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Active Trigger Points are Associated with Anxiety and Widespread Pressure Pain Sensitivity in Women, but not Men, with Tension Type Headache

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Background: A better understanding of gender differences can assist clinicians in further developing therapeutic programs in tension type headache (TTH). Objective: To evaluate gender differences in the presence of trigger points (TrPs) in the head, neck, and shoulder muscles and their relationship with headache features, pressure pain sensitivity, and anxiety in people with TTH. Methods: Two hundred and ten (59 men, 151 women) TTH patients participated. TrPs were bilaterally explored in the temporalis, masseter, suboccipital, upper trapezius, splenius capitis and sternocleidomastoid muscle Headache features were collected with a 4-week headache diary. Trait and state anxiety levels were assessed with State-Trait Anxiety Inventory. Pressure pain thresholds (PPT) over the temporalis, C5/C6 joint, second metacarpal and tibialis anterior were assessed. Results: Women with TTH exhibited a significantly higher number of total (P=0.027) and active (P=0.030), but similar number of latent (P=0.461), TrPs than men with TTH. Active TrPs in the temporalis, suboccipital, and splenius capitis muscles were the most prevalent in both men and women with TTH. The number of active TrPs was associated with anxiety levels (r=0.217; P=0.045) in women, but not in men (P=0.453): the higher the number of active TrPs, the more the trait levels of anxiety. Women exhibited lower PPTs than men (all, P<0.001). In men, the number of active, but not latent, TrPs was negatively associated with localized PPTs (all, P<0.05), whereas in women, the number of active and latent TrPs was negatively associated with PPTs in all points (all, P<0.01): the higher the number of TrPs, the lower the widespread PPTs. **Conclusions**: This study described gender differences in the presence of TrP in TTH. Women with "TTH showed lower PPT than men. The association between TrPs, anxiety levels, and pressure pain hyperalgesia seems to be more pronounced in women than in men with TTH.

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Introduction

Tension type headache (TTH) is a common primary headache disorder showing a worldwide point prevalence of 42%.¹ In fact, in the Global Burden of Disease Study, headaches were found to be the second most prevalent disorder in the world.² Further, TTH also represents an important burden for the society.³ For instance, the general costs in Europe in 2010 were €13.8 billion for headache, including migraine and TTH.⁴

Current knowledge into the pathogenesis of TTH is mainly focused on the role of muscle tissue and facilitation of nociceptive pain processing.⁵ It is argued that TTH has a muscular component contributing to sensitization process related to the transition from acute to chronic TTH.^{6,7} There is clear evidence suggesting that people with TTH exhibit pressure pain hypersensitivity, i.e., lower pressure pain thresholds, in trigeminal- areas,⁸ cervical-related areas,⁹ and distant extra-trigeminal areas¹⁰ when compared to non-headache sufferers. Similarly, there is also evidence supporting the role of referred pain elicited by muscle trigger points (TrPs) as peripheral contributors to TTH.¹¹ A TrP is defined as "a hypersensitive spot in taut bands of skeletal muscle which elicit referred pain, autonomic, and motor symptoms when stimulated".¹² Several studies have found that the referred pain elicited by TrPs reproduced the pattern pain symptoms in patients with TTH.¹³ In fact, Fernández-de-las-Peñas et al proposed a pain model where the TrPs located in those muscles innervated by the trigeminal or upper cervical nerves would be responsible of prolonged nociceptive afferent

barrage into the trigeminal nerve nucleus caudalis, sensitizing the central nervous system, and thereby contributing to widespread sensitization found in TTH.¹⁴ This pain model has been partially confirmed by a recent study reporting that a greater number of TrPs in head, neck and shoulder muscles was associated with widespread pressure pain hypersensitivity in individuals with TTH.¹⁵ In addition, the number of active TrPs has been also associated with trait anxiety levels,¹⁶ another factor contributing to central sensitization by reducing the thresholds to noxious input from peri-cranial muscles.¹⁷

