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Update of Chronic Tension-Type Headache

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Abstract Tension-type headache (TTH) is the most common type of primary headaches, and its chronic form, chronic tension-type headache (CTTH), is affecting 0.5 to 4.8 % of the worldwide population. Although the mechanism underlying CTTH remains unclear, the role of central versus peripheral mechanisms has always been discussed while explaining the pathogenesis of CTTH. There is always a debate on differential diagnosis between CTTH and chronic migraine without aura which are regarded as different aspects of chronic daily headache spectrum because of many similarities and fuzzy boundaries. Compared with pharmacological treatments, non-pharmacological treatments have been popular as alternative interventions for CTTH in recent years. This review summaries the update knowledge on CTTH and discusses the most interested questions regarding pathogenesis and therapeutic strategies of CTTH.

Keywords Chronic tension-type headache · Chronic daily headache · ICHD · Epidemiology · Pathophysiology · Diagnostics

Introduction

Tension-type headache (TTH) is the most prevalent primary headache disorder worldwide [1]. As its chronic form, chronic tension-type headache (CTTH), is one of the most neglected types of headache to treat [2], decreasing greatly quality of life of patients and giving a high economic burden on society.

By its very definition according to the International Classification of Headache Disorders, third edition (beta version) (ICHD-3 beta), CTTH is defined as the occurrence of TTH at a frequency of ≥15 days per month, with typically bilateral, pressing, or tightening in quality, and of mild to moderate intensity, lasting hours to days, or unremitting. The pain does not worsen with routine physical activity but may be associated with mild nausea, photophobia, or phonophobia [3]. Because the exact mechanism of TTH is still poorly understood, the term tension-type has been maintained from ICHD-I [4] to ICHD-3 beta [3, 5]. Given there are many similarities and differences between CTTH and chronic migraine (CM), the diagnostic criteria of CTTH has been improved for its differential diagnosis between the two disorders.

The mechanisms of CTTH may be multifactorial, including peripheral mechanisms and central mechanisms, as well as genetic and psychological factors. Numerous studies have revealed central pain mechanisms play a dominate role in CTTH. The complicated interrelation among the various pathophysiologic aspects of CTTH just might explain why there are so many multimodal therapeutic strategies (pharmacological and non-pharmacological) to manage this disorder.

In this review, we evaluate recent data on the epidemiology, pathophysiology, diagnostics, and specific therapeutic strategies of CTTH.

Epidemiology

Despite being the most prevalent headache type, there is still a relative lack of epidemiologic studies of TTH when compared to that for migraine, in which CTTH is always the most neglected type. Previous epidemiologic data on the prevalence of CTTH are heterogeneous and differ from 0.5 to 4.8 % [6•,

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7–18] (Table 1). The wide variation of estimated prevalence in CTTH might be due to differences in age profiles, racial background, environment, and data collection methodology.

Unlike migraine, TTH is almost as common in men as in women, with a 4:5 male-to-female ratio. As for CTTH, the prevalence reported by several studies seems to be higher in female than male [11, 12, 14, 15]. A largest-scale twins study reported the 1-year prevalence of CTTH in Denmark was 0.9 % with a higher preponderance in women (1.3 %) than in men (0.5 %) [15]. According to Russell et al., CTTH is rare in persons 12–14 years old, and the prevalence of CTTH increased until age 39 and then declined in both sexes [15]. CTTH is a common subtype of chronic daily headache (CDH), which likely be an umbrella term for a group of headache disorders occurring at least 15 days per month but not be universally recognized [19]. The CDH population comprises individuals with CTTH and CM, both of which may often be associated with medication overuse. CTTH is one of the most common subtypes of CDH according to both population-based and clinic-based studies [18, 20–22].

New Sight of Pathophysiology

The exact pathogenesis of TTH remains unclear. Whether TTH originates from peripheral myofascial mechanisms or central mechanisms in the brain is still a matter for debate. Generally, peripheral mechanisms and central mechanisms are intermingled in TTH. It seems that peripheral pain mechanisms are most likely to play a role in episodic TTH, while central mechanisms such as central sensitization might predominate in CTTH.

