Original Article

Profiling of Patients Presenting with Trigeminal Neuralgia and Outcomes of Medical Management in a Tertiary Care Center

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Background: Trigeminal neuralgia (TN) is a chronic orofacial neuropathic pain that affect quality of life of the sufferers.

Objective: To describe retrospectively the clinicodemographic data of patients presenting with TN at a tertiary care center over 4-year period. The data include its natural history, time lapse before diagnosis and outcomes of medical management.

Materials and Methods: A retrospective study was performed using 203 medical and dental records of TN patients that were referred to the Orafacial Pain Clinic, Faculty of Dentistry and Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand over a 4-year period. The collected data were recorded using Case Record Form composing of patient demographic information, natural history of TN, neuroimaging data and treatment modalities.

Results: 203 trigeminal neuralgia (139 females and 64 males) patient records were reviewed. The average age of onset was 52.2 years (between 16 and 85 years), the right side was the most common affected area (61.5%), and intraoral mucosa was the most common trigger point area (54.5%) reported. The character of pain was sharp shooting, sudden onset and intermittent pain. The time lapse before trigeminal diagnosis was less than 12 months (59.9%) while 53.4% of TN patients reported having natural remission periods between 1 and 2 months. Carbamazepine is the most common drug prescribed (48.5%) of which 14.5% patients report maculo-papular rash skin adverse reaction, 1.1% Stevens-Johnson syndrome/toxic epidermal necrolysis and 0.6% erythema multiforme, respectively.

Conclusion: The present study has given some insights into the natural history of TN, notable regarding the management and its outcome. Medical treatment, especially carbamazepine and oxcarbazepine are still the first line drugs recommended for TN; HLA-B*1502 allele testing is strongly recommended before initiating therapy in all Asian patients.

Keywords: Trigeminal neuralgia, Natural history, Time lapse, Remission period

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Trigeminal neuralgia (TN) is a chronic neuropathic orofacial pain with distinct diagnostic criteria which are included in both the International Association for the Study of Pain (IASP) and the International Headache Society (IHS) classification systems[1,2]. Both the IASP and the IHS classification recognize and suggest diagnostic criteria for two forms of TN. Classical trigeminal neuralgia is TN of unknown etiology or due to vascular compression of the trigeminal nerve at the root entry zone. Secondary or symptomatic TN is related to central nervous system lesions, multiple sclerosis or structural abnormalities of the skull base. Both IASP and IHS highlight the brief, sudden, sharp shooting and electric shock-like pain in quality but neither take into account the cyclical nature of TN as some patients report of having complete natural remission period. TN is rare with the crude annual incidence for women and men was 5.7 and 2.5 per 100,000, respectively, and incidence rates increased with age but not with sex[3,4]. However, recent surveys from both the United Kingdom and the Netherlands show much higher incidences of 26.8 and 28.9 per 100,000, respectively[5,6]. The onset of TN pain occurs most frequently in patients aged 50 years and older with higher incidence in females than males for nearly all age group[3,4]. Pain is characteristically triggered by light touch activities, with the major precipitating factors such as chewing, talking, kissing,

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brushing teeth, applying facial make up with some patients report pain that could be provoked spontaneously[7].

Antiepileptic drugs have been shown to be the most effective drugs for the management of TN. Carbamazepine (CBZ) and Oxcarbazepine (OXC) remain the standard of treatment but has a wide range of undesirable side effects and drug interactions which make it difficult to use particularly among East Asian group which has a higher risk of skin adverse reaction from the first line drug for this condition[8]. Other medications that have been evaluated in randomized controlled trial for TN and still in current use include lamotrigine, baclofen, gabapentin, phenytoin and topiramate. However, the medications were used as add on treatment to other anticonvulsants making evaluation of its efficacy difficult[9]. When TN patients that were unresponsive to drugs or had drug allergy or unable to tolerate its adverse effects, neurosurgical interventions including microvascular decompression (MVD) surgery, should be considered with patient decision is important at each proposed change.

