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Differences in the Clinical Characteristics of Persistent Idiopathic Facial Pain (Atypical Odontalgia) Patients with or Without Neurovascular Compression of the Trigeminal Nerve

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Abstract

Background. Persistent idiopathic facial pain (PIFP) is the unexplained pain along the territory of the trigeminal nerve, including nonorganic tooth pain called atypical odontalgia (AO). Though PIFP is debilitating to patients' livelihood and well-being, its pathophysiology remains poorly understood. Although neurovascular compression (NVC) of the trigeminal nerve is known to be associated with trigeminal neuralgia (TN), the relationship between NVC and other orofacial pains has not been fully elucidated. **Methods.** In this study, we investigated the differences in the characteristics of PIFP (primarily AO) patients in the presence or absence of NVC. A retrospective analysis was performed on data from 121 consecutive patients who had been diagnosed with unilateral PIFP according to the criteria of the International Classification of Headache Disorders (ICHD)–3 and underwent magnetic resonance imaging scans of the head. **Results.** In the group without NVC, characteristic findings were significant for psychiatric morbidity, somatization, and pain disability, when compared with the group with NVC. Furthermore, the group without NVC exhibited significant headache, noncardiac chest pain, shortness of breath, and pain catastrophizing. **Conclusions.** These results suggest that PIFP patients can be divided into two groups: one consistent with a neuropathic pain phenotype when NVC is present and a functional somatic symptom phenotype when presenting without NVC. Our findings may enable a more precise understanding of pathophysiology of PIFP and lead to better treatment strategies.

Key Words: Persistent Idiopathic Facial Pain (PIFP); Atypical Odontalgia (AO); Neurovascular Compression (NVC); Trigeminal Nerve; Neuropathic Pain; Functional Somatic Symptom

Introduction

Persistent idiopathic facial pain (PIFP) is a chronic disorder along the territory of the trigeminal nerve. According to the International Classification of Headache Disorders, third edition (ICHD-3), and the International Headache Society (IHS), PIFP is described as "persistent facial and/or oral pain, with varying presentations but recurring daily for more than two hours per day over more than three months, in the absence of clinical neurological deficit" [1].

PIFP, formerly called atypical facial pain (AFP), maybe the result of hyperactivity of central neurons

secondary to damage of primary afferent neurons; on the other hand, it has been suggested that PIFP is likely a combination of both biological and psychosocial elements [2]. Recently, it has been reported that some PIFP patients show neuropathic pain characteristics [3]. However, the pathophysiology of PIFP has not been fully investigated.

Facial pain may be widely divided into two types: tooth-related and non-tooth-related [4]. Atypical odontalgia (AO) is considered a subtype of PIFP [5]. We have previously reported that approximately half of AO patients have psychiatric comorbidities, and this pain might have a larger emotional component than a sensory one in AO patients with psychiatric comorbidities [6]. We have also reported that patients AO and burning mouth syndrome have higher pain intensity than AO-only patients [7]. Regarding the characteristics of AO, it has been reported that some patients have vascular-type pain [8]. However, the neurovascular impact on AO/PIFP pain has not been fully elucidated.

A correlation between trigeminal neuralgia (TN) and neurovascular compression (NVC) has been shown for some time. TN is typically a unilateral pain. NVC is present 53% of the time on the symptomatic side of TN patients, whereas it is present about 13% of the time on the contralateral, asymptomatic side [9]. The relationship between PIFP and NVC has been sparsely reported on, with limited evidence reporting no association between the two [10]. The correlation between NVC and non-TN orofacial region pain, such as PIFP and AO, has not been sufficiently studied.

In this study, we investigated the differences in the characteristics of PIFP (primarily AO) patients in the presence and absence of NVC.

Methods

Subjects
A retrospective analysis was performed on data from 121 consecutive patients diagnosed with unilateral PIFP according to International Classification of Headache Disorders (ICHD)–3 criteria. Patients subsequently underwent a magnetic resonance imaging (MRI) scan of the head. Definitive diagnosis was verified by the Chief Professor of the clinic. All patients were initially seen at the Psychosomatic Dental Clinic at Tokyo Medical and Dental University Hospital, Tokyo, Japan, between April 2016 and February 2018. Inclusion criteria were as follows: 1) age >18 years, 2) unilateral tooth or facial pain for more than six months, 3) absence of organic abnormality per intraoral or radiographic examination. Patients with an obvious peripheral or systemic cause of pain were excluded from this study.