Peripheral Mechanism

Increased pericranial muscle tenderness and generalized pressure pain hypersensitivity are the most prominent findings in CTTH [23]. Possible peripheral mechanisms leading to pericranial muscle tenderness and pressure pain include inflammatory reaction, decreased blood flow, increased muscle activity, and muscle atrophy. Lots of previous studies have provided in vivo evidences of peripheral muscle abnormal metabolism in the pathophysiology of CTTH [24••]. It has been demonstrated that muscle blood flow is decreased in response to static exercise in tender points in CTTH patients [25], although the concentrations of interstitial lactate as well as inflammatory mediators in the trapezius muscle did not differ between CTTH and healthy controls during both rest and static exercise [25, 26]. Women with CTTH showed greater co-activation of antagonist musculature during cervical extension and flexion contractions than that in healthy women did, which may potentially lead to muscle overload and increased nociception [27].

In electromyographic (EMG) studies, the level of the pericranial muscle activity is higher in CTTH patients than in healthy controls [28], however, the EMG level is not associated with headache severity [29, 30]. Higher hardness of the pericranial muscles has also been observed in patients with CTTH, but there is little association between muscle hardness (measured with a hardness meter) and intensity of headache [31]. As a corollary, a 12-week injection of botulinum toxin injection could lead to decreased EMG level of temporalis in patients with CTTH but no decrease in the headache [32].

Magnetic resonance imaging (MRI) study demonstrated muscle atrophy in selective cervical extensor muscles in

Table 1 Prevalence and demographic features of TTH and CTTH in population-based surveys

Country	Year	Reference	*N*	Age range (years)	Prevalence (%)	
					CTTH	TTH
Italy	2013	Ferrante et al. [7]	904	≥18	0.6	19.4
China	2012	Yu S et al. [17]	5041	18–65	..	10.8
Germany	2012	Yoon et al. [10]	9944	18–65	0.5	11.9
Turkey	2012	Ertas et al. [9]	5323	18–65	..	5.1
Russia	2012	Ayzenberg et al. [8]	2025	18–65	..	30.8
Brazil	2009	Queiroz et al. [16]	3848	18–79	0.8	13
Denmark	2006	Russell et al. [15]	28,195	12–41	0.9	86
Denmark	2005	Lyngberg et al. [13]	207	25–36	4.8	89.4
Denmark	2005	Russell [14]	4000	40	2.3	84.7
Taiwan	2001	Wang SJ et al. [18]	3377	≥15	1.41	..
Chile	1998	Lavados et al. [11]	1385	≥14	2.6	26.9
USA	1998	Schwartz et al. [12]	13,345	18–65	2.2	38.3

..=data not available

CTTH [33]. The relative cross-sectional area (rCSA) of cervical extensor muscles was measured in 15 CTTH patients and 15 health controls, and the reduction of rCSA in rectus capitis posterior muscles was negatively associated with the intensity, duration, and frequency of headache. Nevertheless, this selective muscle atrophy in CTTH as a primary or secondary phenomenon remains unclear.

Central Mechanisms

In addition to peripheral mechanisms, central sensitization following continuous nociceptive input of pericranial muscles may play an important role in the pathogenesis of CTTH. The central nervous system is probably sensitized at both the supraspinal level and the spinal dorsal horn/trigeminal nucleus in patients with CTTH. Recently, the cause-effect relationship between pericranial tenderness and central sensitization is being discussed.

Previous studies hypothesized that the central sensitization seen in CTTH is provoked by peripheral nociception initiated in tender muscle [34] and associated with active myofascial trigger points (MTrPs) in multiple sensitive muscles both in the head and neck [35]. An updated pain model for CTTH involving both peripheral sensitization and central sensitization suggested that CTTH can be explained by referred pain from active MTrPs in the pericranial muscles, mediated through the spinal cord and the trigeminal nucleus caudal (TNC), and then sensitizing the central nervous system [36]. A relevant finding was that MTrPs were responsible for peripheral nociception not only locally [37] but also in distant pain-free regions [38], which could initiate motor and sensory changes in both peripheral and central nervous systems. However, a 12-year follow-up longitudinal study has recently demonstrated that subjects who later would develop CTTH showed normal tenderness scores and pressure pain threshold (PPT) levels before the beginning of the symptoms [39]. In accordance with the adult data, children with CTTH also show significantly increased pain sensitivity in a range of pressures compared to that of the ETTH group and the controls [40]. These findings suggested that pressure pain hypersensitivity and pericranial muscle tenderness might be consequences but not causative factors of CTTH, which may be produced by a central dysfunction.