It is important to consider that primary headache, including TTH, exhibit gender differences in their prevalence.¹⁸ In fact, TTH has a female: male ratio of 3:1.¹⁹ Since evidence suggests the presence of gender differences in pain perception,²⁰ particularly in sensitivity to pressure pain,²¹ brain structure development and function,²² previous life experiences and cultural expectations,²³ and biopsychosocial factors associated with pain experience,²⁴ a better understanding of gender differences in the presence of TrPs in TTH could assist clinicians in determining better therapeutic programs accordingly to gender. Interestingly, it has been previously suggested that headache relationships differ according to gender since sex influences on primary headache phenotype are a complex process and needs examination in a greater number of studies.²⁵ However, no study has previously investigated this topic. Therefore, the purpose of this study was to evaluate gender differences in the relationship with clinical features of headache, widespread pressure sensitivity and anxiety levels in men and women with TTH.

Methods

Participants

Patients with headache symptoms were recruited from different university-based hospitals between September 2016 and June 2018. Diagnosis was conducted according to the International Classification of Headache Disorders criteria, third edition²⁶ by four experienced neurologists.²⁶ To be included, patients had to describe the pain features typical of TTH: bilateral location, pressing/tightening pain, moderate intensity (\leq 7 on a 10-points numerical pain rate scale, NPRS) and no aggravation of headache during routine physical activity. Patients should report neither more than one of photophobia, phonophobia, or nausea and neither moderate nor severe nausea nor vomiting as requested by the ICHD-III diagnostic criteria.²⁶

Participants were excluded if presented: 1, other primary or secondary headache including medication overuse headache as defined by the ICHD-III; 2, history of neck or head trauma; 3, history of cervical herniated disk on medical records; 4, any systemic disease, e.g., rheumatoid arthritis, or lupus erythematous; 5, diagnosis of fibromyalgia syndrome; 6, receiving anesthetic block or physical therapy in the previous 6 months; or, 7, pregnancy. Participants read and signed a consent form prior to their participation. The local Ethics Committee approved the study design (URJC 23/2014, HUFA 14/104).

Headache Diary

A headache diary for 4 weeks was used to substantiate the diagnosis and to record the headache clinical features.²⁷ On this diary, patients registered the number of days with headache (days/week), the headache intensity on an 11-points numerical pain rate scale²⁸ (NPRS; 0: no pain, 10: the maximum pain), and the duration of each headache attack (hours/day).

Trigger point (TrP) examination

Trigger Points (TrPs) were explored bilaterally in the temporalis, masseter, upper trapezius, suboccipital, sternocleidomastoid and splenius capitis muscles by a clinician with more than 15 years of experience in TrP diagnosis. The order of examination was randomized between subjects with a 1min rest period between muscles. The diagnosis was conducted following the updated criteria originally described by Simons et al¹³ and recommended in a recent Delphi study:²⁹ 1, presence of a palpable taut band in a skeletal muscle; 2, presence of a painful spot within the taut band, and, 3, presence of referred pain in response to manual compression. For the suboccipital musculature, the protocol as described by Fernández-de-las-Peñas et al was applied.³⁰ In this study, active and latent TrPs were analysed. A TrP was considered active when the referred pain elicited during the examination reproduced, totally or partially, the pain pattern that the subject suffered from during the headache attacks, and, therefore, the pain was recognized as a usual/familiar pain symptom.^{13,29}

Widespread Pressure Pain Sensitivity

Pressure pain threshold (PPT), i.e., the amount of pressure where a sensation of pressure first changes to pain, was also bilaterally assessed with an electronic algometer (Somedic AB®, Farsta, Sweden) over the temporalis muscle (trigeminal point), cervical spine (extra-trigeminal point), second metacarpal, and tibialis anterior muscle (two pain-free distant points). The order of assessment was randomized between subjects. Pressure was increased at a rate of approximately 30kPa/s. Participants were trained with a first trial on the wrist extensors of the right forearm for familiarization of the procedure. The mean of 3 trials on

each point was calculated and used for the analysis. A 30sec-resting period was allowed between trials for avoiding temporal summation.³¹ The reliability of pressure algometry over these areas has been found to be high.^{32,33} Since no side-to-side differences in PPTs were found, the mean of both sides on each point was used in the main analysis.

