INTRODUCTION

Trigeminal neuralgia (TN) is a debilitating craniofacial pain syndrome that is characterized by paroxysms of intense, short-lived electric shock-like pains in the trigeminal nerve distribution. These episodes are precipitated by innocuous stimuli within the affected trigeminal distribution.

Background: Trigeminal neuralgia is a debilitating craniofacial pain syndrome that is characterized by paroxysms of intense, short-lived electric shock-like pains in the trigeminal nerve distribution. Recently, the presence of triggers has become one of the key diagnostic criteria in the 3rd edition of the International Classification of Headache Disorders. Light touch is the most common trigger, however other non-mechanical triggers, such as cold weather and certain foods, have been thought to provoke trigeminal neuralgia anecdotally. We aimed to characterize the prevalence and characteristics of these atypical triggers.

Methods: We conducted a retrospective, cross-sectional study of atypical triggers in trigeminal neuralgia patients seen in a tertiary pain clinic in Singapore. Patients were recruited via clinic records, and study data were identified from physician documentation.

Results: A total of 60 patients met the inclusion criteria. Weather triggers were observed in 12 patients (20%), of which five patients (8%) reported strong winds, 4 patients (7%) reported cold temperatures, and 3 patients (5%) reported cold winds as triggers. Fifteen patients (25%) had a specific food trigger, of which 10 patients (17%) reported hard or tough food, 5 patients (8%) reported hot/cold food, 4 patients (7%) reported spicy food, and 2 patients (3%) reported sweet food as triggers.

Conclusions: Although trigeminal neuralgia is most commonly triggered by mechanical stimuli, atypical triggers such as cold temperatures and certain foods are seen in a significant proportion of patients. These atypical triggers may share a common pathway of sensory afferent Aδ fiber activation.

Key Words: Cold Temperature; Facial Neuralgia; Food; Nerve Fibers; Pain; Precipitating Factors; Prevalence; Trigeminal Neuralgia; TRPV Cation Channels; Wind.
gests that dysfunction of trigeminal afferent neurons is central to its pathogenesis. Injury results in hyperexcitable afferent neurons, causing severe pain from typically non-noxious stimuli [4].

Recently, the presence of these triggers has become one of the key diagnostic criteria in the 3rd edition of the International Classification of Headache Disorders (ICHD-3) [5]. Light touch and facial movements are well known stimuli, and studies have mapped a range of intraoral and extraoral trigger zones [6]. Anecdotally, other non-mechanical triggers, such as cold weather and certain foods, have been thought to provoke TN [7,8], although the literature has been largely limited to case reports and case series [9-13]. Given the increasingly important role that these triggers have on the pathogenesis and diagnosis of TN, our study attempted to characterize the frequency and nature of atypical triggers, specifically food and weather triggers, in patients with TN.

MATERIALS AND METHODS

We conducted a retrospective cross-sectional study of TN patients seen in the Singapore General Hospital (SGH) Pain Management Centre from 2012 to 2017, via a review of their medical records. The study was approved by the Institutional Review Board (SGH-CIRB-2019/2560) prior to commencement. No identifiable personal information was collected, and the requirement for written informed consent was waived by the Institutional Review Board.

Inclusion criteria were adult patients above the age of 18 years old, who had TN based on the ICHD-3 diagnostic criteria (Table 1), and were seen in the study clinic during the study period. Patients with a final alternative diagnosis other than TN were excluded.

Patients were recruited via clinic records of their diagnosis. Clinic notes were then reviewed by the investigators, where relevant for discussion, additional disease-related information was also collected by investigators. No personal identifiable information was collected. Assuming a level of confidence of 95% and precision of 10%, and an estimated prevalence of 20%, the sample size required to estimate the prevalence of a particular trigger was 61 [14].

The primary outcome was the prevalence of atypical triggers, specifically food and weather triggers. These were established a priori at initiation of the study design. Basic demographic information, information on various disease characteristics, and prevalence of classical triggers were also collected for comparison with other studies.

Data was analyzed using SPSS 23.0 for Windows (IBM Co., Armonk, NY). Descriptive statistics were obtained for primary outcomes as well as demographic data. Exploratory univariate analysis was also conducted with the chi-square test and student’s t-test to identify associations between our primary outcomes and demographic and disease characteristic data.

