Original Article

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Clinical characteristics of trigeminal neuralgia in a dental hospital

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Background: Neurovascular compression (NVC) is a well-known cause of trigeminal neuralgia (TN). However, patients with idiopathic TN (ITN) do not have evidence of NVC on magnetic resonance imaging (MRI), and other patients may remain asymptomatic despite evidence of NVC on MRI. This suggests that there may be additional risk factors for TN development other than NVC. Although epidemiological factors, such as age and sex differences, are useful for understanding the pathophysiology of TN, detailed statistics for each TN subtype are currently unavailable. Therefore, this study aimed to classify patients with TN into the following groups based on data extracted from past medical records: classical TN (CTN), secondary TN, and ITN.
Methods: The characteristics of the groups and their differences were explored.
Results: CTN was more common in women than in men, as previously reported, whereas ITN was more common in men than in women. The ratio of pain sites located on the right side of the face was high in all groups. Patients with CTN were also prone to NVC on the asymptomatic side.
Conclusion: By investigating TN subtype, it may be possible to elucidate the pathophysiology of TN. This would greatly improve treatment outcomes.

Keywords: Classical Trigeminal Neuralgia; Idiopathic Trigeminal Neuralgia; Neurovascular Compression; Secondary Trigeminal Neuralgia.

INTRODUCTION

Trigeminal neuralgia (TN), which typically manifests as pain in the orofacial region, is an important disease in dentistry because it may cause pain in the teeth and oral mucosa.

Classical trigeminal neuralgia (CTN) displays characteristic symptoms, such as paroxysmal and electric shock-like pain, and may result from demyelination caused by pressure on the trigeminal root entry zone by blood vessels [1]. However, some patients with TN do not present with evidence of neurovascular compression (NVC) on magnetic resonance imaging (MRI) and are diagnosed with a condition known as idiopathic trigeminal neuralgia (ITN). Additionally, other patients may remain asymptomatic despite evident NVC on MRI. These findings suggest the existence of risk factors for the development of TN other than NVC.

Treatments for CTN and secondary trigeminal neuralgia (STN) include surgical management, stereotactic radiosurgery, and pharmacological treatment. However,

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there are few treatment options for ITN besides drug therapy. This is an important unmet clinical need, and further studies on the pathophysiology and treatment of each subtype of TN are required. Although epidemiological factors, such as age and sex differences, are useful for understanding the pathophysiology of TN, detailed statistics for each TN subtype are lacking. The diagnostic criteria and clinical practice guidelines for TN have been revised in various studies. However, they remain unclarified unclear. TN can be classified into cases of CTN, STN (due to multiple sclerosis and space-occupying lesions, such as cerebellopontine angle tumors, arteriovenous malformations, and meningiomas), and ITN [2]. CTN and STN have clear nerve compression findings with morphological changes in the trigeminal nerve, and causative disorders can be observed during MRI and surgery. However, ITN is not associated with abnormalities on MRI or electrophysiological examinations. There are multiple causes of TN, and clinical statistics for each subtype of TN are useful for elucidating its pathophysiology. However, there is a lack of detailed studies on this topic. Therefore, this study classified patients with TN into the following groups based on data from past medical records: CTN, STN, and ITN. The characteristics of these groups and their differences were explored.

METHODS

This retrospective study was approved by the Tokyo Dental College Ethics Review Committee (approval number: 882). Patients who were clinically diagnosed with TN at Tokyo Dental College Suidobashi Hospital between January 2010 and December 2018 were included. We excluded patients with paroxysmal pain lasting >2 minutes and those with bilateral pain, paresthesia, and pain resistant to carbamazepine.

1. Survey items

Data were extracted from medical records at the time of TN diagnosis. Information on the following was extracted: sex, age, painful area (branch of the trigeminal nerve affected), evaluation of NVC on the symptomatic and asymptomatic sides by MRI, type of compressed blood vessel, treatment administered, and side effects in subjects who received carbamazepine.

