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Temporomandibular Disorder is Prevalent in Chronic Migraine

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Abstract

Background: The aim of this study is to analyse the prevalence of pain-related and intra-articular temporomandibular disorder (TMD) in both episodic migraine (EM) and chronic migraine (CM) and to explore signs of central sensitization (CS) in this patient population.

Methods: A total of eighty patients with CM and 42 patients with EM as defined by the International Classification of Headache Disorders, third edition (beta version) (ICHD-3) were enrolled. TMD was diagnosed according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD). Subgroup analysis - low-frequency EM (n = 22) (less than 4 headache days per month, LFEM) vs. high-frequency EM and CM (n = 89) (over 10 headache days per month, HFEM and CM) - was also performed.

Results: The prevalence of myofascial TMD was higher in CM as compared to EM (52.5% vs. 28.6%, respectively, p = .01). Even larger differences were observed between HFEM and CM and LFEM (51.7% vs. 18.2%, respectively, p = .007). No differences in the prevalence of intra-articular TMD were observed. The prevalence of bruxism was significantly lower than that of TMD in the HFEM and CM population (31.4% vs. 51.7%, respectively, p = .01). The level of anxiety was comparable in HFEM and CM patients with and without TMD.

Conclusions: This study demonstrated high prevalence of myofascial TMD in our CM and HFEM and populations significantly exceeding TMD prevalence in LFEM. Such high prevalence of TMD in high-frequency migraine and CM could not be accounted for by bruxism or anxiety. Patients with CM-in our study-had a higher risk of developing TMD (odds ratio (OR) 2.76 (95% CI 1.24 - 6.15, p = .01)).

Keywords: *Migraine; Chronic Migraine; Comorbidity; Headache; Temporomandibular Disorder, Central Sensitization*

Abbreviations

BR: Blink Reflex; BTA: Botulinum Toxin Type A; CI: Confidence Interval; CM: Chronic Migraine; CS: Central Sensitization; DC-TMD: Diagnostic Criteria for Temporomandibular Disorders; EM: Episodic Migraine; HA: Headache; HADS: Hospital Anxiety and Depression Scale; HFEM: High-Frequency Episodic Migraine; ICHD-3: International Classification of Headache Disorders, 3rd Edition; ICSD: International Classification of Sleep Disorders; LFEM: Low-Frequency Episodic Migraine; MOH: Medication-Overuse Headache; NFR: Nociceptive Flexion Reflex; OR: Odds Ratio; PREEMPT: Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy; RR: Relative Risk; SD: Standard Deviation; TMD: Temporomandibular Disorder; TMJ: Temporomandibular Joint; VAS: Visual Analogue Scale

Introduction

Temporomandibular disorder (TMD) is a group of conditions involving the temporomandibular joint (TMJ), muscles of mastication, and associated surrounding tissues. The prevalence of TMD has still not been firmly established; possibly due to different adopted diagnostic criteria and is believed to be in the range of 3 - 15% [1]. Studies of general populations have reported an overall prevalence of myofascial TMD at 9.7% [2]. In clinical samples, myofascial TMD is also the most common form of the disorder (47.7%), followed by disk displacement with reduction (36.6%) and arthralgia (33.8%) [3]. The current DC/TMD classify TMD into pain-related and intra-articular disorders with myofascial TMD belonging to the first group [4].

Myofascial TMD is commonly comorbid with other conditions, and the association is the strongest for headaches (HA). Gonçalves., *et al.* found that individuals with myofascial TMD were significantly more likely to suffer from chronic daily headaches (relative risk (RR): 7.8; 95% confidence interval (CI) 3.1 - 19.6); migraine (RR: 4.4; 95% CI 1.7 - 11.7), and tension-type headache (RR: 4.4; 95% CI 1.5 - 12.6) in comparison with individuals without TMD pain [5]. Of all headaches migraine is the most closely associated [6] and chronic migraine (CM) seems to be the most common of all chronic daily headaches. For example, TMD prevalence rates range from 53% to 87% in migraine sufferers and reach 91% and even 100% in CM, with myofascial TMD being the most prevalent form [7-9]. Other authors have shown the magnitude of association with painful TMD to be 13.7 times higher for CM (odds ratio (OR) = 95.9; 95% CI 12.51 - 734.64) as compared with episodic migraine (EM) (OR 7.0; 95% CI 3.45 - 14.22) [10]. Moreover, unlike patients with EM, CM sufferers tend to present with more severe TMD [11].