Genetic Mechanisms

Previous genetic epidemiological studies investigated the familial aggregation of TTH, suggesting genetic factors might also contribute to the pathophysiology of TTH [41, 42]. A preliminary genetic study form Turkey has shown that the presence of STin 2.12/12 genotype and STin 2.12 allele of serotonin transporter gene polymorphisms might play a protective role against CTTH. A recent case-control study investigated the possible role of catechol-O-methyltransferase (COMT) polymorphism (Val158Met) in the genetic susceptibility to CTTH in children [43]. Although the distribution of Val158Met genotypes was not significantly different between children with CTTH and healthy children, nevertheless, CTTH children with the Met/Met genotype showed a longer headache history and lower PPT over upper trapezius and temporalis muscles.

Psychological Mechanisms

Psychological factors also play an important role in the pathogenesis of CTTH, and psychiatric co-morbidities are more common in patients with CTTH than in patients who suffer from other chronic pain syndromes [44]. In Indian population, psychiatric co-morbidity was present in 36.4 % of patients with CTTH [45].

The previous study demonstrated differential roles for anxiety and depression in CTTH [46]. In patients with CTTH, depression and anxiety may aggravate existing central sensitization and cause a higher frequency of headache. Psychosocial stressor is known to be another contributing factor to CTTH with the unclear mechanism, and stress is the most commonly reported trigger of CTTH episode [47]. A central mode of CTTH posited that pain sensitivity might mediate the relationship between stress and headache activity [48], which has been supported by Cathcart et al. recently [49].

Other Possible Mechanisms

CTTH cases with vitamin D deficiency have been reported in India [50], and recently, they further investigate the interrelationships between chronic tension-type headache, musculoskeletal pain, and vitamin D deficiency, suggesting vitamin D deficiency may be an important cause of secondary CTTH by causing musculoskeletal pain or even osteomalacia of the skull [51]. Elevated interleukin-1β levels are associated with CTTH in more recent studies, suggesting neurovascular inflammation may play a potential role in the pathogenesis of CTTH [52].

Classification and Diagnosis

Compared with ICHD-II, the classification and diagnostic criteria for CTTH in ICHD-3 beta are almost the same, as well as the stricter diagnostic criteria in the appendix.

Since CTTH is a syndrome of “featureless” headaches characterized by nothing but pain in the head, diagnostic difficulty is most often encountered between CTTH and mild chronic migraine without aura. The diagnostic criteria of CTTH should be adapted to improve its sensitivity against

chronic migraine, so an alternative stricter criterion which is very specific but has low sensitivity was coined in ICHD-II and maintained in ICHD-3 beta (Table 2). Recently, it is shown that CM and CTTH have slightly different risk factors. In a population-based study from Germany, patients with CTTH had a higher intake of alcoholic beverages and a lower education, while patients with CM were more likely to be female, to smoke, and to be obese [53].

New Sight of Therapeutic Strategies

The complication of various pathophysiologic factors of CTTH might explain why this disorder is so difficult to treat. In fact, most CTTH sufferers do not seek medical advice because of the mild or moderate intensity or self-medicate with analgesic such as paracetamol and codeine [54].

Therapies for CTTH can be divided into pharmacological and non-pharmacological treatment. For most patients with CTTH, the combination of pharmacological therapies and non-pharmacological therapies is recommended. However, the therapeutic efficacy of all these approaches is likely to be controversial.

Pharmacological Treatment

Pharmacological therapies for CTTH can be subdivided into the abortive treatment of each acute exacerbation and long-term, prophylactic treatment. CTTH is generally treated with analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) for abortive treatment, but unfortunately, they are often ineffective in patients with CTTH.

For patients suffering from CTTH, prophylactic therapies help reduce the frequency and severity of headaches. Antidepressants, antispasmodic, new antiepileptics, and some local injections are commonly prescribed options for prophylactic treatment.