2. Classification

Based on the MRI findings, TN was classified into three groups—CTN caused by alterations in the trigeminal root due to NVC, such as distortion or atrophy [3] (Fig. 1A); STN caused by the primary disease (Fig. 1B); and ITN without evident NVC.

3. Age and sex of the subjects

The age and sex of the subjects were documented, and age differences according to sex were compared.

4. Age and sex ratio of each group

The age differences by sex were compared for all groups.

5. Age and sex differences between classical trigeminal neuralgia and idiopathic trigeminal neuralgia

We compared the age differences between the two groups by sex.

6. Pain distribution

We determined the overall prevalence of pain as well as of that on the left and right sides for each division of the TN (V_1, V_2, V_3) and in each group.

7. Evaluation of neurovascular compression on magnetic resonance imaging

We investigated the types of NVC and causative blood vessels on the symptomatic (painful) and asymptomatic sides using MRI scans.

8. Treatment received

We calculated the percentages of patients in each group

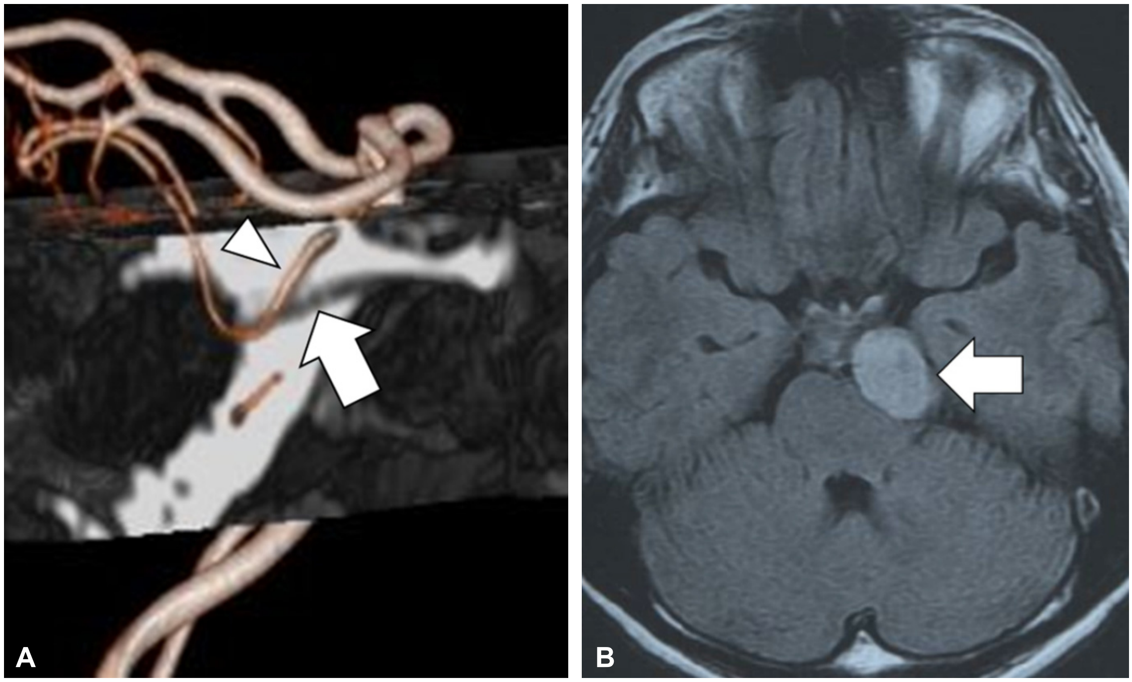

Fig. 1. (A) Typical example of classical trigeminal neuralgia. The superior cerebellar artery (SCA) is compressing the trigeminal nerve. Arrow: Trigeminal nerve, Arrowhead: SCA (B) Typical example of secondary trigeminal neuralgia. This figure presents a case of trigeminal neuralgia due to a brain tumor. Arrow: Brain tumor compressing the trigeminal nerve.

receiving different treatments.

