Korean J Pain 2021;34(1):66-71
https://doi.org/10.3344/kjp.2021.34.1.66
pISSN 2005-9159 eISSN 2093-0569

KJP

Clinical Research Article

Check for updates

Atypical triggers in trigeminal neuralgia: the role of A-delta sensory afferents in food and weather triggers

Wenjun Koh, Huili Lim, and Xuanxuan Chen

Department of Anaesthesiology, Singapore General Hospital, Singapore

Received July 14, 2020
Revised September 10, 2020
Accepted September 11, 2020

Handling Editor: Young-Bok Lee

Correspondence
Wenjun Koh
Department of Anaesthesiology, Singapore General Hospital, Outram Road, 169608, Singapore
Tel: +65-6222-3322
Fax: +65-6224-9221
E-mail: kohwenjun@u.nus.edu

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.

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.

The pathophysiology and etiology of TN are complex and incompletely understood. Peripheral neurovascular compression at the root entry zone (REZ) of the trigeminal nerve root, with resultant demyelination, is the leading etiological theory [1], although central mechanisms may also be important [2,3]. How demyelination causes the classic symptoms of TN is also not entirely clear, although the most common hypothesis, the "ignition theory", sug-

Author contributions: Wenjun Koh: Writing/manuscript preparation; Huili Lim: Supervision; Xuanxuan Chen: Supervision.

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, with the study data identified from physician documentation. 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.

Table 3. Disease characteristics of patients

Characteristic	Value
Etiology (n = 53)	
Classical	30 (57)
Secondary	6 (11)
Idiopathic	17 (32)
Side of involvement	
Right	38 (63)
Left	22 (37)
Bilateral	0 (0)
Site of involvement	
Any V1 involvement	10 (17)
Any V2 involvement	36 (60)
Any V3 involvement	42 (70)
V1 alone	3 (5)
V2 alone	10 (17)
V3 alone	21 (35)
V1 + V2	5 (8)
V1 + V3	0 (0)
V2 + V3	19 (32)
V1 + V2 + V3	2 (3)
Continuous pain	8 (13)
Nocturnal pain	14 (23)

Values are presented as number (%).
V1: ophthalmic division, V2: maxillary division, V3: mandibular division.

Table 4. Triggers of paroxysmal attacks

Trigger	Value
Food or drink triggers	55 (92)
Eating in general	54 (90)
Drinking in general	16 (27)
Chewing	39 (65)
Specific type of food	15 (25)
Weather triggers	12 (20)
Strong wind	5 (8)
Cold temperatures	4 (7)
Cold wind in general	3 (5)
Classical triggers	50 (83)
Toothbrushing	40 (67)
Talking	39 (65)
Washing face	22 (37)
Facial movement	10 (17)

Values are presented as number (%).

Table 5. Specific types of food triggers

Type of food	Value
Hard or tough food	10 (17)
Hot/cold food	5 (8)
Spicy food	4 (7)
Sweet food	2 (3)
Sour food	0 (0)
Salty food	0 (0)
Other foods	4 (7)

Values are presented as number (%).

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.

ACKNOWLEDGMENTS

The study team members would like to acknowledge the nurses and staff of the Singapore General Hospital Pain Management Centre for their administrative help and support for this research.

CONFLICT OF INTEREST

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

FUNDING

No funding to declare.

ORCID

Wenjun Koh, https://orcid.org/0000-0003-2080-034X
Huili Lim, https://orcid.org/0000-0002-4971-945X
Xuanxuan Chen, https://orcid.org/0000-0003-3130-9783