Ethics Approval and Consent to Participate
All patients consented to take part in this study and signed a written informed consent. The study protocol was approved by the Ethical Committee of the Faculty of Dentistry at Tokyo Medical and Dental University (TMDU; D2013–005).

Clinical Characteristics
Clinical characteristics were obtained from the patients' medical charts, including demographic information (sex, age, duration of illness). The investigators in this study were all trained clinicians and researchers in our clinic.

Psychiatric History
Psychiatric history was investigated by reviewing referral letters from attending psychiatrists of patients. All the patients visiting our hospital had to submit referral letters from their attending psychiatrist if they had a psychiatric history. The psychiatric diagnoses in referral letters were categorized according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). Patients with mood disorders such as major depressive disorder and dysthymic disorder were categorized as having a "depressive disorders," those with anxiety disorders such as generalized anxiety disorder and obsessive-compulsive disorder were categorized into "anxiety disorders," and those with bipolar disorders such as bipolar I disorder and bipolar II disorder were categorized into "bipolar disorders."

As mentioned above, we adopted the psychiatric diagnoses of attending psychiatrists, instead of basing diagnoses on clinical interview results. We excluded information about psychiatric diagnoses from patients' memory due to its inaccuracy.

MRI Protocol and Definitions
All patients underwent an MRI scan within one month after the first visit. All magnetic resonance (MR) data were acquired using a 3D MRI scanner (Magnetom Spectra, Siemens Healthcare, Erlangen, Germany) and a 16-channel head coil. The standard MRI protocol for trigeminal neuralgia at our institution included the conventional images for screening of the whole brain, MR angiography (MRA), and MR cisternography. MRA was acquired using 3D time-of-flight (3D-TOF) MRA with the following parameters: TR/TE 24/3.9 ms, flip angle 18°, field of view (FOV) 160×160 mm, matrix 320×192, section thickness 0.5 mm, and number of slab 3, which was reconstructed to a voxel size of $0.5 \times 0.5 \times 0.5$ mm. Also, MR cisternography was obtained using 3D constructive interference in steady state (3D-CISS) with the following parameters: TR/TE 7.4/3.7 ms, flip angle 50°, FOV 160×160 mm, matrix 320×320, section thickness 0.5 mm, which was reconstructed to a voxel size of $0.5 \times 0.5 \times 0.5$ mm. These MR sequences were acquired at the level of the root entry zone (REZ) of the trigeminal nerve with a slab thickness of 44 mm.

All 3D-TOF and 3D-CISS were displayed in triplanar views (transverse, coronal, and sagittal views) on the

visualization system and evaluated by two experienced oral radiologists (JS, NY), who were blinded to symptom side. NVC was defined as contact between a blood vessel at the REZ and the trigeminal nerve without visible cerebrospinal fluid between the two structures in the triplanar views of 3D-CISS. REZ was defined as <5 mm from the trigeminal root according to several previous studies [11,12]. The type of the responsible blood vessel (artery or vein) was evaluated using the triplanar views and memory-in-pixel display of 3D-TOF MRA. If there was disagreement or uncertainty about whether there was a contact, it was considered no NVC in the data analysis. Insets in Figure 1 provide examples of the degree and location of trigeminal NVC.

Pain Scale

The characteristics of pain were evaluated using the Short-Form McGill Pain Questionnaire (SF-MPQ) at the initial visit. The contents of the SF-MPQ have been described previously [13]. The SF-MPQ includes 15 items (11 sensory and four affective). The 11 sensory items are throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, and splitting. The four affective items are tiring-exhausting, sickening, fearful, and punishing-cruel. These items were rated as follows: $0 =$ none, $1 =$ mild, $2 =$ discomforting, $3 =$ distressing, $4 =$ horrible, and $5 =$ excruciating.