The increased comorbidity of TMD and CM (as compared to EM) may mean that migraine and myofascial TMD progression share the same predisposing factors and have common underlying peripheral and/or central mechanisms [12,13].

In migraineurs, greater ictal and interictal sensitization has been reported to be a consequence of the TMD co-occurrence. Some authors have demonstrated more severe cutaneous allodynia and significantly lower nociceptive thresholds to mechanical and heat stimuli in cephalic and extracephalic areas tested with a pressure algometer and quantitative sensory testing in patients with concomitant migraine and TMD as compared to control groups [11,14]. Nevertheless, neurophysiological methods to test for the presence of central sensitization (CS) in migraine and TMD have so far not been employed. Meanwhile, nociceptive flexion reflex (NFR) has been reported to be a reliable measure of central sensitization in fibromyalgia and other chronic pain conditions [15,16].

Understanding the association between TMD and frequent migraine is very important from a clinical perspective. These patients seem to have an additional pain burden and disability, and be more resistant to treatment [11].

Despite increased interest and emerging studies on CM and TMD, evidence of their association using formal diagnostic criteria is still very scarce. The aim of this study is to analyse the prevalence of pain-related and intra-articular TMD in EM and CM and to explore signs of CS in this patient population. The initial hypothesis was that the prevalence of TMD, and particularly myofascial TMD, would be higher in CM patients and these patients would also demonstrate signs of CS in neurophysiological tests as we assume that CS may underlie the strikingly increased comorbidity between migraine and TMD.

Materials and Methods

A total of 122 patients with migraine, including 80 patients with CM and 42 patients with EM were enrolled. All subjects were recruited at a private tertiary headache centre - the Alexander Vein Headache Clinic - in Moscow, Russia.

This study was conducted in accordance with accepted ethical standards for research practice and underwent review and approval by the Ethics Committee of I.M. Sechenov Moscow State Medical University. Written informed consent was obtained from all participants prior to their enrolment.

The inclusion criterion was a diagnosis of CM or EM, according to the International Classification of Headache Disorders, third edition (beta version) (ICHD-3) [17]. The diagnosis was made by a headache neurologist specialist during patient consultation. Only patients presenting at the consultation during their mildest headaches (HA) or when headache-free were enrolled (the pain intensity range was 0 - 5 cm on the 10-cm visual analogue scale (VAS), with a mean intensity of 2.1 cm). Patients who first presented during a HA exacerbation could be included during their next consultation at the time of no/mild HA. Patient demographics data as well as headache history were recorded, and a complete neurological examination was performed to exclude secondary headaches. Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS) [18]. HADS defines depression/anxiety as absent at 0 - 7 points, subclinical at 8-10 points and clinical at over 11 points.

The exclusion criteria for all groups were individuals under 18 or over 65 years of age and the presence of peripheral neuropathy or a major psychiatric disorder (except for mild or moderate depression and anxiety). Participants were only those who have never taken or independently stopped any antidepressants or anticonvulsants or have taken 'rescue' medications within six hours before commencing the examination.

All patients were examined by specialized neurologist for the presence of pain-related and intra-articular TMD according to the DC/TMD diagnostic criteria [4]. EM patients were included at least 48 hours after the attack. This was done to avoid a false positive TMD diagnosis since the area of hyperalgesia and allodynia during an acute headache may be widespread and include muscles of mastication innervated by the trigeminal nerve.

Sleep bruxism was diagnosed with the International Classification of Sleep Disorders (-Revised) (ICSD-R) minimal criteria [19] and it was assessed by participants' self-reporting, answering the question: "Do you grind your teeth or clench your jaw during sleep?". If a 'yes' answer was obtained, additional questions were asked: "Has someone complained of grinding sounds?" and "Do you feel discomfort of the jaw muscles in the morning?" The diagnosis required at least one positive response to the additional questions. According to an international consensus, self-reports of bruxism can be defined as possible bruxism [20].

