET 1 or 2 with 30º plantar flexion, ONSET 1 or 2 with neutral position and SLT) with side (dominant/nondominant) as within-subject factor and group (patients or controls) as between-subject factor. The X^2 *test* was used to analyze the differences in the distribution of pain sensory response (legs, low back, thoracic, cervical, head or none) for dominant or nondominant SLT and LSS tests within both groups. Finally, the Pearson correlation test (r) was used to determine the association between the range of motion in all tests, the intensity of pain sensory responses and the clinical variables relating to symptoms. The statistical analysis was conducted at a 95% confidence level, and a P-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Data of the Sample

Fifty-two consecutive women who presented with headache were screened for eligibility criteria. Twenty subjects were excluded: migraine (n = 8), chronic tension type-headache (n = 6), previous whiplash (n = 4), higher levels of depression (BDI-II>13) and anxiety (n=2). 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%CI 1.1, 1.7) hours per day with headache, and 5.4 (95%CI 5.0, 5.8) points of headache intensity per attack. No significant association between headache intensity, frequency, or duration was observed (all, P>0.7). The HDI score was 29.2 (95%CI 25.5, 32.8) and the BDI-II score was 3.6 (95%CI 2.3, 4.9). A significant positive relationship (r_s=0.388, P=0.034) between HDI and headache intensity was found: the greater the intensity of the headache, the greater the headache burden.

In addition, 32 matched women without headache history, aged 18 to 21 years (mean age: 22±1 years) were recruited as a control group.

Passive Straight-Leg Raise Test

Table 1 shows hip range of motion for both sides within each group. Women with FETTH exhibited less bilateral flexion with 30º plantar flexion and neutral ankle position than healthy control since the mixed-model ANOVA revealed significant between-groups differences for hip flexion range of motion (ONSET 1 - 30º PF: F=21.924, P<0.001; ONSET 2-30ºPF: F=29.351, P<0.001; ONSET 1-ankle neutral position: F=19.321, P<0.001; ONSET 2-ankle neutral: F=27.800, P<0.001) but not between sides (ONSET 1-30º PF: F=0.043, P=0.836; ONSET 2-30º PF: F=1.603, P=0.208; ONSET 1-ankle neutral position: F=0.016, P=0.900; ONSET 2-ankle neutral position: F=0.145, P=0.704).

Table 2 shows pain scores for both sides within each group. Women with FETTH exhibit similar discomfort/pain sensation (ONSET 1) and similar maximum tolerable pain sensation (ONSET 2) than controls since the mixed-model ANOVA did not reveal any significant between-groups difference and between-sides in pain intensity for ONSET1 and ONSET2 in both ankle positions ($P>0.422$)

Long Sitting Slump test (LSS)

Tables 1-2 also summarize cervical range of motion and pain levels, respectively for each group. As it can be observed, women with FETTH had less cervical flexion and greater intensity of sensory response than healthy control during the LSS since significant between-groups differences were observed for cervical flexion ($t=-2.814$, $P<0.001$) and the intensity of sensory response ($t=3.603$, $P<0.001$). No significant differences ($t=1.460$, $P=0.149$) for spinal flexion were reported between groups: women with FETTH showed similar sacrum position (in degrees) than controls during the LSS.

Table 3 details the location of pain during the LSS in both groups. Pain within the lower extremity (41%) was the most prevalent sensory response, followed by pain in the thoracic and cervical spine in both groups. The location of sensory responses during the LSS was not significantly different ($X^2=5.693$, $P=0.337$) between groups.

A significant negative, but small, correlation between headache history and cervical flexion during the LSS ($r_S=-0.37$, $P=0.035$) was found: the greater the headache history, the lower the cervical flexion range of motion on the LSS. No other significant correlation between headache pain features and LSS was observed (all, $P>0.1$)

Seated Slump test (SLT)

As it can be observed on tables 1-2, women with FETTH exhibited less bilateral knee extension range of motion and greater pain intensity responses than healthy controls since the mixed-model ANOVA revealed significant differences between groups, but not between sides, for knee extension (group: $F=33.949$; $P<0.001$; side: $F=0.037$; $P=0.847$) and intensity of sensory response (group: $F=12.334$; $P<0.001$; side: $F=0.156$; $P=0.694$).

Table 3 details the location of pain during the SLT in both groups. Sensory pain in the lower extremities were the most prevalent location in both groups; however, women with FETTH exhibited significantly higher pain responses in the cervical spine (dominant side: 25%; nondominant side: 22%) than healthy women (none). The location of pain was significantly different between women with FETTH and controls for dominant ($X^2=8.908$, $P=0.031$) and non-dominant ($X^2=8.575$, $P=0.036$) sides.

Intensity of sensory response and headache clinical variables

The frequency of headache showed significant, but small, negative correlations with hip flexion range of motion during the SLR at ONSET 1 at both 30º PF ($r=-0.416$; $P=0.01$) and ankle neutral position ($r=-0.390$; $P=0.02$): the higher the frequency of the headaches; the less the hip flexion range of motion during the SLR.

