Trigeminal neuralgia: a retrospective multicentre study of 320 Asian patients

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Objectives. This study was performed to obtain the clinicodemographic data regarding patients with trigeminal neuralgia (TN) treated at oral-maxillofacial medicine clinics, as there is a paucity of such information in the Asian setting.
Study Design. Retrospective multicenter study involving clinicodemographic information of 320 patients with TN diagnosed between 2001 and 2012 at eight regional oral-maxillofacial medicine clinics and followed up for at least 6 months. Statistical tests were performed to assess the associations among the clinicodemographic factors.
Results. TN was mostly diagnosed during the seventh and sixth decades of life, with a median of 58.2 years (interquartile range = 13.0). Females were more commonly affected (61.6%). TN affected the right side more frequently, and the mandibular branch was most commonly involved (58.5%). Carbamazepine was the first-line drug of choice (87.5%).
Conclusions. Asian patients with TN exhibited features similar to those in Caucasian patients except for the increased affliction of the mandibular division. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:51-57)

Trigeminal neuralgia (TN) is an infrequent neurologic disorder that causes severe pain in the facial region. It is also known as paroxysmal trigeminal neuralgia or "tic doloureux." The incidence rate is approximately four per 100,000 per population, affecting mostly females and those above 40 years of age.[1] TN is characterized by recurrent episodes of severe pain in the trigeminal nerve distribution. It can involve one or more divisions of the fifth cranial nerve (CN V), with the maxillary and mandibular branches being more commonly affected than the ophthalmic branch.[1-3] The pain is usually unilateral and has a slight right-sided predominance.[2,3] The pain is often described as lancinating, sharp, shooting or "electric shock—like."[1-3] Common triggering factors include talking, chewing, tooth brushing, touching, or even a cool breeze.[1-3]

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The etiopathogenesis of TN is not entirely clear, and many cases have no apparent cause. However, it is widely accepted that in many cases, TN is related to neurovascular compression at or near the dorsal root entry zone of the nerve.[4-7] Only less than 10% of TN is believed to be caused by traumatic compression of CN V either by tumors, cysts, arteriovenous malformations, or demyelinating conditions, such as multiple sclerosis.[4,5,8] Although diagnosis is usually made on the basis of clinical signs or symptoms, magnetic resonance imaging may be necessary to exclude specific pathology in the posterior cranial fossa.[4,5,8]

Studies have shown that most patients with TN respond well to medication, and pharmacotherapy is considered the first line of management.[9-12] Only refractory TN cases are considered for surgical treatment.[9,13] The most effective drugs for treating TN are anticonvulsants. Most patients respond well to carbamazepine, hence its use as the drug of choice in more than 90% of patients.[9,14] Other commonly used anticonvulsants/anti-epileptic include baclofen, gabapentin, phenytoin sodium, oxcarbazepine, sodium valproate, and lamotrigine.[9,14,15] Although many aspects of TN have been addressed in the literature, most of the

Statement of Clinical Relevance

Predominant involvement of the mandibular division of the trigeminal nerve may be a feature in Asian patients with trigeminal neuralgia. Such patients are more likely to present initially at dental surgeries for management of their pain.

studies have been based on Caucasian/Western populations. With regard to Malaysian patients, only two articles focusing on the demographic and clinical features of patients with TN seen at oral-maxillofacial medicine clinics have been published, both with relatively small populations of patients.[2,16] The study by Loh et al. also consisted of patients from Singapore and, as such, was not truly representative of the Malaysian population.[2] A larger representative population of patients would provide more meaningful information with regard to the clinicodemographic features of Malaysian patients with TN.

MATERIALS AND METHODS

This was a retrospective multicenter research study, involving data on patients with TN from eight hospital-based oral-maxillofacial medicine clinics located in major cities within Malaysia. This study was registered with the National Medical Research Registry and was granted ethical approval from the relevant institutions (National Medical Research Registry Number: NMRR-12-1408-11103).

Records of consecutive patients diagnosed as having TN from January 1, 2001, to December 31, 2012, were retrieved and assessed for suitability to be included into the study. Only patients diagnosed as having TN by oral-maxillofacial medicine specialists following the diagnostic criteria published in the first and second editions of the International Classification of Headache Disorders (ICHD)[17,18] and followed-up for a minimum period of 6 months with complete patient records were included in the study. Medical conditions that may contribute to TN or trigeminal neuropathy were recorded. Cases with incomplete records (missing data points) were excluded from the study. As this was a retrospective study, calibration of clinicians with regard to diagnostic criteria for TN was not performed.