To evaluate antinociceptive function, NFR and blink reflex (BR) were measured in the first 47 consecutive patients with HFEM or CM. Briefly, BR is an electromyographic investigation assessing the threshold of blinking in response to electric stimulation of the supraorbital nerve. The threshold of the ultralate component (R3) was measured, which probably follows a multisynaptic trigeminal pathway in the medullar reticular formation involving antinociceptive structures such as periaqueductal gray and raphe nuclei and mediated by activation of cutaneous A- delta fibres [21]. The NFR R3 component assesses activation of myelinated A- delta fibres and eventually supraspinal structures in response to noxious stimulation of the sural nerve [16]. The detailed methodology and reference values have been previously described elsewhere [22]. The NFR method has gained particular attention as a research tool in studies of central sensitization [16].

Statistical Analysis

All analyses were performed with the Statistica 12 software (Statsoft). The independent samples t-test was used for between-group comparisons of patient demographics, clinical characteristics, NFR and BR data, and HADS scores. Fisher's exact test was used to compare proportions. Significant difference was set at a two-tailed p value of $< .05$. Continuous values are presented as mean ± standard deviation (SD).

Results

Demographic and clinical characteristics of the patient population are presented in table 1. There were no significant differences between groups in age, gender composition or age of HA onset. Average headache frequency was 5.3 days per month in EM and 25.1 days per month in CM ($p < .01$). Fifty percent (50%) of CM patients had concomitant medication-overuse headache (MOH).

	EM (n = 42)	CM (n = 80)	p
Sex (male/female)	4/38	8/72	.6
Age (years)	35.0 ± 12.2	37.3 ± 10.2	.27
HA frequency (days/month)	5.3 ± 3.5	25.1 ± 4.7	.005*
Age of HA onset (years)	17.3 ± 5.9	18.0 ± 7.6	.77
Body mass index (BMI)	21.8 ± 3.5	24.6 ± 5.0	.005*
Anxiety (HADS), points	6.7 ± 3.4	8.8 ± 4.6	.03*
Depression (HADS), points	4.1 ± 3.4	6.8 ± 3.5	.0006*

Table 1: *Study population demographics and clinical characteristics.*

**: Significant differences.*

HA: Headache; HADS: Hospital Anxiety and Depression Scale.

Compared to EM, CM patients had higher anxiety levels, which corresponded to HADS-defined subclinical anxiety (Table 1). Depression levels were also significantly higher in the CM population, being however very low in both groups (HADS-defined absence of depression).

The study population was divided into two subgroups based on HA frequency. The first group included patients with HA frequency ≤ 4 days per month (low-frequency EM, LFEM, n = 22); the second group included patients with HA frequency over 10 days per month (high-frequency EM (HFEM) plus CM, n = 89). The remaining eleven patients had 5 - 9 HA days and were excluded from this analysis. There is evidence to suggest that patients with 10 or more HA days per month have practically no clinical differences compared with CM patients [23]. As with the CM population, HFEM patients show poor outcomes in functional and emotional disability.

In both subgroups (HFEM and CM and LFEM), anxiety and depression were absent or subclinical (8.7 ± 4.0 vs. 6.3 ± 3.1 for anxiety, p = .07; 6.4 ± 3.4 vs. 3.6 ± 3.2 for depression, p = .006, respectively).

The prevalence of pain-related TMD was higher in the CM group as compared to EM (52.5% vs. 28.6%, respectively, p = .01) (Table 2). All patients had myofascial pain with spreading or referral. Patients with CM had a higher risk of developing TMD (odds ratio (OR) 2.76 (95% CI 1.24 - 6.15, p = .01)). The distinction was even more pronounced when HFEM and CM were compared to LFEM (51.7% vs. 18.2%, respectively; p < .007) (Figure 1). In the MOH subgroup the prevalence of TMD was 57.5% and comparable to that in CM (p = .37).