Pain Catastrophizing Scale

Pain catastrophizing was evaluated using the Pain Catastrophizing Scale (PCS) at the first visit. The PCS contains following 13 items: 1) I worry all the time about whether the pain will end. 2) I feel I can't go on. 3) It's terrible and I think it's never going to get any better. 4) It's awful and I feel that it overwhelms me. 5) I feel I can't stand it anymore. 6) I become afraid that the pain will get worse; 7) I keep thinking of other painful events. 8) I anxiously want the pain to go away. 9) I can't seem to keep it out of my mind. 10) I keep thinking about how much it hurts. 11) I keep thinking about how badly I want the pain to stop. 12) There's nothing I can do to reduce the intensity of the pain. 13) I wonder whether something serious may happen. These items were rated as follows [14,15]: $0 =$ not at all, $1 =$ to a slight degree, $2 =$ to a moderate degree, $3 =$ to a great degree, and $4 =$ all the time.

Somatic Symptom Scale

The comorbidities of functional somatic symptoms were examined using the Somatic Symptom Scale–8 (SSS-8) at
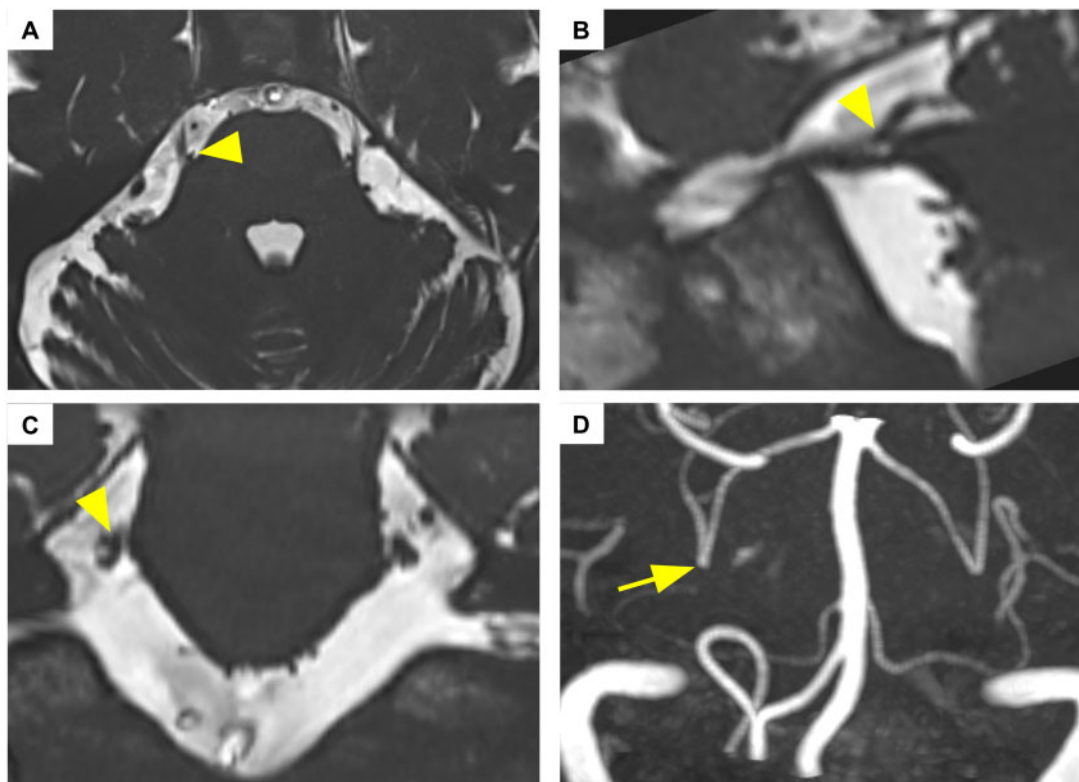
Figure 1. The examples of the degree and location of trigeminal neurovascular compression (NVC). A 73-year-old female with a suspected right-sided trigeminal neuralgia. Transverse view of 3D-CISS (A), coronal view (B), sagittal view (C), and memory-in-pixel display of 3D time-of-flight magnetic resonance angiography (D). NVC on the symptomatic nerve was revealed in the triplanar views of 3D constructive interference in steady state (arrowheads). The responsible blood vessel was superior cerebellar artery (arrow).
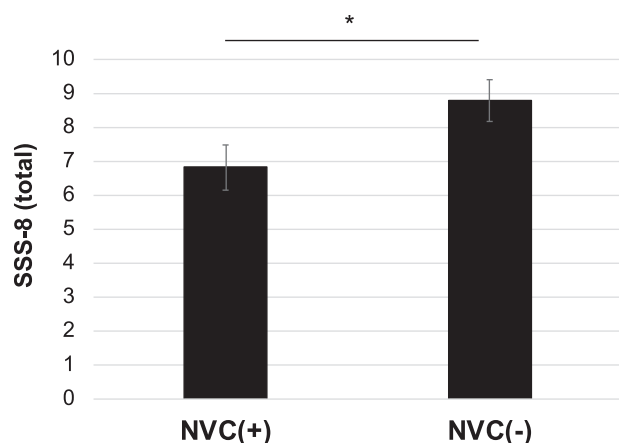
Figure 2. Neurovascular compression (NVC) (–) patients tend to have severe functional somatic symptoms compared to NVC(+) patients. The severity of somatic symptoms was examined using the Somatic Symptom Scale–8 (SSS-8). Error bars = SE (*$P < 0.05$, Student t test).