Although several authors have reported on various aspects of clinical features of TN in the Asian population[4,8,10-12], there are currently no published data on the natural remission period and the delay in the diagnosis of TN in these group of patients. Moreover, previous Asian TN studies were collected entirely in the clinical dental setting resulting in nearly all TN symptoms presented mainly at the area of the lower face and in the oral cavity. The aims of this study were to describe the clinical signs, symptoms, causes, time lapse before diagnosis and outcomes of the medical management in TN patients presenting to the tertiary care center including medical and dental care settings.

Materials and Methods

A total of 203 TN patients were consulted over 4 years at the Orofacial Pain Clinic, Faculty of Dentistry and Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand between 2006 and 2010. The present study obtained ethical approval by the local ethics committee in Human Research of Khon Kaen University (No. HE541030). Inclusion criteria were records of patients diagnosed with TN by orofacial pain and oral medicine specialist or neurologist using the diagnostic criteria of the International Classification of Headache Disorder of the IHS[2]. The collecting data was recorded in Case Record Form (CRF) composing of patient demographic information, natural history of TN, MRI reports by radiologists and treatment modalities. Content validity by three experts in orofacial pain and oral medicine was calculated. After that, the reliability test of the CRF was performed by two observers. Each observer was blinded to the other's judgement. The reliability testing was tested by inter-observers. Within 5% of the recorded charts, the agreement between two observers on the similarity of the content was 80.9%. The agreement of data from the first observer was 87.7%; while, the agreement from the second observer was 88.4%. Then, the result obtained from CRF was statistically analyzed using SPSS (version 11.5) for Windows.

Statistical analysis

Descriptive statistics were used to describe the frequency and percentage of demographic characteristics of the patients, natural history of TN, MRI interpretation and treatment modalities.

Results

Two-hundred and three TN patients' medical and dental records (139 females and 64 males) were reviewed. The female-to-male ratio was 2.17: 1. Their ages of onset ranged from 16 to 85 years (the mean age being 52.2 years). The right side of the face was mostly affected (61.5%), while bilateral side was found only in 2 patients (1.1%). The mandibular division (27.3%) and the combined maxillary and mandibular divisions (27.3%) were most frequently involved, followed by the combined ophthalmic maxillary and mandibular divisions (18.2%). The least frequently affected division was the ophthalmic division (0.9%). Intraoral mucosa was the most common trigger point area (54.5%) reported. The character of pain was described as "sharp shooting" with sudden onset and intermittent pain as shown in Table 1. The time lapse before TN diagnosis was less than 12 months in the most cases (59.9%) while 53.4% of TN patients reported of having natural remission period between 1 and 2 months (Table 2). The MRI reports showed the majority of TN patients were diagnosed as classical TN (90.9%) due to vascular compression to the root entry zone of the trigeminal nerve and TN patients were symptomatic TN (9.1%) caused by structural lesions such as meningioma (2.6%), epidermoid cyst (3.9%), schwannoma (1.3%) and brainstem arteriovenous malformation (1.3%) as shown in Table 3.

Medical management of TN patients presented in Table 4, the authors found that the most common drug prescribed was CBZ (48.5%), followed by CBZ combined with amitriptyline (13%), OXC (11%) and multiple drugs used (7%), composing of CBZ, OXC, baclofen, amitriptyline, nortriptyline, gabapentin and phenytoin. Patients allergic to CBZ reported of having maculo-papular rash (14.5%), Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (1.1%) and erythema multiforme (0.6%) (Table 5).

Discussion

Without proper pain control, TN can be a chronic and debilitating disease affecting the quality of life of patients and their care givers. From the present study of the natural history of TN, it indicated that the majority of patients were female with the peak age at onset was in the fourth decade of life. The condition mostly affected right side of the face, and intraoral mucosa was the most common trigger point area. These results were similar to the previous studies[4,8,10-12]. Even though the present study was done in both medical and dental clinics, predominant involvement of the mandibular division or the combined mandibular and maxillary divisions of the trigeminal nerve described is similar to findings in the Malaysian[8], Singaporean[4], Indian[11] and Sri Lankan[12] populations and this maybe a feature found in Asian patients with TN. This may be the reason why they are more likely