State-Trait Anxiety Inventory (STAI)

The STAI is a 40 items scale assessing the state (items 1-20, STAI-S) as well as trait levels (items 21-40, STAI-T) of anxiety.³⁴ The STAI-S items assess relatively enduring symptoms of anxiety. Participants use a 4-points response scale ranging from "not at all" to "very much", to indicate the extent to which they experience each emotion. The STAI-T items assess stable propensity to experience anxiety, and tendencies to perceive stressful situations as threatening. Participants use a 4-points response scale to rate how they generally feel. In both scales, higher scores indicate greater state or trait levels of anxiety. Both scales have shown good internal consistency and high reliability.³⁵

Statistical analysis

Data were analyzed with the SPSS statistical package (22.0 Version). Means and confidence intervals were calculated for all the outcomes by gender. The Kolmogorov-Smirnov test revealed that all data exhibited a normal distribution (P>.05). Differences in headache clinical data (i.e., frequency, intensity or duration), anxiety, the number of TrPs (active or latent TrP) and PPTs between men and women were assessed with the unpaired Student t-test. The chi square (χ 2) test was used to assess gender differences in the distribution of TrPs (active or latent) for each muscle. The Pearson correlation test (r) was used to determine the associations between the number of active or latent TrPs, anxiety (STAI-S, STAI-T), PPTs, and clinical variables relating to headache (frequency, intensity, duration) in men and women separately. Correlations were considered weak when r<0.3,

moderate when 0.3 < r < 0.7, and strong when r > 0.7.³⁶ The statistical analysis was conducted at a 95% confidence level, and a P-value less than 0.05 was considered statistically significant.

Results

Two hundred and fifty (n=250) subjects with headache were screened for eligibility criteria. Of these, 59 men and 151 women satisfied all the criteria, agreed to participate and signed the informed consent. Forty patients (16%) were excluded for the following reasons: co-morbid migraine (n=25), previous neck trauma (n=6), medication overuse headache (n=6), and fibromyalgia diagnosis (n=3). Demographic and clinical data are listed in **Table 1**. No gender differences were observed for clinical data (all, P>.299) except for trait levels of anxiety (t=2.419; P=.017): women showed higher trait levels of anxiety than men (**Table 1**).

Trigger points in men and women with tension type headache

The mean number of TrPs in the selected and examined muscles for each man with TTH was 5.3 ± 4.0 (active TrPs: 4.0 ± 3.3 ; latent TrPs: 1.3 ± 2.0), whereas the number of TrPs on each woman with TTH was 6.5 ± 3.5 (active TrP: 5.9 ± 2.8 , latent TrP: 1.5 ± 2.3). Women exhibited a significantly higher number of total (t=2.231; P=0.027) and active (t=2.187; P=0.030) but similar number of latent (t=0.739; P=0.461), TrPs than men. The distribution of TrPs in the analyzed musculature was only significantly different for the temporalis and suboccipital muscles between men and women with TTH (both, P<0.05) but not for the remaining muscles (all, P>0.156): women exhibited a greater proportion of active TrPs in the temporalis and splenius capitis muscles were the most prevalent in either men or women with TTH (**Table 2**).

No associations were observed between the number of active TrPs and any clinical pain feature of headache, i.e., intensity, frequency or duration, for either men or women with TTH (all, P>0.202). The number of active TrPs was significantly and positively associated with

trait anxiety levels (STAI-T: r=0.217; P=0.045) in women, but not in men (P=0.453): the higher the number of active TrPs, the more the trait level of anxiety.

Pressure pain sensitivity in men and women with tension type headache

In general, women exhibited lower PPTs than men in all point (all, P<0.001). **Table 1** summarizes PPTs of men and women with TTH.

In men with TTH, the number of active, but not latent, TrPs was significantly and negatively associated with PPTs within trigeminal (temporalis: r=-0.268, P=0.042) and extra-trigeminal (cervical spine: r=-0.337, P=0.01) points, but not with distant pain-free points (second metacarpal: r=-0.157, P=0.338; tibialis anterior: r=-0.139, P=0.397): the higher the number of active TrPs, the lower the localized PPTs in the head and neck in men with TTH.