Tricyclic antidepressants are the most widely used first-line therapies for CTTH. Amitriptyline, a nonselective tricyclic antidepressant, was the first medication shown to be effective in TTH [54] and remains to be the first-line therapy in treating CTTH. Interestingly, its analgesic property is independent of its antidepressant effect. Although its antinociceptive mechanism is not precisely known, it is believed that the blockade of tetrodotoxin-resistant sodium channels (Nav1.9 and Nav1.8) in nociceptive trigeminal neurons through modulating the activation and inactivation kinetics might contribute to pain control of amitriptyline in treating various headaches [55, 56]. An analysis of 10 related studies supported the recommendation in favor of using amitriptyline in the preventive treatment of CTTH [57]. The treatment usually begins with a low dosage (between 10 and 25 mg before bed) increasing gradually until a considerable decrease or the total disappearance of the symptoms [58]. Surprisingly, many patients can be satisfied by such a low starting dose. In an open randomized study, the combination of tizanidine (4 mg per day) and amitriptyline (20 mg per day) during the first 3 weeks of treatment gave faster relief of headache in patients with CTTH than that of amitriptyline did alone [59]. Other tricyclic antidepressants, such as clomipramine and nortriptyline, doxepin, maprotiline, and mianserin can also be used as a second choice.

Mirtazapine, an antidepressant with both noradrenergic and specific serotoninergic effects, has been found to be as effective as amitriptyline at 15–30 mg per day in treatment of CTTH but has fewer side effects [60]. In a recent double-blind RCT study, however, the combination of low-dose mirtazapine (4.5 mg) and ibuprofen (400 mg) was not

Table 2 ICHD-3 beta diagnostic criteria for CTTH and chronic migraine without aura

	CTTH	Stricter criteria of CTTH	Chronic migraine without aura
	At least two of the following	At least three of the following	At least two of the following four characteristics
Pain features	1. Bilateral location 2. Non-pulsating (pressing/tightening) quality 3. Mild or moderate intensity 4. Not aggravated by routine physical activity		1. Unilateral location 2. Pulsating quality 3. Moderate or severe intensity 4. Aggravation by or causing avoidance of routine physical activity
Associated features	Both of the following: 1. No more than one of photophobia, phonophobia, or mild nausea 2. Neither moderate or severe nausea nor vomiting	No nausea, vomiting, photophobia, or phonophobia	At least one of the following: (on 8 days per month for >3 months) 1. Nausea and/or vomiting 2. Photophobia and phonophobia
Pain lasting time	Hours to days or unremitting		4–72 h (untreated or unsuccessfully treated)
Pain frequency	>15 days per month on average for >3 months (>180 days per year)		Same as CTTH (tension-type like and/or migraine like)

effective for the treatment of CTTH at 8 weeks [61]. Paroxetine, a selective serotonin reuptake inhibitor (SSRIs), was not effective in patients with CTTH who had not responded to tricyclic antidepressant (amitriptyline) [62].

Topiramate (TPM), as an antiepileptic drug, has been shown to be a highly effective and well-tolerated therapy in patients with epilepsy. In a prospective, open-label, long-term study, TPM has been found to be an effective and safe prophylactic agent for CTTH [63]. However, there was no more evidential study to confirm it.

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, had limited benefit in lowering headache intensity in women with CTTH at a dose of 20–40 mg per day according to a double-blind, randomized, crossover clinical trial [64]. The most common side effects were dizziness and nausea.

Botulinum toxin A (BTA) was approved for prophylactic treatment for chronic migraines by the US Food and Drug Administration in October 2010, based on The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program [65, 66]. Recently, BTA has been increasingly advocated as a prophylactic treatment for CTTH. Because of mixed results, its effectiveness in treatment of CTTH is still a matter of debate. Several previous studies reported that BTA was associated with better outcomes than that of placebo [67] and methylprednisolone [68] for CTTH. In an open-label, prospective study, BTA was found to be an effective and safe treatment for CTTH patients resulting in significant reductions in headache frequency, intensity, and analgesic consumption which persisted up to a long term (1 year) [69]. Nevertheless, the previously reported beneficial effects in open-label or single-blind [70] studies have not been confirmed in recent multicentre, randomized, double-blind, placebo-controlled trials [71–73]. A recent pilot study shows a reduction in headache frequency when BTA was directly injected into MTPs, while such results dissipated after 12 weeks [74]. A recent meta-analysis to assess 11 relevant RCTs suggested that BTA was not associated with greater benefit than that of placebo in prophylactic treatment of CTTH [75]. Given the unestablished efficacy of BTA in CTTH may be associated with several adverse effects including facial weakness, difficulty in swallowing, and disturbed local sensation, whether BTA should be used in patients with CTTH needs to be deliberatively determined.