the initial visit. The SSS-8 contains eight descriptors. The eight descriptors have been previously reported (Figure 2A) [16]. These descriptors were rated as follows: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much [16].

Self-Rating Depression Scale

Severity of depression was rated using Zung's Self-Rating Depression Scale (SDS), which consists of 20 questions. The contents of the SDS have been previously described [17]. Subjects with a total score of ≤38 are regarded as normal, 39–52 as having a tendency to neuroticism, and ≥53 as having a tendency to depression [17].

Scale for Disability due to Chronic Pain

Disability due to chronic pain was examined using the STarT Back five-item screening tool (STarT-G) at the first visit. The five items are as follows: 1) It's really not safe for a person with a condition like mine to be physically active. 2) Worrying thoughts have been going through my mind a lot of the time in the last two weeks. 3) I feel that my problem is terrible and that it's never going to get any better. 4) In general in the last two weeks, I have not enjoyed all the things I used to enjoy. 5) Overall, how bothersome has your condition been in the last two weeks? Items 1–4 were rated as follows: disagree = 0, agree = 1. Item 5 was rated as follows: not at all, slightly, moderately = 0; very much, extremely = 1. The STarT-G threshold was set to 4 [18].

Statistical Analysis

Data were analyzed using the Wilcoxon signed-rank test, Student t test, and Fisher exact test using EZR (Easy R), which is based on R and R Commander [19]. Results are expressed as the mean (± standard error [SE]) or the number of patients (%).

Results

The Ratio of PIFP Patients Without NVC who Have a Psychiatric History Is Larger than That with NVC

Table 1 shows the clinical–demographic data of patients in the PIFP patients with NVC group (N = 49) and the PIFP patients without NVC group (N = 72). There were no significant differences in age, sex, duration of the chief complaint, onset event, or distribution of pain location between the two groups. However, psychiatric comorbidity ($P = 0.44$) was statistically higher in the PIFP patients without NVC group compared with those in the PIFP patients with NVC group. Moreover, we examined scores from the STarT-G, which is the scale for disability due to pain. The STarT-G cutoff score is 4. The number of patients without NVC whose STarT-G score was >4 was significantly larger than that of patients with NVC (Table 1.).

PIFP Patients Without NVC Tend to Have More Severe Functional Somatic Symptoms Compared with Those with NVC

We investigated the difference of psychosomatic tendencies due to the presence or absence of NVC. We examined psychosomatic tendencies of patients using the SSS-8. The SSS-8 value of PIFP patients without NVC was significantly higher than that of PIFP patients with NVC (Figure 2).

PIFP Patients Without NVC Tend to Have More Severe Headache, Chest Pain, or Shortness of Breath Compared with Those with NVC

SSS-8 can be classified by eight factors (Figure 3A). As a result, PIFP patients without NVC have significantly higher values in "headache" and "chest pain or shortness of breath" compared with PIFP patients with NVC (Figure 3B).