	LFEM (n = 22) (≤4 days/ month)	**HFEM and CM (n = 89) (≥ 10 days/month)**	**EM (n-42) (≤14 days/ month)**	**CM (n = 80) (≥ 15 days/ month)**	p
TMD, % (n)	18.2% (4)	51.7% (46)	28.6% (12)	52.5% (42)	.01* (CM vs. EM); .007* (LFEM vs. HFEM and CM)
Pain-related TMD, % (n)	18.2% (4)	51.7% (46)	28.6% (12)	52.5% (42)	.01*(EM vs. CM); .007*(LFEM vs. HFEM and CM)
Intra-articular TMD, % (n)	4.5% (1)	11.2% (10)	4.7% (2)	12.5% (10)	.1 (EM vs. CM); .7 (LFEM vs. HFEM and CM)
Bruxism, % (n)	18.2% (4)	31.4% (28)	16,7% (7)	27,5% (22)	.26 (EM vs. CM) .3 (LFEM vs. HFEM and CM)

Table 2: *TMD Prevalence in EM and CM.*

**: Significant differences.*

TMD: Temporomandibular Disorder; EM: Episodic Migraine; CM: Chronic Migraine; LFEM: Low Frequency Episodic Migraine; HFEM: High Frequency Episodic Migraine

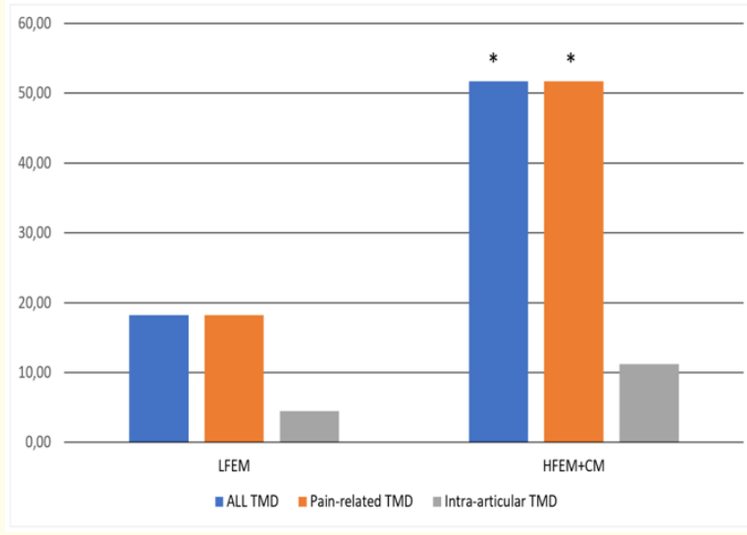

Figure 1: *Prevalence of TMD in LFEM and HFEM and CM populations.*
Prevalence of TMD in LFEM compared to the HFEM and CM population, p = .007 for pain-related TMD, p = .7 for intra-articular TMD.
**: Significant differences LFEM vs. HFEM and CM.*

The prevalence of intra-articular TMD was similar in all groups (Table 2). Amongst the population of this study, intra-articular TMD co-existed with pain-related TMD and was not observed separately.

The prevalence of sleep bruxism was similar in both groups (18% vs. 31.4% in LFEM and HFEM and CM, respectively, p = .3). In the HFEM and CM population the prevalence of TMD significantly exceeded that of bruxism (51.7% vs. 31.4%, respectively, p = .01). In LFEM, at the same time, the prevalence of bruxism was similar to that of TMD (Table 2). None of the patients had a history of TMJ trauma. Anxiety levels were similar in the HFEM and CM population with and without TMD (8.8 ± 4.9 vs. 8.6 ± 4.2, respectively, p = .9).

Neurophysiologically, in the CM population the BR R3, NFR R3 and NFR pain thresholds were significantly lower than the previously reported respective reference values for headache-free subjects [22]. At the same time, no significant differences in BR and NFR thresholds were detectable between HFEM and CM populations (Table 3). The BR and NFR R3 thresholds were also comparable across CM and HFEM patients with and without TMD (BR 7.11 ± 3.0 vs. 7.09 ± 2.3, respectively, p = .98, NFR 7.17 ± 4.3 vs. 6.89 ± 3.9, respectively, p = .8).