9. Side effects of carbamazepine

The type and frequency of side effects in patients who received carbamazepine therapy were investigated. In patients whose carbamazepine therapy was discontinued, subsequent treatment was also recorded.

10. Statistical analyses

Student's t-test was used when variables in both groups were normally distributed; otherwise, the Mann–Whitney U test was used. The level of significance was set at $P < 0.05$. Statistical Package for the Social Sciences version 24 (International Business Machines Corp., Armonk, NY, USA) was used.

RESULTS

1. Age and sex

Among the 133 patients diagnosed with TN, seven were excluded because of persistent pain (n = 2), carbamazepine ineffectiveness (n = 4), or bilateral pain (n = 1). The average patient age was 60.4 ± 15 years. The ratio of women to men among all patients was 1.57:1, with 77 women (average age 63.17 ± 15 years) and 49 men (average age 55.25 ± 14 years; Table 1). The average age of women was significantly higher than that of men (Mann–Whitney U test, P = 0.004).

2. Age and sex ratio of each group

Ninety-six patients (average age 61.4 ± 15.5 years) were diagnosed with CTN. CTN was significantly more common in women than in men (ratio 2:1) (Mann–Whitney U test, P = 0.003). Five patients (59.6 ± 12.8 years), including three women and two men, were classified as having STN. Twenty-five patients (56.7 ± 17.8 years) were classified as having ITN. The male-to-female ratio in the ITN group was 3:2. There was no sex difference according to age (Mann–Whitney U test, P = 0.279).

Table 1. Comparison of ages between men and women according to each TN subtype, and according to age difference, between CTN and ITN

	CTN			STN			ITN			All TN		
	Total	Women	Men	Total	Women	Men	Total	Women	Men	Total	Women	Men
n	96	64	32	5	3	2	25	10	15	126	77	49
Mean (±SD)	61.4 (15.5)	64.4 (15.6)	55.5 (13.8)	59.6 (12.8)	55.3 (14.6)	66.0 (9.9)	56.7 (17.8)	59.5 (17)	52.4 (19.1)	60.4 (15.9)	63.2 (15.8)	55.3 (15)
Median (IQR)	64.0 (24.3)	69.0 (22.3)	50.5 (20.3)	59 (23)	49.0 (13.5)	66 (7)	57(33)	62 (26.5)	49(31.8)	62(25.8)	66.5 (22.8)	55 (21.8)
P value	0.003*						0.279			0.004*		

Type of TN		n	Median	Average rank	P-value
Men	CTN	32	50.5	22.2	0.506
	ITN	15	49	19.3	
Women	CTN	64	69	41.3	0.288
	ITN	10	62	34.3	
All	CTN	96	64	62.9	0.235
	ITN	25	57	53.6	

*Significant difference in the Mann–Whitney U test. CTN, classical trigeminal neuralgia; IQR, interquartile range; ITN, idiopathic trigeminal neuralgia; SD, standard deviation; STN, secondary trigeminal neuralgia; TN, trigeminal neuralgia.
There was no age difference between CTN and ITN.

Table 2. Laterality of pain and distribution across trigeminal nerve divisions

n (%)	Right	Left	Total
CTN			
V_2	22 (22.9)	15 (15.6)	37 (38.5)
V_3	25 (26)	12 (12.5)	37 (38.5)
V_1 and V_2	2 (2.1)	1 (1)	3 (3.1)
V_2 and V_3	13 (13.5)	6 (6.3)	19 (19.8)
Total	62 (64.6)	34 (35.4)	96 (100)
STN			
V_2	1 (20)	0	1 (20)
V_3	2 (40)	0	2 (40)
V_1 and V_2	0	0	0
V_2 and V_3	1 (20)	1 (20)	2 (40)
Total	4 (80)	1 (20)	5 (100)
ITN			
V_2	10 (40)	3 (12)	13 (52)
V_3	3 (12)	6 (24)	9 (36)
V_1 and V_2	0	0	0
V_2 and V_3	2 (8)	1 (4)	3 (12)
Total	15 (60)	10 (40)	25 (100)
All TN			
V_2	33 (26.2)	18 (14.3)	51 (40.5)
V_3	30 (23.8)	18 (14.3)	48 (38.1)
V_1 and V_2	2 (1.6)	1 (0.8)	3 (2.4)
V_2 and V_3	16 (12.7)	8 (6.3)	24 (19)
Total	81 (64.3)	45 (35.7)	126 (100)