RESULTS

A total of 72 patients with TN were included in our study. Twelve patients were excluded due to an alternative final diagnosis, or unavailability of medical records. Sixty patients were available for study analysis. The demographics of patients are presented in Table 2. Forty cases were female (67%), with a mean age of 62.9 ± 10.1 (median 61.9, interquartile range 56.6 to 68.6). The mean duration of illness at first consultation was 5.5 ± 5.3 years.

Thirty patients (57%) had classical TN, 6 patients (11%) had secondary TN, and 17 patients (32%) had idiopathic TN. Seven patients either declined to have magnetic resonance imaging done, or had performed it in an external institution. The majority (n = 38, 63%) had right-sided

Table 1. Diagnostic and classification criteria for trigeminal neuralgia in the 3rd edition of the international classification of headache disorders (ICHD-3)

| ICHD-3 diagnostic criteria for trigeminal neuralgia |
|-----------------------------------------------|
| A. Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C |
| B. Pain has all of the following characteristics: |
| 1. Lasting from a fraction of a second to 2 minutes |
| 2. Severe intensity |
| 3. Electric shock-like, shooting, stabbing or sharp in quality |
| C. Precipitated by innocuous stimuli within the affected trigeminal distribution |
| D. Not better accounted for by another ICHD-3 diagnosis |

Table 2. Demographics of patients

| Demographic                  | Value     |
|------------------------------|-----------|
| Sex                          |           |
| Male                         | 20 (33)   |
| Female                       | 40 (67)   |
| Race                         |           |
| Chinese                      | 47 (78)   |
| Malay                        | 7 (12)    |
| Indian                       | 3 (5)     |
| Other                        | 3 (5)     |
| Age (yr)                     | 62.9 ± 10.1|
| Duration of illness at first consultation (yr) | 5.5 ± 5.3 |

Values are presented as number (%) for categorical data or mean ± standard deviation for continuous data.
involvement, and the rest (n = 22, 37%) had left-sided involvement. None had bilateral involvement. The mandibular division (V3) was the most common site of involvement (n = 42, 70%), and the most common pattern of disease was V3 alone (n = 21, 35%), followed by both the maxillary and mandibular divisions (V2 + V3) (n = 19, 32%). Eight patients (13%) had continuous pain, and 14 patients (23%) had nocturnal pain (Table 3).

Weather triggers were observed in 12 patients (20%). Specifically, five patients (8%) reported strong winds as a trigger, 4 patients (7%) reported cold temperatures as a trigger, and 3 patients (5%) reported cold winds in general as a trigger. Food or drink triggers were observed in 55 patients (92%). Fifty-four patients (90%) were triggered by eating in general, while 16 patients (27%) were triggered by drinking in general. Thirty-nine patients (65%) were triggered by chewing. Fifteen patients (25%) had a specific type of food that triggered their attacks. Other classical triggers are presented in Table 4.

Out of the 15 patients who had a specific food trigger, 10 patients (17%) were triggered by hard or tough food, and 5 patients (8%) were triggered by hot/cold food. Four patients (7%) were triggered by spicy food, two patients (3%) were triggered by sweet food, and no patients were triggered by sour food or salty food (Table 5).

In the exploratory univariate analysis, no associations were seen between having a specific food trigger and the various demographic and disease characteristics data. In particular, V2 involvement (P = 0.385) and V3 involvement (P = 0.491) were not associated with having a specific food trigger.

## DISCUSSION

Overall, our cohort of patients had basic demographics and disease characteristics similar to those reported in the literature [3,15,16]. While a number of patients had less common features of classical TN, namely nocturnal pain and continuous pain, this has been increasingly described in other studies [6].

As expected from anecdotal evidence, a significant percentage of patients reported that they have specific weather patterns and foods that trigger their symptoms. The most common weather trigger was strong winds, and the most common food trigger was hard/tough food, both of which appear to have a mechanical component. This is unsurprising, given than TN is classically triggered by non-noxious touch stimuli, and intra-oral trigger points
are known [6]. More strikingly, a number of patients reported specific gustatory stimuli as triggers. Gustatory stimuli are transmitted via the facial and glossopharyngeal nerve, not the trigeminal nerve. Since gustatory afferents do not run in the trigeminal nerve, it follows that they should not trigger TN. We propose that sensory afferent Aδ fibers running in the trigeminal nerve are responsible for this phenomenon.