The data collected were link-anonymized, and the variables recorded were divided into demographic factors, clinical features, and management-related factors. The information was collected into a standardized datasheet and tabulated by using Microsoft Excel 2003. Data analysis was done by using the Statistical Package for Social Sciences for Windows software (version 18, SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test showed that age at diagnosis (continuous variable) was not normally distributed. Nonparametric (Mann-Whitney, Kruskal Wallis, and Pearson Chi-square) and binomial tests were used to assess the associations among the variables. P value $<.05$ was considered statistically significant. Age at time of diagnosis is appropriately expressed as either median with interquartile range or mean $\pm$ standard deviation.

RESULTS

Records of 354 patients were retrieved; of these, 34 were excluded as they were incomplete records (missing data), and thus a final number of 320 cases were included.

Demographic characteristics

TN occurred most frequently in the later decades of life, predominantly the sixth decade. The patients' age ranged between 26 and 91 years. TN was diagnosed at a mean age 58.7 (standard deviation $\pm$10.8) years, and the median was 58.2 (interquartile range = 13.0). TN presented predominantly in females (61.6%), with a ratio of 1.6:1 ($P < .0001$; binomial test). The majority of patients were from the ethnic Malay group (56.3%), followed by Chinese (24.7%) and Indian (8.8%). The remainder of the cohort was made up of other Malaysian indigenous ethnic groups ("Others"). There were no statistically significant differences in age between the different ethnic groups ($P = .154$; Kruskal Wallis test). The results are displayed in Table I.

Medical history

With regard to medical comorbidities that may contribute to trigeminal neuropathy, it was found that 34 patients had diabetes mellitus, 12 patients had some form of craniofacial trauma before diagnosis, five patients had a history of stroke, and three patients had some form of connective tissue disease, such as systemic lupus erythematosus. No patients from this cohort had a history of multiple sclerosis.

Clinical features

TN was seen to present most frequently as a unilateral condition with bilateral involvement in only 1.3% of the cases. Right-sided unilateral involvement was seen more commonly (56.3%) than involvement of the left side only (Table I). The CN V3 branch was the most frequently involved branch of the trigeminal nerve in this series of patients with 149 (46.6%) patients having pain solely in the mandibular division (Table I). The least frequently involved branch was the ophthalmic division, with only 6.9% of the patients having some involvement of this branch. No cases of TN solely affecting the ophthalmic division were seen in this cohort of patients. TN was mostly described by these patients as "sharp or shooting pain" (45%), followed by "throbbing pain" (19.1%), "electric shock/current−like pain" (16.6%), and "stabbing pain" (9.1%). A diverse number of trigger factors were reported, with many patients having more than one triggering activity. The most commonly reported trigger factor in this cohort of

Table I. Clinical features of TN patients according to gender

Clinical features	*Gender*		*Total (n, [%])*	P *value*
	Male (n)	*Female (n)*		
Age				
Median age [interquartile range]	60.2 [11.98] (123)	57.8 [9.92] (197)	58.2 [13.00] (320)	.073*
Side				
Right	54	126	180 (56.3)	.001†
Left	67	69	136 (42.5)	
Bilateral	2	2	4 (1.3)	
Total, n, (%)	123 (38.4)	197 (61.6)	320 (100)	
Branch of fifth cranial nerve				
Maxillary only	51	72	123 (38.4)	.265†
Mandibular only	57	92	149 (46.6)	
Ophthalmic and maxillary	6	4	10 (3.1)	
Maxillary and mandibular	5	21	26 (8.1)	
Ophthalmic, maxillary, and mandibular	4	8	12 (3.8)	
Total, n, (%)	123 (38.4)	197 (61.6)	320 (100)	

*Mann-Whitney test.
†Pearson Chi-square test.

patients was eating or chewing (36.3%). Almost a quarter of the patients (23.4%) reported no triggering factor or activity. In these patients, the pain was completely spontaneous.

Management

Thirty-nine patients (12.2%) were sent for neuroimaging (eight for computed tomography and 31 for magnetic resonance imaging) as a result of atypical clinical findings. Of these patients, seven (2.2%) had some form of tumor involving the trigeminal nerve. Carbamazepine was the first-line drug of choice in most instances (87.5%). Other drugs used included gabapentin, lamotrigine, pregabalin, baclofen, phenytoin, and amitriptyline. In 12.2% of patients, various combinations of medications were used to achieve adequate pain control as monotherapy was unsuccessful. With regard to side effects of medications, dizziness was the most commonly reported at 87.3%. The least frequently encountered adverse effects were altered levels of liver enzymes (2.5%), carbamazepine induced Stevens-Johnson syndrome (SJS) (1.3%), and leukopenia (1%).