In women, the number of active was significantly and negatively associated with PPTs in all the points (temporalis: r=-0.313, P<0.001; neck: r=-0.210, P=0.009; second metacarpal: r=-0.256, P<0.001; tibialis anterior muscle: r=-0.258, P<0.001): the higher the number of active TrP, the higher the widespread pressure pain sensitivity, i.e., the lower the widespread PPTs. Similar findings were obtained between the number of latent TrPs and PPTs (temporalis muscle: r=-0.213, P=0.008; cervical spine: r=-0.169, P=0.037; second metacarpal: r=-0.380, P<0.001; tibialis anterior muscle: r=-0.297, P<0.001): the higher the number of latent TrP, the higher the widespread pressure pain sensitivity.

Discussion

This study found that women with TTH exhibited a significantly higher number of active, but similar number of latent, TrPs than men with TTH. The number of active TrPs was weakly associated with anxiety levels and widespread pressure hyperalgesia in women, but not in men with TTH. Our findings suggest the presence of potential gender differences in the role of TrPs between men and women with TTH.

There is consistent evidence supporting that pain referral elicited by active TrPs reproduces headache features in people with TTH;^{11,13-16} however no previous study has investigated if the presence of TrPs is different by gender. The current study is the first one reporting gender differences in the presence of TrPs and its associations in individuals with TTH. We found that women exhibited higher number of active TrPs and similar number of latent TrPs, than men with TTH. Active TrPs in the temporalis, suboccipital and splenius capitis muscles were the most prevalent in general, however, the proportion of active TrPs in the temporalis and suboccipital muscles was higher in women. A potential underlying mechanism for this finding may be related to sex-related differences in muscle architecture. Animal studies have observed that female rats show greater cross-sectional areas of type I fibers in skeletal muscles, while male rats have more type IIb fibers.³⁷ Similarly, human studies reported that men had larger muscle fibers³⁸ and more type II muscle fibers than women.³⁹ These muscular differences could explain the higher prevalence of myofascial pain syndromes in female.⁴⁰ Nevertheless, other studies have not observed differences in the number and presence of active TrPs between men and women in other conditions, e.g., knee osteoarthritis.⁴¹ It is possible that some body areas or specific muscles would be more sensitive to this sex-difference.

An interesting finding was the association, although weak, of active TrPs with trait anxiety levels in women, but not men, with TTH. Previous studies have reported that higher levels of anxiety increase the likelihood of muscular tenderness.^{42,43} In fact, general distress is a risk factor for the presence of muscle referred pain.⁴⁴ Therefore, this would support the fact that people with higher levels of trait anxiety also exhibit a greater number of active TrPs; however, that situation was significant in women, but not men, with TTH. There is evidence supporting that anxiety symptoms are more frequent in women than in men (female: male ratio 1.8:1),⁴⁵ which agrees with our results since women with TTH also reported higher

levels of trait anxiety than men with TTH. Thorn et al. determined that gender differences in response to pain stimulus could be partially attributed to potential disparities in personality traits, i.e., emotional vulnerability, between men and women.⁴⁶ Therefore, biological, cultural, and experiential factors may underlie gender differences on the presence of mood disorders, e.g., anxiety, and its association with pain.⁴⁷