CTN, classical trigeminal neuralgia; ITN, idiopathic trigeminal neuralgia; STN, secondary trigeminal neuralgia; TN, trigeminal neuralgia; V1, ophthalmic division of the trigeminal nerve; V2, maxillary division of the trigeminal nerve; V3, mandibular division of the trigeminal nerve.

3. Age and sex differences between patients with classical trigeminal neuralgia and idiopathic trigeminal neuralgia

There was no significant difference in age between the groups (Mann–Whitney U test, $P > 0.05$) (Table 1). Similarly, there was no difference in age between the sexes (Mann–Whitney U test, $P > 0.05$).

Table 3. Evaluation of NVC and responsible vessels by MRI

	Symptomatic (painful) side		Asymptomatic side			
Type of TN	CTN	STN and ITN	CTN	STN	ITN	Total
n	96	30	96	5	25	126
SCA	67	No NVC	22	1	2	25
AICA	10		2	0	1	3
PICA	1		0	0	0	0
BA	3		0	0	0	0
VA	2		0	0	0	0
Vein	13		10	0	1	11
Total NVC	96		34	1	4	39
NVC (%)	100		35.4	20	16	31

AICA, anterior inferior cerebellar artery; BA, basilar artery; CTN, classical trigeminal neuralgia; ITN, idiopathic trigeminal neuralgia; MRI, magnetic resonance imaging; NVC, neurovascular compression; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; STN, secondary trigeminal neuralgia; TN, trigeminal neuralgia; VA, vertebral artery.

Table 4. Treatments administered for each TN subtype

n (%)	CTN	STN	ITN	All TN
Pharmacological treatment	77 (80.2)	0	22 (88)	99 (78.6)
GKS	6 (6.3)	1 (20)	0	7 (5.6)
MVD	11 (11.5)	4 (80)	0	15 (11.9)
Follow-up	1 (1)	0	1 (4)	2 (1.6)
Interruption	1 (1)	0	2 (8)	3 (2.4)
Total	96 (100)	5 (100)	25 (100)	126 (100)

CTN, classical trigeminal neuralgia; GKS, gamma knife surgery; ITN, idiopathic trigeminal neuralgia; MVD, microvascular decompression; STN, secondary trigeminal neuralgia; TN, trigeminal neuralgia.

4. Pain distribution

The laterality of the pain across all patients with TN was as follows: right side (64.3%) and left side (35.7%) (Table 2).

In the CTN group, pain affected the right and left sides in 64.6% and 35.4% patients, respectively. The overall distribution of pain in the trigeminal nerve divisions was as follows: V_2 (38.5%), V_3 (38.5%), V_1 and V_2 (3.1%), and V_2 and V_3 (19.8%).

In the STN group, 80% and 20% patients had pain on the right and left sides, respectively. The overall distribution of pain in the trigeminal nerve divisions was as follows: V_2 (20%), V_3 (40%), and V_2 and V_3 (40%).

In the ITN group, 60% and 40% patients had pain on the right and left sides, respectively. The overall distribution of pain in the trigeminal nerve divisions was as follows: V_2 (52%), V_3 (36%), and V_2 and V_3 (12%).