Table 1. Clinicodemographic features of trigeminal neuralgia patients

Natural history	n (%)	n
Gender		
Male	64 (31.5)	203
Female	139 (68.5)	
Age of onset		
10 to 19	3 (1.6)	189
20 to 29	7 (3.7)	
30 to 39	26 (13.8)	
40 to 49	43 (22.8)	
50 to 59	55 (29.1)	
60 to 69	31 (16.4)	
70 to 79	20 (10.5)	
80 to 89	4 (2.1)	
Side of face and division of nerve		
Right		
V1	1 (0.9)	
V2	19 (17.2)	
V3	30 (27.3)	110 (61.5)
V1 + V2	10 (9.1)	
V2 + V3	30 (27.3)	
V1 + V2 + V3	20 (18.2)	
Left		
V1	5 (7.5)	
V2	8 (11.9)	
V3	19 (28.3)	179
V1 + V2	6 (9.0)	67 (37.4)
V1 + V3	1 (1.5)	
V2 + V3	20 (29.9)	
V1 + V2 + V3	8 (11.9)	
Bilateral		
V3	1 (50)	2 (1.1)
V1 + V2 + V3	1 (50)	
Character of pain		
Dull pain	24 (13.0)	184*
Stabbing pain	23 (12.5)	
Sharp shooting pain	134 (72.8)	
Electric like shock pain	72 (39.1)	
Burning	28 (15.2)	
Numbness	3 (1.6)	
Duration of pain		
Less than 1 min	13 (13.4)	97
1 to 10 min	72 (74.2)	
More than 10 min	12 (12.4)	
Onset of pain		
Sudden pain	174 (99.4)	175
Gradual pain	1 (0.6)	
Periodicity of pain		
Continuous pain	15 (8.8)	171
Intermittent pain	156 (91.2)	
Trigger point		
Forehead	4 (3.6)	110*
Periocular	8 (7.3)	
Perinasal	12 (10.9)	
Cheeks	30 (27.3)	
Ears	3 (2.7)	
Perioral	29 (26.4)	
Intraoral	60 (54.5)	
Chin	3 (2.70)	
Neck	1 (0.9)	
Time lapse before TN diagnosis		
12 months or less	97 (59.9)	162
12 to 24 months	31 (19.1)	
24 to 36 months	11 (6.8)	
36 months or more	21 (14.2)	

* More than one type of pain characters and trigger points were described

Table 1. cont.

* More than one type of pain characters and trigger points were described

Table 2. Natural remission period in 101 patients with trigeminal neuralgia

	n (%) n = 101
Remission period	54 (53.4)
Once time	47 (87.0)
<3 month	20 (42.6)
3 to 6 month	9 (19.1)
7 to 12 month	14 (29.8)
13 to 24 month	4 (8.5)
Twice times	5 (9.3)
Three times	2 (3.7)
No remission period	47 (46.6)

to present at dental clinic for management of their pain. In contrast, studies from the United States and Scotland report a slight preponderance of the maxillary division[13,14]. The bilateral involvement of TN is however a rare occurrence (1 to 6%)[15]; our study has reported 1.1% of TN patients with bilateral symptoms. In bilateral cases, pain rarely begins on both sides concurrently and there is often a gap of several years before the other side is affected. However, if only the more symptomatic side was treated, contralateral symptoms often became more disabling with time. Besides this, the data of the time lapse before TN diagnosis was collected and the authors found that the duration between the first onset of TN symptoms and diagnosis in the majority of patients (59.9%) was at 12 months or less. For 14.2% of patients there was a further delay of up to 36 months or more before the diagnosis was made due to its cyclical nature and similarity to the odontogenic pain symptoms, resulting in unnecessary dental treatments such dental extractions and root canal treatment[16]. The clinical history is therefore crucial for a correct diagnosis and time has to be taken over this aspect as there are no diagnostic tests. The need for minimizing the time lapse before diagnosis and management is important to reduce patients' suffering and unnecessary treatments.

