RECENT ADVANCEMENTS IN TENSION TYPE HEADACHE

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Abstract

Tension type headache (TTH) is the most prevalent neurological disorders, with a significant socioeconomic burden. It is characterized by a featureless bilateral headache usually with a tightening or pressing quality and its diagnosis should be followed by the elimination of other primary and secondary headaches. TTH can be classified to episodic form -frequent or infrequent- and chronic form, according to the 3rd edition of the International Classification of Headache Disorders. Pathophysiology of the disorder is still not fully understood but recent findings support the contribution of peripheral mechanisms in generating the pain and central mechanisms in pain chronification. The treatment approach is a process which starts with establishing a good and solid patient-doctor relationship for joined decisions to be made and ends with the selection of a treatment strategy, that usually involves both non-pharmacologic and pharmacologic treatments, either acute or prophylactic.

Key words: Tension Type Headache, ICHD-3, Migraine, treatment, pathophysiology

Introduction

Tension Type Headache (TTH) is the most common headache type globally with a prevalence ranging from 46% to 78% in different studies [1]. Including the non-frequent TTH cases (less than 1 headache per month) the virtual prevalence of TTH may be 100% of the population. Nevertheless, not all cases need medical attention. While TTH is so common with a significant socioeconomic burden there are scant clinical and epidemiological studies, patient awareness and education are insufficient resulting in large numbers of untreated patients. Furthermore, targeted treatment for TTH is still limited, thus reducing patients' compliance. TTH is characterized by mild to moderate severity pain bilaterally in the head. The pain has a pressing or tightening quality and may last form minutes to a week. TTH has no special characteristics like other primary headaches (migraine, cluster headache). This, along with our incomplete knowledge of the pathophysiology of TTH, drove to a somewhat "neglection" of these patients. Recent advancements in migraine pathophysiology and therapeutics highlighted this discrepancy. In this review we aim to provide insight into the epidemiology, pathophysiology diagnosis and treatment of TTH and raise awareness of medical practitioners for this common and burdensome disease.

Epidemiology – burden

TTH is the most prevalent neurological disease in the European region of the World Health Organization (WHO) and globally according to the Global Burden of Disease study 2017 [2]. The prevalence of TTH was 309,8 million cases in WHO European region and 2,3 billion cases globally with an estimated incidence of 114,4 million new cases in Europe and 882,4 million new cases globally. The respective prevalence for migraine was 195,8 million in Europe and 1,3 billion globally. In the Greek population the prevalence of TTH was calculated as 3.4% (95%CI: 3.4-4.2) with a mean age of 45.4 and 59.5% of them being female [3].

The estimated DALYs (Disability-adjusted life years) for TTH was 7,1 million globally while for migraine 47,2 million DALYs. Hence, it is evident that TTH is the most common neurological disease, but its contribution to the overall burden of neurological disorders in the European Union is 3%, while the respective contribution of migraine is 20% [2]. Regardless of the disability caused though, the impact of both TTH and migraine on Health-related Quality of life (HRQoL) seems to be similar, according to a recent population-based Danish study [4]. This was more evident in Chronic TTH (CTTH) suggesting that headache frequency is related with lower HRQoL indices.

Pathophysiology

Pain is the subjective experience one feels because of the activation of the nociceptive system; thus, the trigemino-thalamic nociceptive system plays a central role in TTH pathophysiology.

It has been suggested that myofascial tenderness and hardness may be the initial disruption causing the generation of noxious stimuli on the face and head of patients with TTH. Myofascial tenderness and hardness has been found to be increased in both episodic (ETTH) and CTTH patients in days both with and without headache [5]. Furthermore, pericranial muscle tenderness was found to be increased in patients with TTH than in controls [6]. In addition, it has been theorized that chronic pain may lead to abnormal sensitivity of the low-threshold Aβ mechanosensitive fibers –on top of the Aδ and C fibers– who normally carry only innocuous stimuli [7].

The role of peripheral vascular mechanisms in TTH pathophysiology had also been investigated in a somewhat analog scheme of migraine. Although there are some indications that NO and CGRP-induced vasodilation may play a role, further studies are needed to clarify this association [8]. However, it has been found that high levels of nitric oxide induce headache, whereas low levels reduce headache intensity in patients with chronic TTH [9-11]. Other molecules known for their role in other primary headaches like CGRP, substance P and VIP were investigated, but no relation of their levels and the presence of headache was found [12-14].