5. Evaluation of neurovascular compression on magnetic resonance imaging

All subjects underwent MRI on a 3.0-Tesla scanner (Philips Ingenia 3.0 T, Philips Healthcare, Best, the Netherlands). The results of the NVC evaluation are presented in Table 3. In the CTN group, the offending vessel on the symptomatic side was the superior cerebellar artery (SCA), anterior inferior cerebellar artery (AICA), posterior inferior cerebellar artery (PICA), basilar artery, vertebral artery (VA), and vein in 70%, 10%, 1%, 3%, 2%, and 14% patients, respectively. NVC on the asymptomatic side was found in 31% patients; this was significantly higher in the CTN group than in the ITN group (Fisher's exact test, $P = 0.048$), predominantly in the CTN group. Asymptomatic NVC was found in 35.4%, 20%, and 16% patients in the CTN, STN, and ITN groups, respectively.

Table 5. Side effects of carbamazepine in each group and changes in treatment

n (%)		Carbamazepine decreased	Pregabalin	GKS	MVD	Alcohol block	Total
		Changes in treatment					
CTN N=17/77 (22.1%)							
Side effects	Allergic rash	0	2 (11.8)	1 (5.9)	2 (11.1)	0	5 (29.4)
	Liver dysfunction	0	3 (17.6)	1 (5.9)	0	0	4 (23.5)
	Light-headedness	0	3 (17.6)	1 (5.9)	0	0	4 (23.5)
	Drowsiness	0	1 (5.9)	0	0	0	1 (5.9)
	Diminished warfarin action	2 (11.8)	0	0	1 (5.6)	0	3 (17.6)
	Total	2 (11.8)	9 (52.9)	3 (17.6)	3 (17.6)	0	17 (100)
ITN N=6/22 (27.3%)							
Side effects	Allergic rash	0	3 (50)	0	0	1 (16.7)	4 (66.7)
	Liver dysfunction	0	1 (16.7)	0	0	0	1 (16.7)
	Light-headedness	0	0	0	0	0	0
	Drowsiness	0	0	0	0	0	0
	Diminished warfarin action	0	0	0	1 (16.7)	0	1 (16.7)
	Total	0	4 (66.7)	0	1 (16.7)	1 (16.7)	6 (100)
Total N=23/99 (23.2%)							
Side effects	Allergic rash	0	5 (21.7)	1 (4.3)	2 (8.7)	1 (4.3)	9 (39.1)
	Liver dysfunction	0	4 (17.4)	1 (4.3)	0	0	5 (21.7)
	Light-headedness	0	3 (13)	1 (4.3)	0	0	4 (17.4)
	Drowsiness	0	1 (4.3)	0	0	0	1 (4.3)
	Diminished warfarin action	2 (8.7)	0	0	2 (8.7)	0	4 (17.4)
	Total	2 (8.7)	13 (56.5)	3 (13)	4 (17.4)	1 (4.3)	23 (100)

CTN, classical trigeminal neuralgia; GKS, gamma knife surgery; ITN, idiopathic trigeminal neuralgia; MVD, microvascular decompression; STN, secondary trigeminal neuralgia; TN, trigeminal neuralgia.

6. Treatment

The treatments administered to the subjects are shown for each group in Table 4. The predominant line of treatment was pharmacological therapy. Gamma knife surgery was used in a significantly small number of patients, while in a few patients, carbamazepine was discontinued.

7. Side effects of carbamazepine

Table 5 shows the side effects of CBZ and changes in treatment. The incidence of side effects was 23.2% (of 23/99). The side effects included allergic reaction, liver dysfunction, light-headedness, drowsiness, and diminished warfarin action. The reasons for discontinuation included side effects, oral administration of warfarin, and symptom remission. Overall, the most common side effect was allergic reactions (39.1%), the second most common was liver dysfunction (21.7%), and the next most common were light-headedness and diminished warfarin action (17.4%). Management following the onset of side effects included a reduction in carbamazepine dose in two patients (8.7%), commencement of pregabalin in 13 patients (56.5%), gamma knife surgery in three patients (13%), microvascular decompression (MVD) in four patients (17.4%), and nerve block in one patient (4.3%). No side effects were observed in the STN group (five subjects). The incidence of side effects in the CTN group was 22.1% (17/77), with the most common being allergic reaction (29.4%). The incidence of side effects in the ITN group was 27.3% (6/22); in this group, allergic reaction was the most common side effect (66.7%).