PIFP Patients Without NVC Tend to Have More Severe Pain Catastrophizing than Those with NVC

Moreover, we examined pain catastrophizing using the PCS and performed depression assessments using the SDS. PCS scores were higher within the PIFP without NVC group than the PIFP with NVC group, indicating higher pain catastrophizing levels (Figure 4A). On the other hand, there was no significant difference in the value of SDS (Figure 4B).

PIFP Patients Without NVC Tend to Have Heavy Pain Compared with Those Without NVC

The characteristics of pain were examined using the SF-MPQ at the initial visit. As a result, the quantitative value of "heavy" pain at the sensory component of SF-MPQ descriptors was significantly higher in patients without NVC than that in patients with NVC).

Table 1. Clinical characteristics of subjects

Characteristics			NVC(+)	NVC(-)	P Value
No.			49	72	
Age, mean±SE, y			54.4±2.0	54.1±1.7	0.911
Sex, No. (%)					
Male			11 (22)	15 (21)	
Female			38 (78)	57 (79)	0.344
Duration of the problem, mean±SE, days			32.0±5.8	40.3±6.9	0.388
Triggered by dental procedures, No. (%)	Absent		23 (47)	34 (44)	1.000
	Present	Root canal treatment	8 (16)	11 (14)	1.000
		Extraction	4 (8)	6 (8)	1.000
		Prosthesis treatment	5 (10)	6 (8)	0.756
		Resin filling/inray	3 (6)	5 (7)	1.000
		Orthodontic treatment	1 (2)	1 (1)	1.000
		Oral surgery	5 (10)	8 (11)	1.000
		Detail is unknown	0	6 (8)	0.060
Distribution of pain location, No. (%)					
Maxillary right			7 (14)	17 (24)	0.250
Maxillary left			20 (41)	39 (54)	0.195
Mandibular right			7 (14)	18 (25)	0.119
Mandibular left			16 (33)	16 (22)	0.215
Facial pain			5 (10)	5 (7)	0.524
History of psychiatry, No. (%)			20 (41)	43 (60)	0.044
Schizophrenia			1 (2)	2 (3)	0.646
Depression			3 (6)	12 (17)	0.099
Depressive state			1 (2)	3 (4)	0.646
Bipolar disorder			3 (6)	1 (1)	0.302
Dysthymia			1 (2)	1 (1)	1.000
Anxiety disorder			6 (12)	9 (13)	1.000
Insomnia			2 (4)	2 (3)	1.000
Pain disorder			1 (2)	0 (0)	1.000
Detail is unknown			3 (6)	14 (20)	0.080
Because of oral symptom			0 (0)	1 (1)	1.000
STarT-G, positive (≥4), No. (%)			1 (2)	10 (14)	0.028

Statistical analyses of age and duration of the problem were performed using the Student t test. The others were performed using the Fisher exact test.