DISCUSSION

Our findings are similar to those reported in the literature, with peak incidences in Asian patients falling between the fifth and seventh decades of life.[2,3,19] As TN is quite uncommon in relatively younger patients (<40 years of age), it is advisable to conduct thorough clinical and radiographic assessments to exclude TN secondary to tumors or demyelinating conditions in young patients or those with atypical clinical findings or pain symptomology.[8,11,12,20]

Diagnosis of TN is primarily based on clinical findings, especially pain symptomology. Although most of our patients described the pain primarily as intense, sharp, shooting pain, some described their pain as "throbbing pain," "pulling," or "stabbing pain." The findings parallel Asian studies by Loh et al. and Jainkittivong et al.[2,19] Others have also reported the pain being described as "electric shock–like," "burning," "excruciating," "lightning," "terrifying," and "unbearable."[2,19,21] Although some descriptors, such as "throbbing pain," are not commonly used by patients with TN, uncommon pain descriptors have been reported by other Asian studies as well.[2,16,19]

Description of pain is significantly influenced by the culture, language, and prior pain experience of the individual, and it is imperative that the clinician elucidate and record detailed pain symptomology and perform a thorough clinical assessment before arriving at a diagnosis of TN. All the study patients, however, did fulfill the diagnostic criteria of the first, second, and third editions of the ICHD and did not have any other special characteristics setting them apart from those patients with more usual pain descriptors.[17,18,22] Furthermore, the majority of these patients also responded well to pharmacotherapy with carbamazepine, alluding to the nature of classic TN.

The present study found a female predominance, with a ratio of 1.6:1, similar to findings in Thai, Indian, and Western populations (Table II).[1-3,19,23] In our study, we discovered that the right side was more commonly affected than the left side, with a ratio of 1.3:1 (excluding bilateral cases). This finding is consistent with other studies.[1,19] There is a possibility of anatomic variants on the right trigeminal nerve. Neto

Table II. Comparison of clinical features of patients with trigeminal neuralgia with data from other Asian studies

Clinical features	Total n (%)				
	Present study	*Loh et al. (1998)*[2]	*Ariyawardana et al. (2003)*[23]	*Jainkittivong et al. (2011)*[19]	*Yadav et al. (2015)*[3]
Number of patients, n	320	44	61	188	72
Gender					
Male	123 (38.4)	16 (36.3)	26 (43.0)	70 (37.2)	23 (31.9)
Female	197 (61.6)	28 (63.7)	35 (57.0)	118 (62.8)	49 (68.1)
Age					
Median age (interquartile range [IQR])/Mean (standard deviation [SD])	58.2 (13.00)	54.9 (SD not available)	Not available	52.5 (IQR not available)	54.9 (SD not available)
Side					
Right	180 (56.3)	24 (54.5)	42 (68.9)	119 (63.3)	45 (62.5)
Left	136 (42.5)	17 (38.6)	19 (31.1)	67 (35.6)	27 (37.5)
Bilateral	4 (1.3)	3 (6.8)	0 (0.0)	2 (1.1)	0 (0.0)
Branch of fifth cranial nerve					
Maxillary only	123 (38.4)	13 (29.5)	21 (34.0)	47 (25.0)	27 (37.5)
Mandibular only	149 (46.6)	22 (50.0)	40 (66.0)	57 (30.3)	41 (56.9)
Ophthalmic and maxillary	10 (3.1)	1 (2.3)	0 (0.0)	17 (9.0)	0 (0.0)
Maxillary and mandibular	26 (8.1)	8 (18.2)	0 (0.0)	55 (29.3)	4 (5.6)
Ophthalmic, maxillary, and mandibular	12 (3.8)	0	0 (0.0)	12 (6.4)	0 (0.0)

et al. showed that in most cases, the foramen ovale on the right of the human skull is narrower than that on the contralateral side.[24] Both of these foramina are the passage through which the maxillary and mandibular branches pass. Thus, Neto et al. hypothesized that the propensity of TN to be present on the right side of face may be caused by entrapment of the second and third divisions of the trigeminal nerves when crossing these foramina.[24] Bilateral involvement is rare, and 1.3% of our cases were found to have bilateral involvement. This finding is similar to reports from Thai and Western populations, reflecting a lower incidence of bilateral affliction.[1,19] However, Loh et al. reported bilateral involvement in 6.8% of Singaporean and Malaysian populations.[2] That study, however, had a very small sample size and may not be truly representative of those populations.[2]