DISCUSSION

This study was based on data from a single facility at a dental university hospital, which we believe will contribute to future TN research. However, the results require further confirmation through conduct of multicenter studies with larger sample sizes.

1. Benefits of a dentist seeing a patient with trigeminal neuralgia

It is important to distinguish TN from dental diseases, because the chief complaint associated with TN is temporary pain caused by chewing or toothbrushing. Therefore, dentists can play a significant role in confirming the diagnosis of TN by first examining the teeth for dental caries and cracks and screening for potential temporomandibular disorders. Moreover, it should be noted that no prior studies conducted among patients with TN in dental hospitals have reported a chief complaint of isolated pain in the region supplied by the V_1 division of the trigeminal nerve, which is supported by the results of the present study. TN localized to the V_1 region is considered rare; however, previous reports have indicated that a prevalence ranging from 1% to 2% [4].

2. Selection of subjects and reasons for exclusion

TN can be difficult to diagnose due to severe pain; therefore, studies should have precise inclusion and exclusion criteria for subjects. There are various differential diagnoses of TN, including toothache, temporomandibular disorders, myalgia, post-herpetic neuralgia, and trigeminal autonomic cephalalgias [5]. Since this was a retrospective study, a detailed investigation of differentiation was not possible for setting the exclusion criteria. However, because the International Classification of Headache Disorders [2] criteria can potentially diagnose TN in cases that meet our exclusion criteria, the study results should be interpreted with caution.

3. Age and sex

The average age of the patients was 60 years, which is similar to that reported in a previous study [4], confirming that TN is more common after the age of 50 years. In addition, TN was significantly more common in women than in men. This suggests that males were younger at the time of TN onset, which may be related to the fact that men also develop arteriosclerosis at a younger age than women [6]. The female-to-male ratio was 1.57:1, which was similar to a previous report [1].

4. Age and sex of each group

There are no reports comparing age and sex ratios by classifying TN into CTN, ITN, and STN subtypes. NVC has been cited as the causal factor in 80%–90% of all TN cases [1]; however, the proportion observed in the present study was slightly lower. There was no difference in average age between the CTN and ITN groups. The STN group was not included in the comparison because of the significantly small number of cases. Although ITN may be one of the most common sources of head and neck pain in men, along with more well-known causes (i.e., cluster headache and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing), additional confirmation through studies with larger sample sizes is necessary.

5. Site of pain occurrence and distribution of pain

There have been previous reports on sites of pain in TN patients; however, there have been no reports regarding the ratio of left- to right-sided TN, or investigation of a detailed ratio for each TN subtype. TN has been reported to be more common on the right side [1]. In this study, right-sided TN affected 64% patients. TN pain was mainly associated with either the V_2 or V_3 division, and there were no cases solely involving pain in the region innervated by the V_1 division. Although V_2 and V_3 pain coexisted in approximately one-fifth of the patients, V_1 and V_2 pain only coexisted in 2.4% patients. The possibility of referred pain should be considered when pain affects multiple branches of the trigeminal nerve. When pain distribution laterality was considered, the right V_2 was the most common location. Since the number of STN cases in the present study was small, the nature of the pain location in this subtype remains unclear. However, we found that the ratio of CTN to ITN was high for right-sided pain. The higher prevalence of TN on the right side is attributed to the fact that the foramen rotundum, foramen ovale, and foramen spinosum are smaller on the right side than those on the left side [7]; however, whether CTN and ITN are truly more common on the right side necessitates further clarification.