The present study showed that 53.4% of all patients had a spontaneous natural remission period of less than 3 months. It is different from Rushton and MacDonald who reported the analysis of 155 TN patients which pointed

Table 3. Results of MRI in 76 patients with trigeminal neuralgia

Type of trigeminal neuralgia	Results of MRI	n (%)	n = 76
Classical trigeminal neuralgia	No significant finding	41 (53.9)	69 (90.9)
	Vascular compression	28 (36.8)	
Symptomatic trigeminal neuralgia	Meningioma	2 (2.6)	7 (9.1)
	Epidermoid cyst	3 (3.9)	
	Schwannoma	1 (1.3)	
	Brainstem arteriovenous malformation	1 (1.3)	

Table 4. Medical treatments in 200 patients with trigeminal neuralgia

Medical treatment	n (%)
Carbamazepine (including carbamazepine CR)	97 (48.5)
Oxcarbazepine	22 (11.0)
Gabapentin	10 (5.0)
Valproic acid	2 (1.0)
Phenytoin	2 (1.0)
Carbamazepine + amitriptyline	26 (13.0)
Carbamazepine + nortriptyline	1 (0.5)
Carbamazepine + baclofen	6 (3.0)
Carbamazepine + gabapentin	7 (3.5)
Carbamazepine + clonazepam	1 (0.5)
Carbamazepine + valproic acid	1 (0.5)
Oxcarbazepine + amitriptyline	2 (1.0)
Oxcarbazepine + baclofen	1 (0.5)
Gabapentin + amitriptyline	5 (2.5)
Gabapentin + baclofen	1 (0.5)
Phenytoin + baclofen	2 (1.0)
Multiple drugs used*	14 (7.0)

* Multiple drugs used: 3 or more medications for treatment trigeminal neuralgia patients consists of carbamazepine, oxcarbazepine, baclofen, amitriptyline, nortriptyline, gabapentin and phenytoin

out 50.3% of patients had experienced one or more spontaneous remission periods lasting 6 months or longer and 24.5% of them had natural remissions of one year or longer[17]. It was suggested that the spontaneous natural remission period, may be caused by remyelination of the myelin sheath of the affected trigeminal nerve, resulting in the rapid recovery of nerve conduction across the indented root[18,19]. When these spontaneous remissions occur, some patients may not choose to continue medical treatment until the pain recurred. Moreover, the duration and number of spontaneous natural remission could influence on the patients' decision making for choices of other interventions as Rushton and Macdonald (1957) showed that patients who had the longest remission periods were least likely to choose to have MVD surgery[17].

Routine neuroimaging for all TN patients is a necessary tool to distinguish classical TN from symptomatic TN that caused by specific pathology in the posterior cranial fossa. From our study, the most common type of TN found was classical TN (90.9%), in which MRI revealed vascular compression in 36.8% of our TN patients. Not a single case in our study was found to have multiple sclerosis, which was similar to other Asian reports[4,8,10-12]. However, the cohort study of 120 TN patients by Cruccu et al[20] found that 80% of TN patients had classical TN, while 16% of these patients' MRI revealed neurovascular contact. Goh et al[21] reported 14.3% of their patients had symptomatic TN; however, our report found only 9.1% of our TN patients had this condition, but this maybe from the fact that not all of our new TN patients underwent routine brain imaging. Routine head imaging is considered useful to identify other intracranial structural abnormalities in symptomatic TN. On the other hand, high-resolution brain CT or MRI is still unable to identify accurately classical TN patients with neurovascular compression as they have shown inconsistency in comparing the symptomatic side to the asymptomatic side and may have resulted from differences in the imaging techniques employed.

Antiepileptic drug CBZ and OXC, are recommended by guidelines of the European Federation of Neurological Societies[22] and the American Academy of Neurology[23] to be used as first-line treatment for TN. From our study CBZ is the most prescribed medication either used as a monotherapy (48.5%) or combined with other drugs and this conforms with other studies[10,24]. Although the evidence for CBZ is stronger than for OXC due to the lack of high quality RCT for the latter, it is reported to have fewer side effects and similar antineuralgic efficacy[9]. Besides this, other drugs are commonly used in TN such as phenytoin, baclofen, lamotrigine, clonazepam, gabapentin and amitriptyline. Considering the relative mode of action, CBZ and phenytoin block voltage-dependent sodium channels and its analgesic mechanism is therefore believed to be related to a reduction in ectopic nerve discharges and stabilization of neural membranes[25]. Whereas valproic acid and clonazepam act as gamma-aminobutyric acid (GABA) analogues that decrease neural membrane action potentials and therefore decrease nerve excitability. Gabapentin blocks L-type voltage dependent Ca^{2+} channels which is the probable reason for its antiepileptic and analgesic properties[26]. Baclofen is a centrally acting muscle relaxant; its anti-neuralgic activity is through GABA channels similar to the mechanism of valproic acid and clonazepam[27]. Tricyclic antidepressant, amitriptyline, inhibit serotonin and noradrenaline reuptake inhibitor and enhancing descending inhibitory controls in pain