Through sparce genetic studies it is hypothesized that infrequent ETTH is caused primarily by environmental factors, while frequent ETTH and CTTH are caused by a combination of environmental and genetic factors (15). This conclusion was drawn mainly by twin studies that showed that monozygotic twins and same-sex dizygotic twins had greater difference in concordance rates in infrequent and frequent ETTH [16, 17]. A threefold increase in CTTH risk in first-degree relatives of the cases was found in a family aggregation study [18].

Although very common, the infrequent ETTH has a somewhat minor burden. It is the frequent ETTH and CTTH that carries the most burden on patients and society. Thus, understanding the mechanism of chronification of TTH is crucial. The main theory of chronification is based on the notion that repetitive painful stimulus leads to the sensitization of nociceptive second-order neurons at the level of the spinal trigeminal nucleus and the dorsal horn of the spinal cord [19]. At the same time there may be a reduction of the antinociceptive (descending) effect of supraspinal structures [20]. The overall effect of these changes may lead to increased excitability of dorsal horn neurons and motor neurons of skeletal muscle, [21] producing greater muscle tenderness and lower pain thresholds and therefore increased headache frequency. Furthermore, systemic inflammation may play a role in TTH chronification, since it has been shown that systemic inflammation markers like neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and C-reactive protein were significantly higher in CTTH patients [22].

Diagnosis – Classification

The lack of specific characteristics of TTH unlike migraine (photophobia, phonophobia, nausea) and Trigeminal Autonomic Cephalalgias (autonomic symptoms), makes the diagnosis a process of eliminating these disorders for a new patient reporting headache. Nevertheless, TTH, and mostly its frequent episodic and chronic type, has some characteristics that appear to be more common in TTH patients. These are the mild or moderate pain intensity, the bilateral location, the pressing or tightening quality and the lack of pain aggravation by routine physical activity [23]. Frequently, patients report a band-like pressing sensation around the head. The 3rd edition of the International Classification of Headache Disorders (ICHD-3) provides criteria for the diagnosis of TTH and further classification in infrequent and frequent ETTH and CTTH sub-types, based mostly on the average headache frequency during a time period (Table 1) [24]. Though uncommon, mild nausea may be a manifestation of CTTH.

Diagnostic approach is primarily based on headache and overall medical history. A headache calendar may be of great help towards this. In terms of classification, when another medical condition is recognized in close temporal relation with the headache onset and it is known that this condition may cause headache, then we must classify this headache as a secondary one, according to ICHD-3 [24]. At the same time, it is of great importance to recognize or eliminate any potential secondary headache disorder which carries great risk for the patient. Although neuroimaging is not recommended during the diagnostic work-up of primary headache disorders[25], it is common in clinical practice to perform some sort of neuroimaging (CT scan or MRI) at least once and indubitably when a red flag for secondary headaches is recognized [26]. Cases of increased intracranial pressure and Medication Overuse Headache (MOH) are easily overlooked, so specific questions regarding the relation of headache with the time of the day, or patients' position and the painkillers used, are of great importance. In case of doubt, a fundoscopic examination may be an easy and much informative examination.

Triger factors – Risk factors - Comorbidities

A great portion of TTH patients may report one or more triggering factors that precipitate headache. Commonly reported triggers are psychological pressure or anxiety, weather changes, sunlight exposure, dehydration, or certain foods and drinks [20, 27]. Endogenous melatonin status and nutrient status

Table 1. Diagnostic criteria of TTH according to ICHD-3

	Basic characteristics	Frequency (on average)	Special cha racteristics	Nausea and vomiting	Duration	Pericranial tenderness	
2.1 Infrequent ETTH	At least 2 of: 1. bilateral location 2. pressing or tightening (non-pulsating) quality 3. mild or moderate intensity 4. not aggravated by routine physical activity	<1 day/month	No more than one: phonophobia, photophobia	No nausea or vomiting	30 min t o 7 days	Yes	2.1.1
						No	2.1.2
2.2 Frequent ETTH		1-14 days/month				Yes	2.2.1
						No	2.2.2
2.3 CTTH		>15 days/month	No more than one: photophobia, phonophobia, mild nausea	Neither moderate or severe nausea nor vomiting	Hours to days or unremitting	Yes	2.3.1
						No	2.3.2