Over half the patients in this present study had mandibular branch involvement, which is similar to other Asian studies (Table II).[2,3,19,23] None of our patients had TN affecting only the ophthalmic branch. In contrast, studies on American and Scottish populations revealed a slight preponderance of the maxillary division.[1,25] We concur with Loh et al. that it is possible that patients with TN involving the maxillary division, the ophthalmic division, or both may have been managed by physicians, otorhinolaryngologists, or even ophthalmologists and neurologists.[2] As such, a retrospective study looking at data from all of the different specialties that manage TN maybe the most objective way to obtain concrete evidence on the suspected increased involvement of the mandibular branch in Asian patients.

About 17% of patients in this study had medical comorbidities, with the most common being diabetes mellitus. The reason may be that diabetes mellitus is more frequently encountered in the older population. Two previous studies described patients with diabetes and TN becoming asymptomatic (pain-free) by successful control of glycemia.[26,27] An electrophysiologic study has shown that diabetes often affects trigeminal nerve function and, therefore, it may play a role as a causative factor in some cases of TN.[28]

Although painful trigeminal neuropathy can be caused by craniofacial trauma, in this cohort of patients, the area affected by TN was not in the region of trauma and, as such, was considered to be noncontributory to the etiology of TN in these patients.

In 1997, Balestrino and Leandri[29] reported a case of TN related to an ischemic event in the pontine region; however, TN secondary to stroke is rare, with only a few case reports being published.[29-34] It is usually accompanied by other clinical signs and symptoms suggestive of a central lesion. Central pain after a stroke is a separate entity that may mimic the pain symptomology of trigeminal neuropathy or TN.[22,35] Central pain after a stroke is thought to be caused by lesions of the ascending projections of the trigeminal nuclei, and the pain should have developed within 6 months of the stroke, with an obvious vascular lesion being demonstrable at the appropriate site with neuroimaging modalities.[22,35]

Although trigeminal neuropathy in connective tissue disease has been reported by several authors, the exact pathogenesis and level of involvement are not entirely understood, as most of the studies had very small numbers of patients or were single case reports.[36-39] TN-like trigeminal neuropathy has also at times been found to precede the features of some connective tissue diseases, such as Sjogren syndrome, systemic lupus erythematosus, mixed connective tissue disease, and systemic sclerosis.[40-43] The association appears to be stronger with mixed connective tissue disease compared with other connective tissue diseases.[37,40,44] It is, therefore, highly advisable to screen patients with idiopathic TN having some signs and symptoms of trigeminal neuropathy or rheumatologic disease for antiribonucleoprotein antibodies to identify the presence of connective tissue disease so that suitable early intervention can be instituted.[36,40]

The etiologic role of stroke and connective tissue disease in our cohort of patients with TN was difficult to assess; because of the retrospective nature of the study, it was difficult to ascertain and accurately assess the timing of TN in relation to the diagnosis of stroke or connective tissue disease. However, all of our patients were thoroughly examined and assessed for signs and symptoms of stroke as well as connective tissue disease; if these were present, patients would have been referred for further assessment by the relevant specialties.

A small number of patients (2.2%) had TN secondary to intracranial tumors with involvement of the trigeminal nerve. However, this figure is not a true representation of TN secondary to tumors, as not all patients underwent neuroimaging studies. Although a recent review suggested that routine neuroimaging for all patients with TN may be useful in detecting structural lesions,[12] this is not very practical because of the limited availability of imaging modalities. The same review, however, did highlight that clinical findings are useful in distinguishing TN secondary to tumors ("symptomatic TN) from classic TN.[12] At our clinics, patients are usually sent for neuroimaging only when clinical features are suggestive of an underlying space-occupying lesion or demyelinating disease.