It has been shown experimentally that small myelinated Aδ fiber dysfunction plays an important role in TN [2,17]. DaSilva and DosSantos [18] first described how sensory fiber demography affected the pathogenesis and clinical manifestations of TN. Specifically, the rostral portion of the REZ contains a larger proportion of A fibers (both Aβ and Aδ) compared to C fibers, known as rostral convergence. These A fibers are especially vulnerable to compressive injury, which occurs most commonly over the superior portion of the REZ by the superior cerebellar artery in classical TN [19], and can transmit pain after injury.

There is also clinical evidence of Aδ fibers involvement in the literature—cold wind has been shown to be a known trigger for TN in up to 50% of patients [16]. Winter is hence a difficult time for TN patients, especially in temperate climates. Our study provides further evidence that a significant proportion of patients can be triggered by cold temperatures, and that it is a separate trigger from strong winds. Hot/cold foods have also been reported as a trigger in 3%-6% of patients in other studies [6], and was also seen in our cohort of patients, likely related to intraoral thermoreceptors. Both extra-oral and intra-oral temperature stimuli are mediated in part by Aδ fibers [20], and the presence of cold wind and hot/cold food triggers suggests the involvement of Aδ fibers in TN pathogenesis.

Two cases in our cohort reported that sweet food was a trigger, and sweet food has been reported in at least two other case reports in the literature [11,12]. Then, it was postulated to be due to the convergence of gustatory and trigeminal afferents in the brainstem. However, while there is some evidence for central facilitation in TN [2], conflicting evidence suggests that gustatory stimuli are independent of trigeminal nerve transmission [21]. Moreover, one of the two cases in our study reported an improvement in symptoms when the sugar substitute Equal® (Aspartame) was used instead of sugar. As aspartame binds to the same heterodimeric sweet taste receptor (comprising T1R2 and T1R3) as sugar, to stimulate gustatory stimuli [22], this implies other non-gustatory mechanisms at play.

We suggest that tooth pulp nociceptors, innervated by afferent Aδ fibers, mediate triggering by sweet foods. Exposed dentin surfaces, either from gingival recession or loss of enamel, causes dental hypersensitivity [23]. Dentinal pulp is innervated by Aδ fibers, which are stimulated not only by heat, cold, and drying, but also osmotic stimuli (as encountered in hypertonic sugary foods) [24]. As per the ignition hypothesis, a small amount of such stimuli might serve as the trigger for TN in susceptible patients. Non-nutritive sweeteners are hundreds of times sweeter than their sugary counterparts, and have a lower osmotic load, hence explaining our patient’s improvement with Aspartame [25]. While both our patients were cleared of dental causes, mild forms of exposed dentin can be challenging to diagnose [26], and is especially difficult if the pain is felt in the distribution of the trigeminal nerve rather than the tooth itself. Potentially, at-risk patients may be treated with a trial of occlusion of dentin tubules (e.g., resins, varnishes, toothpastes).

Spicy foods have been shown to trigger TN via specific trigger zones in the literature, and were initially thought to be mediated by unmyelinated C fibers [10]. The main active compounds of spicy foods are capsaicin and other capsaicinoids, which induce their characteristic “spice” sensation via activation of transient receptor potential vanilloid 1 (TRPV1) receptors. While the TRPV1 is known to stimulate unmyelinated C fibers, it has also been shown to stimulate Aδ fibers, resulting in nociceptive stimuli [27]. Such stimuli would then trigger TN via the ignition hypothesis. We propose that stimulation of these Aδ fibers may instead be how spicy foods trigger TN.

Our study estimates have limitations, as it was a single-institution study with a smaller-than-expected sample size. We also relied on physician documentation for triggers, which may have underestimated the true prevalence of triggers. Given the observational nature of our study, conclusions are inherently based on indirect evidence, and more direct experimental evidence is required for firmer conclusions.

In conclusion, we studied the various atypical non-touch triggers of TN. Although TN is most commonly triggered by mechanical stimuli, cold temperatures and certain foods are important triggers as well. In particular, type of food is an underreported and underrecognized cause of distress among TN patients. Improved recognition may also aid in accurate diagnoses in atypical cases. We also described how these atypical triggers may share a common pathway of sensory afferent Aδ fiber activation, based on rostral convergence, and proposed mechanisms for the pathogenesis of their triggering. Greater appreciation of how these atypical triggers relate to Aδ fibers can lead to advancements in our understanding of the pathogenesis and treatments of TN.
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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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