	HFEM	CM	p
NFR; pain	5.8 ± 2.4	6.3 ± 3.7	.6
NFR; R3 (mA)	7.0 ± 3.0	7.0 ± 4.6	.99
BR; R3 (mA)	6.6 ± 2.8	7.2 ± 2.6	.5

Table 3: *NFR and BR Thresholds in HFEM and CM.*

NFR: Nociceptive Flexion Reflex; BR: Blink Reflex; HFEM: High-Frequency Episodic Migraine; CM: Chronic Migraine; NFR pain: Nociceptive Flexion Reflex Pain Threshold; NFR R3: Nociceptive Flexion Reflex R3 Threshold; BR R3: Blink Reflex R3 Threshold.

Discussion

This study shows that TMD is much more prevalent in CM compared to EM and the general population. Notably, the risk of CM sufferers reporting TMD signs and symptoms is almost three times as great. This remarkable association has also been reported by others [5-7,10,24].

As with other studies [5,7-10] all individuals with TMD presented with myofascial pain although the prevalence was higher in CM. The prevalence of intra-articular disorders was markedly lower and did not vary with increasing HA frequency. This may suggest that muscular TMD could be strictly associated with headaches. This may also mean that muscular tenderness and myofascial pain may be explained by pathological mechanisms underlying chronic HA unrelated to the TMJ function.

In this study the prevalence of TMD has been found to be higher with increasing HA frequency. TMD is more closely associated with frequent (not only chronic) migraine. Recently, some clinicians have suggested that HFEM may represent a "pre-chronic migraine" state [25]. Data from the research being discussed here support this hypothesis, with the prevalence of pain-related TMD in HFEM and CM significantly higher when compared to LFEM. Furthermore, this study has not found any neurophysiological differences in pain thresholds between HFEM and CM, suggesting that central pain control is disrupted in patients with migraine frequency over 10 days a month.

Sleep bruxism may play a role in the relatively high prevalence of TMD in LFEM. However, it cannot be a significant cause of pain-related TMD in HFEM and CM, as its prevalence is significantly lower than that of TMD.

Given that this is a cross-sectional study, it has not been possible to establish a cause-effect relationship between TMD prevalence and migraine chronification. Two hypotheses may be suggested to explain the relationship between migraine and TMD. Firstly, TMD may be a consequence of CS underlying migraine chronification.

Widespread pain and hyperalgesia are signs of CS, and the area may spread from the head to the face, decreasing the threshold for pain and tenderness in the muscles of mastication. It is noteworthy that TMD and cervicalgia seem to be the most prevalent chronic pain conditions comorbid to CM suggesting that trigeminal sensitization rather than peripheral pain sources is the underlying process.

According to the current criteria, these symptoms (familiar pain with muscle palpation) would be classified as pain-related TMD. In line with this hypothesis, some authors have shown that the presence of hyperalgesia and allodynia in both the trigeminal and extra-trigeminal regions among women with a painful TMD indicated the presence of CS [26]. Also, female patients with myofascial TMD, when compared to healthy controls, exhibited a bilateral and widespread decrease in pressure pain threshold in joint and muscle tissue both in the craniofacial region and in sites remote from the source of pain in these conditions, such as the fingers [27]. This study has also demonstrated decreased NFR and BR thresholds in patients with CM and TMD as evidence of CS. Contreras., *et al.* have shown that patients with TMD and migraine have significantly more comorbid painful conditions such as cervicalgia and back pain compared to those presenting with only painful TMD, suggesting underlying trigeminal and even extra-trigeminal CS [28].

The second hypothesis which might explain the relationship between CM and TMD is that TMD may itself become a source of peripheral nociceptive input to the trigeminovascular system which would aggravate CS and, consequently, contribute to migraine chronification. For example, Dahan., *et al.* have shown that individuals with myofascial TMD have a higher prevalence of self-reported migraine than those with non-myofascial TMD [29].