Table 5. Carbamazepine drugs allergy in patients with trigeminal neuralgia

Drugs allergy	Type of allergy	n (%)	n
No carbamazepine drugs allergy		150 (83.8)	179
Carbamazepine skin adverse reactions	Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN)	2 (1.1)	
	Erythema multiforme	1 (0.6)	
	Maculo-papular rash	26 (14.5)	

modulation[28]. Considering the narrow mechanism of action of the drug available, combination treatments seem to be an alternative choice. However, there are no published studies comparing polytherapy with monotherapy in TN management.

In the past few years, many new drugs have been used and studied in TN patients, however CBZ remains the most effective drug, despite its poor tolerability and possible skin adverse reactions in some ethnic groups. Using CBZ can be troublesome in groups of patients with higher risk of hypersensitivity reaction. Our report showed 16.2% of TN patients had CBZ-induced drugs allergy including maculo-papular rash (14.5%), erythema multiforme (0.6%) and SJS/TEN (1.1%). Similarly, the study of Gayford and Redpath reported CBZ-induced cutaneous reaction such as maculo-papular rash (3.3%), SJS (0.2%) and discoid lupus eryhtematosus (0.2%)[29]. Furthermore, recent reports have shown that the frequency of human leukocyte antigen (HLA) allele B*1502 (HLA-B*1502) is high among Asians, particularly in Han Chinese (10.2%), Thais (6.1%), Singaporean (11.6%), Filipino (5.3%) and Malays (8.4%) and it is now a marker for CBZ and OXC-induced SJS/TEN[30]. In addition, the United States Food and Drug Administration (FDA) as well as other public health authorities have recommended genotyping all Asian for the allele before starting these medications[30]. Thus, newly diagnosed TN patients with HLA-B*1502 allele may be suitable for the use of lamotrigine. However, lamotrigine is not recommended for TN patients with severe pain as rapid dose escalation could result in skin rashes. Due to limitation of medication available at present and there are higher risks for skin adverse drug reaction for the main drugs used in Asian population, neurosurgical options maybe suitable or maybe faster than other ethnic group.

Conclusion

The present study has given some insights into the natural history of TN with periods of remission and time lapse before TN diagnosis, notably regarding the management and its complications. It also emphasizes the need to explain early options of MVD surgery to TN sufferers for their future decision-making. Medical treatment, especially CBZ and OXC are still the first line treatment, when patients do not tolerate its side effects or when pain in poorly controlled, add on medications such as baclofen. As CBZ and OXC are still the first line drugs recommended for TN, HLA-B*1502 allele; testing is strongly recommended before initiating therapy in all Asian patients.

Limitations of the study

This study was a retrospective descriptive study in which clinical data of TN symptoms on the initial consultation was based entirely on the patients' recall. The missing and inconsistent data on the patients' records are the main limitation of this design. The medical and dental records from the university clinics were also completed by numerous medical and dental staff making data collecting difficult and incomplete.

What is already known on this topic?

The present study demonstrated the similarities of numerous clinicodemographic features of TN such as gender, side, age of onset and pharmacological management.

What this study adds?

The new findings from the present study revealed time lapse before the establishment of TN diagnosis and duration of natural remission period as they were never mentioned in any of the previous Asian studies. Unfortunately, there were up to 36 months delay in nearly 15% of TN patients seen in our tertiary care center before TN diagnoses were made; hence the reduction of this delay can be achieved if primary care doctors and dentists were made more aware of the unique symptoms of this condition.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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