More recently, local application of gonyautoxin [76] or lidocaine [77] was also shown to be effective methods in the treatment of CTTH.

Non-pharmacological Treatment

Since pharmacologic interventions are not optimally effective, interest in non-pharmacologic interventions for CTTH has increased in recent years. Non-pharmacological therapies include behavior treatments, physical therapies, acupuncture, and recent transcutaneous electrical nerve stimulation (TENS), which are often implemented in conjunction with one another or other pharmacological treatments.

Efficacy of behavioral treatments (relaxation training, electromyography biofeedback training, and cognitive behavioral therapy) in the management of CTTH has been empirically validated. Relaxation training and EMG biofeedback therapy could lead to a nearly 50 % reduction in headache activity, both alone and in combination [78]. EMG biofeedback therapy has been seen as an effective form of behavioral therapy that allows patients to learn to develop control over pericranial muscle tension [79]. Cognitive behavioral therapy (CBT), such as stress-management therapy, has been shown to be an effective adjuvant treatment when combined with tricyclic antidepressant (amitriptyline or nortriptyline) in patients who suffer from low-severity CTTH [80, 81]. Although the efficacy of behavioral treatments is well-documented for the treatment of CTTH, there are mixed results recently. A recent systematic review assessed the evidence from RCTs concerning the efficacy of behavioral treatments in adult patients with CTTH, and there is no indication that these behavioral treatments are better than no treatment, waiting list, or placebo controls [82].

In addition, given most behavioral treatments are time consuming for both patients and therapists, a self-management treatment model was also proposed for recurrent chronic headache, including CTTH [83]. The self-management model focuses on empowering and training patients to manage themselves in both behavioral and pharmacological treatment in conjunction with health professionals. Other psychological treatments, such as guided imagery with perceived happy memory [84] and brief mindfulness-based therapy (MBT) [85], may be effective interventions for CTTH.

Manual therapy has been shown to reduce headache frequency in participants with CTTH, even though there is much debate in its efficacy [86, 87]. In a recent prospective longitudinal study, the mechanism of manual therapy mediated by increased neck flexor endurance in CTTH has been discussed [88].

Previous double-blind or single-blind studies have demonstrated that both needle and laser acupuncture had a significant clinical effect on CTTH [89, 90]. A study that compared acupuncture, relaxation techniques, and physical training for the treatment of CTTH showed that relaxation techniques produced the most pronounced effects, immediately after the treatment period, compared with acupuncture and physical training. However, there were no long-lasting differences between the three interventions [91].

In addition, another suggested treatment for CTTH is the use of TENS. A comparison of the efficacy between imipramine and TENS in the prophylaxis of CTTH has been conducted, and both treatments significantly reduced the severity

of headache suggesting TENS may be a good alternative non-pharmacological treatment for CTTH [92]. It is also suggested that repetitive low-frequency electrical stimulation (LFS) could induce prolonged pain inhibition in CTTH patients [93].

Conclusion

In conclusion, it needs further discussion whether pericranial muscle activity and pressure pain hypersensitivity are contributing factors or consequences to CTTH. Current interventions for CTTH are not optimally effective, especially prophylactic treatment with the aim to reduce the intensity as well as the occurrence of the headache attacks. Both pharmacological and non-pharmacological strategies should always be considered in the overall treatment plan for patients with CTTH. In order to increase the clinical effect of the interventions, more comprehensive and specific treatment options should be applied to treat different subgroups of CTTH patients with relevant clinical prediction rules. Compared with migraine, research addressing CTTH remains quite limited. It is clear that future studies investigating the pathogenesis and the different therapeutic strategies for CTTH are urgently needed.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Shengyuan Yu and Dr. Xun Han each declare no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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