6. Evaluation of neurovascular compression on magnetic resonance imaging

SCA is the most common blood vessel that causes NVC, followed by the AICA, PICA, and VA [1]. In this study, the proportion of cases attributed to veins was higher than that previously reported [1]. As MRIs were acquired at 3.0 T, the higher resolution of the scanner may have visualized venous compression in more detail. Although the number of NVC cases on the asymptomatic side were smaller than that on the symptomatic side, this has been frequently observed [8]. However, the observed proportion was smaller than that previously reported [9,10]. In addition, the incidence of asymptomatic NVC involving the CTN was relatively high. This might suggest that CTN patients are likely to develop NVC, and further investigation is needed. Furthermore, of the different blood vessels causing NVC on the asymptomatic side, SCA was the most common. Veins were second in frequency, which was followed by AICA. Notably, this study differs from previous reports based on MRI findings at the time of craniotomy. The presence of NVC on the asymptomatic side should also be considered as a “false CTN” (i.e., ITN disguised as CTN). It is possible that cases with a poor prognosis after surgical intervention, such as MVD, may be falsely diagnosed CTN cases.

7. Treatment and side effects of carbamazepine

A dentist worked with a neurosurgeon to treat TN at the facility where this study was conducted. Dentists are proficient in the assessment of the trigeminal nerve and can provide a more accurate and rapid management of TN by coordinating their care with a neurosurgeon. Among the patients in our study, 79% received pharmacological therapy. Many patients choose pharmacological therapy because such agents could sufficiently control of their pain, with a low potential of having side effects. Another reason is that surgery is not recommended for elderly patients and those with ITN. In the present study, the ITN group had no available options other than pharmacological therapy. This is an important clinical issue, particularly because there is no effective alternative treatment available when the action of carbamazepine is diminished. Therefore, it is important to identify causative factors other than NVC in patients with TN. The first-line drugs for TN are carbamazepine and oxcarbazepine [8]. However, in Japan, oxcarbazepine is not licensed for the treatment of TN. The side effects of carbamazepine include drug eruption, drowsiness, light-headedness, and decreased mental function, which may be reversible on treatment discontinuation. Similarly, there may be serious adverse effects, such as Stevens–Johnson syndrome and toxic epidermal necrolysis [8]. According to the results of this study, 23.2% (23/99) of patients who received carbamazepine treatment discontinued it because of the presence of one or more side effects, with drug eruption being the most common. Carbamazepine should be administered with care, and its potential side effects should always be explained to patients. In the present study, the most common treatment administered after the discontinuation of carbamazepine was pregabalin. Although a few studies have assessed the efficacy of pregabalin in the treatment of TN [8], it was often found to be effective in this study. MVD was the next most commonly performed treatment. Although MVD is an established operation, its success rate is 68%–88% within 1–2 years of surgery [8]. Thus, caution should be exercised to ensure appropriate patient selection. We believe that further elucidation of ITN will contribute to improving the accuracy of case selection. The next most common management option was stereotactic radiosurgery or gamma knife surgery. Although the initial treatment success rate of gamma knife surgery was lower than that of MVD, recent studies have indicated improved results [11]; currently, this procedure is commonly performed in Japan. However, the effect of this surgery on the ITN is unclear. Thus, clinical statistics according to the TN subtype are an important first step in the analysis of treatment outcomes. Verification of the pathophysiology and therapeutic effects of ITN will be clinically useful. The fact that approximately 20% subjects in this study were diagnosed with ITN, with 30% having asymptomatic one-sided NVC, suggests the existence of risk factors other than NVC for TN.

8. Conclusions

A detailed study of TN was conducted for each subtype. CTN was more common in women than in men, as previously reported; however, ITN was more common in men than in women. The ratio of pain sites located on the right side of the face was high in all groups. Patients with CTN may also be prone to NVC on the asymptomatic side. By investigating TN subtypes, it may be possible to elucidate its pathophysiology and improve treatment results.

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