Discussion

The results of this study indicate that women with FETTH exhibited generalized lower mechanical pain thresholds to different clinical tests of mechanical provocation of nerve tissues such as the SLR, the LSS and the SLT. Lower thresholds were manifested by decreased range of motion in all tests and higher reports of pain in 2 out of 3 tests, as compared to asymptomatic subjects, and the responses were mostly bilateral.

While this is the first study examining the response to mechanical stress to neural structures in women with FETTH, the results are similar to what has been reported in children with cervicogenic or migraine headaches. Von Piekartz et al (2007) observed increased pain responses in the lower extremities in children with migraine while those experiencing cervicogenic headache were more likely to experience increased responses in the spine region. Interestingly, in the population of women with FETTH we found that main differences in sensory responses were also greater in the spine (cervical) suggesting possible similar physiological mechanism between cervicogenic headache and FETTH, at least from nerve tissue sensitization point of view. However, future studies are needed to examine this hypothesis.

These lower thresholds to mechanical stress of neural structures could be related to the presence of heightened nerve mechanical sensitivity potentially due to an increased responsiveness of nociceptive neurons to potentially non-noxious stimuli (Woolf, 2007). The presence of heightened nerve mechano-sensitivity in women with FETTH could also support a potential role of nerve trunk pain in this condition. In such a scenario, peripheral sensitization of neural tissues may act as nociceptive barrage to the central nervous system and alter pain mechanisms. In fact, it has been suggested that excessive peripheral afferent stimulation found in subjects with nerve tissue involvement may drive central adaptations potentially leading to chronic pain (Schmid et al, 2018). Furthermore, it has been reported that nerve endings located in the nervi nervorum may be stimulated by lower thresholds of stimuli potentially resulting in neurogenic inflammation (Bove and Light, 1997). These sensitized nociceptors may result in a prolonged barrage of impulses resulting in ectopic activity in the dorsal root ganglion and result in central hyperexcitability (Hansson, 2003). Although most theories support a role of muscle tissues in TTH (Fernández-de-las-Peñas, 2015; De Tommaso and Fernández-de-las-Peñas, 2016); our results would also suggest a potential role of nerve tissues in the pathogenesis of this headache. This hypothesis would be confirmed if treatment of sensitized neural tissues would lead decrease the symptoms experienced by patients with TTH. A randomized clinical trial found that the inclusion of neural mobilization techniques into a multimodal treatment approach was effective for decreasing headache features and pressure pain hypersensitivity in individuals with TTH (Ferragut-García et al, 2017). These results support a potential involvement of nerve tissue mechanical pain sensitivity in the clinical course of TTH (Ferragut-García et al, 2017). Further studies are needed to confirm the effectiveness of neural interventions on TTH.

Nevertheless, it should be recognized that neural tension tests were not structurally differentiated by using sensitizing movements of distal areas, such as the ankle, in patients with headache (Shacklock, 2005). Therefore, it is not possible to confirm whether or not the applied tests could be considered as positive from a neurodynamic perspective in our sample of women with FEETH since we did not evaluate the reproduction of headache symptoms. In fact, the reduced range of motion and exacerbated pain responses observed in our sample of women with FETTH may be attributed to different tissues, and not just exclusively to nerve tissues. This hypothesis should also be taken into account since we did not exclude previous history of thoracic, lumbar or lower extremity symptoms which could have also contributed to hyperalgesic responses found in the tests used in this study.

Finally, we should recognize limitations to the current study. First, since headache is more prevalent in females than males with a ratio of 3:1 (Manzoni and Stovner 2010), and due to gender differences in nociceptive pain processing (Racine et al, 2012), we only included women with FETTH. Therefore, our results should not be extrapolated to men with TTH. Similarly, we do not know if these results would be similar in patients with chronic tension-type headache. Larger population-based studies examining the sensitivity of neural structures including people with the chronic form, will assist with increasing the generalizability of the results. Second, the results must be understood in the context of the study considering the methodology (lack of structural differentiation) and inclusion and exclusion criteria (symptoms in potential places related to hyperalgesic responses). In fact, it should be also considered that some of the outcomes used, e.g., SLT or LSS, in the study could be not accurate if not properly controlled. Third, we did not collect outcomes such as kinesiophobia, fear avoidance or pain catastrophizing which often can also accompany persistent pain conditions and may result in heightened central nervous system. Similarly, also did not assess other outcomes which could determine the presence of sensitization of the central nervous system, e.g., central sensitization inventory, and if the presence of nerve sensitivity could also be related to the presence of sensitization. Finally, the study design does not allow us to make inferences regarding if the heightened nerve mechano-sensitivity identified in this study proceed the onset of the headache.

Conclusion

In the current study, women with FETTH exhibited generalized lower mechanical pain threshold to some neurodynamic tests purported to stress sensitized neural structures. These findings suggest the presence of heightened nerve mechanical sensitivity in women with FETTH which may drive the sensitization processes in this population. Futures studies should examine the effects of treating neural tissues in the clinical course of TTH.

Legend of Figures

Figure 1: Neurodynamic testing set-up for the Straight-Leg Raise (SLR) test.

Figure 2: Test position of the Long Sitting Slump (LSS) test. Measurement of the spinal flexion during LSS as Von Piekartz et al (2007)

Figure 3: Neurodynamic testing set-up for the Seated Slump test (SLT)

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