Abbreviations: ETTH: Episodic Tension Type Headache; CTTH: Chronic Tension Type Headache

of patients with TTH has also been studied. Lower serum 25(OH)D was related to the presence of FETTH [28, 29]. A well-kept calendar may help patients and their treating physician to recognize these factors. Although commonly reported, these triggers factors and their relationship with TTH are not enough studied by randomized or epidemiological trials. On the other hand, many risk factors were reported by cross sectional and longitudinal studies. Examples are young age, female sex, poor self-rated health and few sleeping hours per night [30].

The presence of comorbidities in TTH patients is a well-known feature for clinicians. Many comorbidities were shown to have a greater prevalence in patients suffering from primary headache than the general population. Psychiatric comorbidities and sleep disturbances are the most studied TTH comorbidities. Insomnia, poor sleep quality, excessive daytime sleepiness, insufficient sleep and shift working are some of the sleep disorders that have been reported as having higher prevalence in TTH patients than among subjects without headache [31]. Depression and anxiety are also more prevalent in TTH patients than in headache free patients and are also associated with the frequency and severity of TTH attacks [32]. Arterial hypertension (AH) is another frequent comorbidity of TTH, a fact that led to the description of an AH+TTH phenotype and the study of potential pathophysiologic implications and therapeutic targets [33]. A search in PubMed database for potential TTH comorbidities has recognized a total of 21 disturbances/diseases that have been studied, including Restless Legs Syndrome, Fibromyalgia, Hypothyroidism, neck pain and back pain, temporomandibular dysfunction, tinnitus, and sexual dysfunction (data not published).

Treatment

Management of TTH patients and primarily infrequent ETTH may start with just reassurance that there is no potential hazard to the patient. By labeling the disorder as a primary headache, patients tend to cope with it more positively and manage to live with it by just using some symptomatic treatment when needed. In more frequent TTH though, reassurance alone is not enough.

Patient education about the nature of the disease and all the coping strategies is of paramount importance. Patients should be aware about trigger management, the life-style modifications required and the available pharmacologic and non-pharmacologic treatments. At the same time trained physicians should get to know their patients, their socioeconomic and psychologic status and establish a potent patient-doctor relationship to form a treatment strategy according to the patients' expectations. This

approach may maximize patients' commitment in non-pharmacologic treatment approaches that may need time to show a positive effect, compliance in pharmacologic treatment and minimize nocebo effect.

Non-pharmacologic approach

European Federation of Neurological Societies (EFNS) guidelines (34) recommends the use of a non-pharmacologic approach as the first step in headache prevention in eligible patients. Such strategies include psycho-behavioral treatments, physical therapy, and acupuncture. Along with these methods, more recently, mindfulness-based intervention and transcranial magnetic stimulation (TMS) were also considered as alternative therapeutic approaches, yet with limited quality supporting studies [35, 36].

Psycho-behavioral treatments

EMG biofeedback is the only non-pharmacologic therapy with a class A level of recommendation by the EFNS based on a large meta-analysis that showed medium to large effect on reducing headache frequency [37]. During biofeedback sessions patients are trained to recognize and control muscle tension by continuous feedback about muscle activity.

Cognitive Behavioral Treatment (CBT) and relaxation are less supported by quality studies. The aim of CBT is to provide patients with a learned behavioral strategy to take conscious control over their physiologic response to pain. The same stands for relaxation training, where patients are tought to recognize and control tension in every-day activities by implementing cognitive and behavioral techniques as well as breathing exercises and meditation [38].

Even though these approaches have limited, good quality supporting data, it is recommended that they are used with caution. The excellent safety profile though gives us the opportunity to offer this choice to suitable patients. Patients who exhibit psycho-behavioral problems may benefit by CBT, while relaxation training and biofeedback may benefit more tense patients [34].

Physical therapy

Many different modalities of physical therapy have been and still are in widespread use by TTH patients, with a great economical cost. These methods include joint manipulation techniques, massaging, trigger point therapy, oromandibular treatment and posture improvement. Yet there is no robust scientific evidence regarding its efficacy. EFNS guidelines recommend the use of physical therapy in patients with frequent TTH [34] and NICE guidelines found no convincing data to make a recommendation for or against manual therapies [39]. A more recent review and meta-analysis found some potential positive effect of manual joint mobilization and supervised physical activity in headache frequency, but with low certainty of evidence, due to risk of bias [40]. Physical activity in general, aerobic exercise and yoga, are choices that clinicians often offer to their patients, but they have not been adequately evaluated, even though there is some evidence of efficacy [41, 42].