The current study also observed lower PPTs in women with TTH as compared to men which is in agreement with current evidence since there is strong evidence showing that female had greater sensitivity to pressure stimuli than male²¹ and that activation of conditioned pain modulation analgesia is reduced in female than in male.⁴⁸ There are several underlying mechanisms explaining the gender differences in pain perception but their discussion is beyond the scope of this paper.²¹ In addition, we also observed gender differences in the association between the TrPs and pressure pain hyperalgesia since a greater number of active TrPs was weakly associated with higher widespread pressure pain sensitivity in women with TTH, but associated with localized pain sensitivity in men. These results would suggest that the association between active TrPs and pressure pain hyperalgesia previously observed in patients with TTH⁴⁹ would seem to be more pronounced in women than in men. These associations can suggest that spatial (greater number of) summation of the nociceptive barrage from active TrPs could lead to central sensitization in a more pronounced manner in women than in men with TTH supporting the theoretical pain model proposed by Fernández-de-las-Peñas et al.¹⁴ Current findings also agree with a study showing that experimental-induced muscle pain is able to inhibit descending pain modulation in female but not in male.⁴⁸ Therefore, anatomical³⁷⁻³⁹ and neurophysiological²¹ gender differences would suggest that muscle pain could be more relevant in women than in men.

Uncertainty over biological mechanisms withstanding in gender differences, our results have potential clinical implications for the management of patients with TTH.⁵⁰ First, proper identification of active TrPs reproducing the headache symptoms is highly relevant in individuals with TTH; nevertheless, since a greater number of active TrPs is related to higher widespread pressure hypersensitivity, suggesting spatial summation of TrP activity, in women with TTH, identification of all potential affected muscles maybe highly relevant in women. In fact, there is preliminary evidence suggesting the presence of multiple TrPs in the temporalis muscle in women with TTH⁵¹ Therefore, it is possible that clinical presentation of muscle TrPs could be slightly different between women and men with TTH and, hence, carefully clinical examination should be conducted. Second, a recent meta-analysis provided preliminary evidence suggesting that manual treatment of active TrPs may be effective for TTH; however, the quality of evidence was still low because of the presence of few studies and the imprecision of results.⁵² It is possible that the results of our study provide a potential explanation for discrepancies in the effects of TrP treatment. Since the number of active TrPs were associated with anxiety levels and widespread pressure pain sensitivity in women, but not in men, with TTH; management of women with TTH should include psychological aspects and central nervous system therapeutic strategies and not just tissue-based (just TrP manual therapies) interventions.

Although strengths of the current study include a large sample size, the inclusion of patients accordingly the most updated diagnostic criteria, the use of diagnostic diaries and the use of standardized examination procedures; our study has also some potential limitations. First, we included patients referred to a tertiary headache center and thus not representative of the general headache population. Second, the study was cross-sectional and causal relations should not be inferred. Third, TrP diagnosis is still a controversial topic due to lack of golden clinical standards; nevertheless, we conducted a restrictive diagnostic criterion.^{13,29} Finally,

we did not evaluate socioeconomic status, a factor associated with TTH in women, since women are more susceptible to socioeconomic influences.⁵³

Conclusions

This study found gender differences in the presence of TrPs in TTH. Women with TTH exhibited higher number of active TrPs and lower widespread PPT than men with TTH. Further, the number of active TrPs was weakly associated with anxiety levels and widespread pressure pain hyperalgesia in women but associated with localized pressure pain hyperalgesia in men. Future longitudinal studies will help to determine the clinical implications of these findings.

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| T | able 1: Clinical | and demographic characterist | ics of patients by ger | nder | |
|------------------------------|------------------|--------------------------------|------------------------|---------------|--|
| | Mon (n-50) | | Women (n-151) | | |
| | Mean | 95%CI | Mean | 95%CI | |
| | | Clinical Data | | | |
| CTTH/FETTH | 30/29 | | | 77/74 | |
| Age (years) | 44 | 41 - 47 | 45 | 42 - 48 | |
| | | Headache Pain Characteristics | | | |
| Time of onset (years) | 11.2 | 8.2 - 13.2 | 10.3 | 8.0 - 12.6 | |
| Frequency (days/month) | 15.5 | 11.4 - 19.6 | 15.5 | 11.8 - 19.2 | |
| Intensity (NPRS, 0-10) | 6.1 | 5.7 - 6.5 | 6.0 | 5.7 - 6.3 | |
| Duration (hours/day) | 7.4 | 6.1 - 8.7 | 7.4 | 6.6 - 8.2 | |
| Prophylactic treatment (Y/N) | | 14/45 | 40/111 | | |
| | | Psychological Outcomes | | | |
| STAI-S (state, 0-60) | 21.6 | 19.8 - 23.4 | 21.7 | 20.6 - 22.8 | |
| STAI-T (trait, 0-60)* | 21.4 | 19.0 - 23.8 | 24.5 | 23.2 - 26.8 | |
| A | | Psychophysical Outcomes | | | |
| PPT cervical spine (kPa)# | 311.0 | 265.0 - 357.0 | 194.0 | 178.0 - 210.0 | |
| PPT temporalis muscle (kPa)# | 263.5 | 235.0 - 292.0 | 193.5 | 180.5 - 206.5 | |
| PPT second metacarpal (kPa)# | 322.5 | 291.5 - 353.5 | 232.0 | 208.0 - 256.0 | |
| PPT tibialis anterior (kPa)# | 505.0 | 418.5 - 591.5 | 353.5 | 330.0 - 377.0 | |