REFERENCES

1. Dandy WE. Concerning the cause of trigeminal neuralgia. Am J Surg 1934; 24: 447-55.
2. Obermann M, Yoon MS, Ese D, Maschke M, Kaube H, Diener HC, et al. Impaired trigeminal nociceptive processing in patients with trigeminal neuralgia. Neurology 2007; 69: 835-41.
3. Lee A, McCartney S, Burbidge C, Raslan AM, Burchiel KJ. Trigeminal neuralgia occurs and recurs in the absence of neurovascular compression. J Neurosurg 2014; 120: 1048-54.
4. Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: the ignition hypothesis. Clin J Pain 2002; 18: 4-13.
5. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018; 38: 1-211.
6. Di Stefano G, Maarbjerg S, Nurmikko T, Truini A, Cruccu G. Triggering trigeminal neuralgia. Cephalalgia 2018; 38: 1049-56.
7. National Health Service. Trigeminal neuralgia - treatment [Internet]. London: National Health Service; 2019. Available at: https://www.nhs.uk/conditions/trigeminal-neuralgia/treatment/.
8. Facial Pain Association. Pain-triggering and pain-safe foods [Internet]. Gainesville: Facial Pain Association; 2019. Available at: https://fpa-support.org/pain-triggering-and-pain-safe-foods/.
9. Delzell JE Jr, Grelle AR. Trigeminal neuralgia. New treatment options for a well-known cause of facial pain. Arch Fam Med 1999; 8: 264-8.
10. Eisenberg E. Trigeminal neuralgia induced by sour and spicy foods: what is the underlying mechanism? A case report. J Oral Facial Pain Headache 2016; 30: 267-70.
11. Sharav Y, Benoliel R, Schnarch A, Greenberg L. Idiopathic trigeminal pain associated with gustatory stimuli. Pain 1991; 44: 171-4.
12. Helcer M, Schnarch A, Benoliel R, Sharav Y. Trigeminal neuralgic-type pain and vascular-type headache due to gustatory stimulus. Headache 1998; 38: 129-31.
13. Guardiani E, Sadoughi B, Blitzer A, Sirois D. A new treatment paradigm for trigeminal neuralgia using Botulinum toxin type A. Laryngoscope 2014; 124: 413-7.
14. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. Gastroenterol Hepatol Bed Bench 2013; 6: 14-7.
15. Han KR, Kim YS, Kim C. Clinical features of trigeminal neuralgia. Korean J Pain 2007; 20: 174-80.
16. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia--a prospective systematic study of clinical characteristics in 158 patients. Headache 2014; 54: 1574-82.
17. Cruccu G, Leandri M, Iannetti GD, Mascia A, Romaniello A, Truini A, et al. Small-fiber dysfunction in trigeminal neuralgia: carbamazepine effect on laser-evoked potentials. Neurology 2001; 56: 1722-6.
18. DaSilva AF, DosSantos MF. The role of sensory fiber demography in trigeminal and postherpetic neuralgias. J Dent Res 2012; 91: 17-24.
19. Barker FG 2nd, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome of microvascular decompression for trigeminal neuralgia. N Engl J Med 1996; 334: 1077-83.
20. Schepers RJ, Ringkamp M. Thermoreceptors and thermosensitive afferents. Neurosci Biobehav Rev 2009; 33: 205-12.
21. Boucher Y, Simons CT, Carstens MI, Carstens E. Effects of gustatory nerve transection and/or ovariectomy on oral capsaicin avoidance in rats. Pain 2014; 155: 814-20.
22. Maillet EL, Cui M, Jiang P, Mezei M, Hecht E, Quijada J, et al. Characterization of the binding site of aspartame in the human sweet taste receptor. Chem Senses 2015; 40: 577-86.
23. West NX, Lussi A, Seong J, Hellwig E. Dentin hypersensitivity: pain mechanisms and aetiology of exposed cervical dentin. Clin Oral Investig 2013; 17 Suppl 1: S9-19.
24. Byers MR, Närhi MV. Dental injury models: experimental tools for understanding neuroinflammatory interactions and polymodal nociceptor functions. Crit Rev Oral Biol Med 1999; 10: 4-39.
25. Shankar P, Ahuja S, Sriram K. Non-nutritive sweeteners: review and update. Nutrition 2013; 29: 1293-9.

26. Türp JC. Discussion: how can we improve diagnosis of dentin hypersensitivity in the dental office? Clin Oral Investig 2013; 17 Suppl 1: S53-4.

27. Willis WD Jr. The role of TRPV1 receptors in pain evoked by noxious thermal and chemical stimuli. Exp Brain Res 2009; 196: 5-11.