Acupuncture

Acupuncture has better quality evidence than other non-pharmacological treatments to support its effectiveness in reducing headache frequency in ETTH and CTTH patients comparing with placebo/sham intervention or routine therapy [43, 44]. Still, there are some methodological drawbacks in those studies, but the convenient safety profile of acupuncture makes it a choice for TTH patients.

Pharmacologic approach

Acute treatment

The mainstay of TTH pharmacologic treatment is an acute treatment, meaning medications used to fight every single episode of headache. Ibuprofen (200-800mg), ketoprofen (25mg) aspirin (500-1000mg), naproxen (375-550mg) and paracetamol (1000mg) are all recommended by the Hellenic Headache Society as class A treatment options for acute TTH. Simple analgesics and non-steroidal anti-inflammatory drugs are also recommended as a first choice according to the EFNS guidelines, while combination analgesics containing caffeine, come as a second choice [34].

Since paracetamol and aspirin are widely used for other indications in different dosages (paracetamol 500mg for other pain syndromes or fever and aspirin 100mg for arterial thrombosis prophylaxis) it is crucial to inform TTH patients that only the recommended dose has shown efficacy for reducing pain intensity.

Preventive treatment

In the case of frequent ETTH and CTTH, clinicians should offer the choice of a prophylactic treatment. The goal by using a prophylactic treatment is to reduce the headache frequency, measured by headache days per month and monitored by a headache calendar. A reduction of headache by at least 50% is considered as successful treatment, but patients characteristics, comorbidities and expectations should also be taken into consideration.

Amitriptyline, venlafaxine and mirtazapine are currently the available options for TTH prophylaxis. Amitriptyline is considered as first choice drug since its efficacy was documented by multiple studies [45, 46]. Side effects of usual maintenance dose (25-75mg)

are not too common and include drowsiness, dry mouth and weight gain. Slow titration and nighttime intake may reduce some of them. Mirtazapine and venlafaxine where both evaluated as prophylaxis in CTTH in small, randomized trials showing effectiveness against placebo and comparable effectiveness of mirtazapine of that of amitriptyline [47-49]. Major side effects of mirtazapine (30mg) are drowsiness and weight gain and of venlafaxine (150mg) are dizziness and loss of libido.

Selective serotonin reuptake inhibitors citalopram, sertraline, fluoxetine, paroxetine and fluvoxamine showed similar effectiveness as amitriptyline and placebo in reducing headache frequency in CTTH patients [50]. Clomipramine, maprotiline and mianserin are also recommended as third line treatment options based [34, 51, 52]. Botulinum toxin type A showed ineffectiveness for the prevention of CTTH [53].

The duration of prophylaxis in CTTH patients is a matter of debate. EFNS recommends a trial discontinuation of prophylaxis in 6 to 12 months of treatment. Taking into consideration the patients' expectations and comorbidities may dictate the path. The same stands for the overall selection of the prophylactic approach in every individual patient. Personality traits, medical history, age, comorbidities socioeconomic status and accessibility in different medical or physical therapy services, could form a multimodal treatment plan aiming in better compliance and closer monitoring.

Conclusion

TTH is the most prevalent headache with a significant burden. Even though it is called the "simple headache" it is a complex disease with many environmental, physiological, and psychological factors contributing to its presence. The more stressful everyday life gets, the more prevalent TTH will be with these conditions showing a comorbid association. The pathophysiology of TTH is still not fully understood, but there is convincing evidence supporting both central and peripheral mechanisms.

The diagnosis is made by headache history and by ruling out other types of primary or secondary headache. TTH can be classified in infrequent and frequent episodic TTH and chronic TTH based on average headache days per month, according to ICHD-3 criteria.

The treatment approach is a process which starts with establishing a good and solid patient-doctor relationship so shared decision making can be achieved and ends with the selection of treatment strategy that usually includes both non-pharmacologic and pharmacologic treatments, either acute or prophylactic.

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