* Significant differences between women and men with tension type headache (P<0.05);

Significant differences between women and men with tension type headache (P<0.001);

CTTH: Chronic Tension Type Headache; FEETH: Frequent Episodic Tension Type Headache; STAI: State-Trait Anxiety Inventory; PPT: Pressure Pain Thresholds

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| | Temporalis in men (n=59)* | | Masseter in men (n=59) | | Sternocleidomastoid in men (n=59) | |
|------------------------|-------------------------------|------------------|--------------------------------|------------------|------------------------------------|------------|
| | Right Side | Left Side | Right Side | Left Side | Right Side | Left Side |
| Active TrPs n (%) | 27 (46%) | 29 (49%) | 16 (27%) | 16 (27%) | 16 (27%) | 19 (33%) |
| Latent TrPs n (%) | 11 (18%) | 10 (17%) | 9 (15%) | 10 (17%) | 12 (21%) | 9 (15%) |
| No TrPs n (%) | 21 (36%) | 20 (34%) | 34 (58%) | 33 (56%) | 31 (52%) | 31 (52%) |
| | Temporalis in women (n=151)* | | Masseter in women (n=151) | | Sternocleidomastoid in women (n=15 | |
| | Right Side | Left Side | Right Side | Left Side | Right Side | Left Side |
| Active TrPs n (%) | 100 (66%) | 99 (65.5%) | 50 (33%) | 41 (27%) | 50 (33%) | 48 (31.5%) |
| Latent TrPs n (%) | 22 (14%) | 18 (12%) | 28 (18.5%) | 32 (21%) | 40 (26.5%) | 40 (26.5%) |
| No TrPs n (%) | 30 (20%) | 34 (22.5%) | 73 (48.5%) | 78 (52%) | 61 (40.5%) | 63 (42%) |
| | Upper trapezius in men (n=59) | | Splenius capitis in men (n=59) | | Suboccipital in men (n=59)* | |
| | Right Side | Left Side | Right Side | Left Side | Bilateral | |
| Active TrPs n (%) | 20 (34%) | 18 (31%) | 25 (43%) | 27 (46%) | 25 (42%) | |
| Latent TrPs n (%) | 10 (17%) | 6 (10%) | 4 (7%) | 3 (5%) | 6 (10%) | |
| No TrPs n (%) | 29 (49%) | 35 (59%) | 30 (50%) | 29 (49%) | 28 (48%) | |
| Upper trapezius in wor | | in women (n=151) | Splenius capitis | in women (n=151) | Suboccipital in women (n=151)* | |
| | Right Side | Left Side | Right Side | Left Side | Bilateral | |
| Active TrPs n (%) | 69 (46%) | 65 (43%) | 81 (54%) | 87 (57%) | 96 (63.5%) | |
| Latent TrPs n (%) | 22 (14.5%) | 17 (11%) | 14 (9%) | 9 (6%) | 16 (10.5%) | |
| No $T_n D_n n (0/)$ | 60 (39 5%) | 69 (16%) | 57 (37%) | 56 (37%) | 39 (26%) | |

Table 2: Distribution of active and latent trigger points (TrPs) by gender

* Significant differences between women and men with tension type headache (P<0.05)