The management aim of TN is long-term relief from the intolerable pain. Several pharmacologic and surgical treatments for TN are available. In most circumstances, pharmacotherapy remains the favored treatment, with carbamazepine proving to be the most effective.[10,11,45] In this study, all our patients were treated pharmacologically. Most were treated with carbamazepine, and they responded favorably. Our finding corresponds with most studies.[3,10,19] Sato et al. reported that 90% patients with TN experienced pain relief with initial treatment with carbamazepine.[46] An international guideline and evidence-based review by the European Federation of Neurologic Societies and the American Academy of Neurology also recommended carbamazepine as the preferred initial drug in managing TN symptoms.[11,12] In this study, other drugs, including gabapentin, lamotrigine, pregabalin, baclofen, phenytoin, and amitriptyline, were used for patients who did not respond to carbamazepine. In more refractory cases, a combination of these drugs was employed. Cheshire reported that gabapentin could be useful as a first-line or second-line drug for TN, especially in cases resistant to gold-standard drug therapy.[47] Other medications with some published evidence are lamotrigine, baclofen, and pregabalin.[48-50]

Watson stated that about 40% patients treated with carbamazepine experience side effects.[10] The most frequently reported side effects of carbamazepine were drowsiness, dizziness, and gastrointestinal disturbances.[10] In the present study, 87.5% of the patients treated with carbamazepine experienced dizziness, similar to the rate reported by Watson.[10] Other possible side effects are leukopenia, abnormal liver function, cerebellar dysfunction, aplastic anemia, and hepatitis. We routinely monitor our patients for these possible side effects. The most serious potential side effects of carbamazepine are severe cutaneous adverse reaction, SJS, and toxic epidermal necrolysis.[51] Only four of our patients treated with carbamazepine developed carbamazepine-induced SJS.

It has been reported that genetic factors play an important role in developing drug hypersensitivity. Chung et al. were the first to describe the relationship between human leucocyte antigen (HLA)-B*1502 and SJS induced by carbamazepine in the Han-Chinese.[52] Subsequently, the U.S. Food and Drug Administration made genetic screening mandatory in patients of Asian ancestry before initiating treatment with carbamazepine.[52] A study in Malaysia showed that HLA-B*1502 was also present in 75% of Malay patients with carbamazepine-induced SJS or toxic epidermal necrolysis.[51] However, because of logistical problems, not all clinics are able to perform HLA-B*1502 genotyping for these patients.

A major limitation of this study is its retrospective nature. In-depth information on pain symptomology and duration of disease were not uniformly available. This is further compounded by the multicenter study design. Many different specialists were involved in the diagnosis and management of these patients, and it was not possible to perform calibration, because of the retrospective nature of this study. Although the diagnosis of TN was based on established guidelines,[17,18] variability among clinicians was unavoidable. Information obtained from patient records is bound to be less consistent and accurate than that obtained from reports

of prospective studies. Inadequate record keeping is a recurring, but often overlooked, problem in patient management at institutions. In this study, the retrospective nature of data collection was a limiting factor, as was the reliance on data obtained from medical records completed by numerous medical staff. Another factor that needs to be considered is that TN patients may be managed by medical specialists (e.g., neurologists, physicians, otorhinolaryngologists, etc.) or even general practitioners.

Routine neuroimaging for all TN patients was not performed at all centers, as this is logistically difficult because of limited resources, and currently there is only weak evidence (Level C) for routine head imaging.[11,12] One must also consider that the study period was over a duration of more than 10 years and as such many changes affecting clinical practice would have occurred during this time frame. This is also the reason for using both the first and second editions of the ICHD as guides for classification. It is also worth reemphasizing that routine neuroimaging for all TN patients is not a recommended practice because of lack of availability and cost.[11,12,20] Neuroimaging is recommended when the clinical findings are more suggestive of TN secondary to tumors or other pathologic processes; however, what is important and most useful is performing a thorough clinical examination, with emphasis on CN examinations and pain symptomology, as abnormal trigeminal reflexes, bilateral involvement, and trigeminal sensory deficits have been found to be useful in distinguishing secondary TN from classic TN.[11,12,20]

CONCLUSIONS

This study has demonstrated that there is very little difference between Caucasian and Malaysian TN patients in terms of their clinical and demographic features. Prominent involvement of the mandibular branch may be a feature that is unique to Asian patients; further epidemiologic studies involving other clinical disciplines will need to be performed to confirm this. However, Asian patients with TN are quite likely to present initially at dental clinics for management of their pain because of the frequent involvement of the mandibular division, and thorough history taking and clinical examination are vital to obtaining an accurate diagnosis. As carbamazepine is still the main pharmacologic agent used for the management of TN, HLA-B*1502 testing before initiation of therapy in Malaysian patients is advisable.

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