Both hypotheses of this study may prove to be true, simultaneously forming a self-perpetuating, vicious cycle (Figure 2). Other research has found more pronounced levels of hyperalgesia (especially in extracephalic sites) and cutaneous allodynia in patients with concomitant TMD and migraine, as compared to patients with only one condition, suggesting that the concomitant presence of TMD and migraine may be related to intensification of CS [11,30].

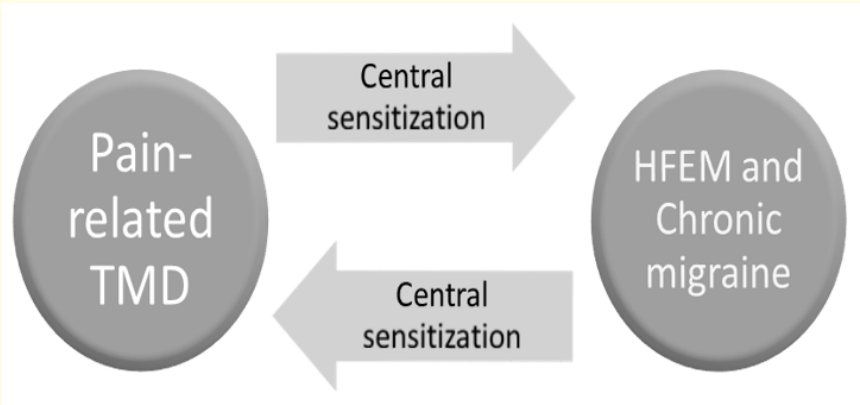

Figure 2: *TMD may be both a cause and consequence of central sensitization in patients with frequent migraine.*

The clinical relevance of the present study includes a better understanding of the relationship between migraine and TMD with an emphasis on factors that might underlie their striking comorbidity. CM is a complex disorder for which meticulous search and management of any comorbid condition is mandatory in many cases. Consequently, therapeutic strategies targeting TMD would be helpful for migraine sufferers. The only currently available study of comprehensive migraine management has shown that parallel treatment of TMD may improve migraine outcomes [31]. However, it is suggested here that myofascial TMD may be viewed as nonspecific musculoskeletal pain, very similar to nonspecific low back pain where TMJ problems are only a minor factor if at all. Splints and night guards only reduce peripheral nociceptive input, while muscular tenderness and pain might be a consequence of CS. Moreover, it has been shown that patients with TMD exhibiting signs of CS respond differently to physical therapy, with exercise increasing pain severity [12,32], necessitating more tailored approaches where myofascial TMD in some patients is viewed as a sign of dysfunctional pain control.

Such patients with TMD may require, for instance, tricyclic antidepressants. There is also emerging evidence of botulinum toxin type A (BTA) efficiency in TMD [33]. The potent effect of repeated BTA injections in CM has been shown in Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical trials and further real-life studies [34-36]. It is thought to be due to its ability to block the

release of pronociceptive substances and indirectly reduce CS [37]. In addition to temporal, masseter and pterygoid muscle relaxation and reduced nociceptive trigeminal input, this 'central' action might increase the efficacy of BTA in patients with myofascial TMD and signs of CS, especially those suffering from CM. Further studies are warranted to evaluate the effectiveness of comprehensive CM treatment programmes.

Limitations

This study has two main limitations. Firstly, because a cross-sectional study design has been used, causality between TMD prevalence and migraine cannot be identified. Furthermore, the sample was recruited from a specialized private clinic, and the frequency of more severe conditions with multiple co-morbidities might be overestimated because the participants were already seeking treatment.

Conclusion

The prevalence of pain-related TMD was high in migraine and, particularly, in high-frequency migraine. The prevalence of intra-articular TMD was, in contrast, low and not related to migraine frequency. The study corroborates the previously postulated association between TMD and HA. Moreover, the association of pain-related TMD with migraine frequency opens the discussion of TMD as a possible risk factor for migraine chronification.

Acknowledgements and Conflict of Interest

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