NVC = neurovascular compression; STarT-G = STarT Back five-item screening tool.
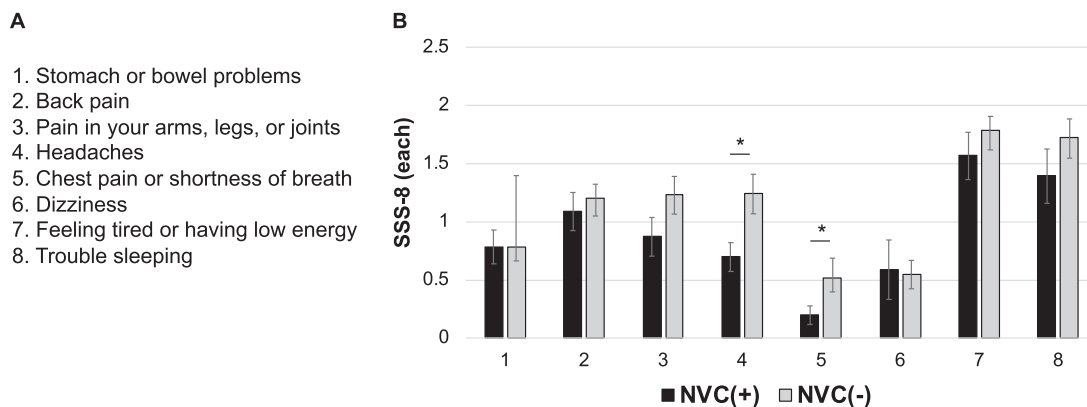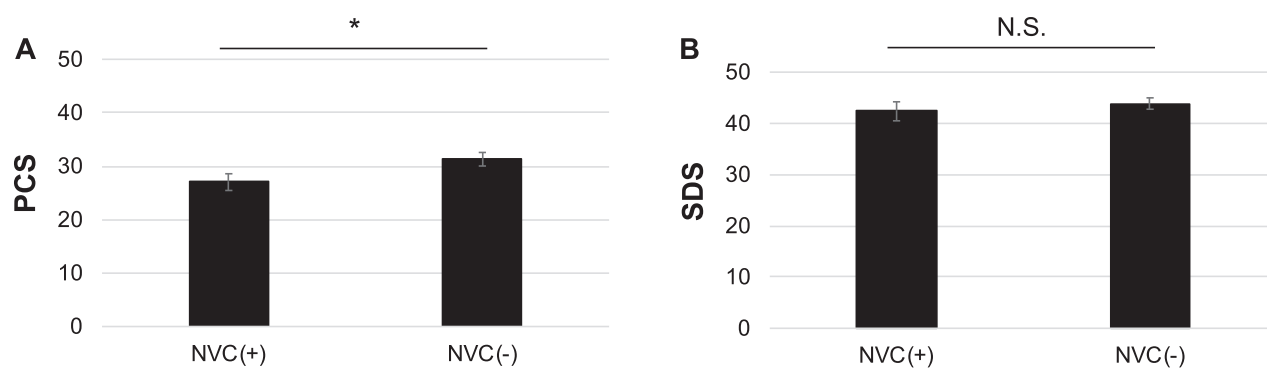

Figure 3. Neurovascular compression (NVC) (–) patients tend to have severe headache chest pain or shortness of breath compared with NVC(+) patients. The severity of each somatic symptoms was examined using the Somatic Symptom Scale–8 (SSS-8). A) The SSS-8 contains eight descriptors. B) Error bars = SE (*$P < 0.05$, Student t test).

Discussion

A large number of PIFP patients present with a history of moderate trauma and subclinical sensory changes. Thus, PIFP is considered a neuropathic pain syndrome [5]. On the other hand, the relationship between PIFP and certain psychiatric comorbidities has been well reported; however, a causal relationship between the two remains to be elucidated [20]. Moreover, it has been suggested that there may be a relationship among functional somatic symptoms, anxiety, and depression, sometimes referred to as the "somatization–anxiety–depression triad" [21,22]. Our data suggest that patients without NVC tend to have psychiatric morbidity, disability due to pain

Figure 4. The value of Pain Catastrophizing Scale (PCS) of the group without neurovascular compression (NVC) showed significantly higher than that with NVC. A) Pain catastrophizing was examined using the PCS. B) The severity of depression was rated using Zung's Self-Rating Depression Scale (SDS). Error bars = SE (*$P < 0.05$, Student t test).

Table 2. Comparison of SF-MPQ between NVC(+) and NVC(–) patients

			NVC(+)	NVC(–)	P Value
SF-MPQ descriptors	Sensory	Throbbing, mean±SE	0.91±0.16	0.97±0.13	0.78
		Shooting, mean±SE	0.41±0.11	0.53±0.10	0.431
		Stabbing, mean±SE	0.87±0.16	0.7±0.12	0.386
		Sharp, mean±SE	0.85±0.16	0.8±0.13	0.828
		Cramping, mean±SE	1±0.27	1.02±0.13	0.956
		Gnawing, mean±SE	0.6±0.14	0.8±0.13	0.305
		Hot-burning, mean±SE	0.26±0.12	0.45± 0.11	0.231
		Aching, mean±SE	1.12±0.18	1.73±0.19	0.055
		Heavy, mean±SE	0.78±0.16	1.24±0.13	0.029
		Tender, mean±SE	1.2±0.15	1.24±0.14	0.823
		Splitting, mean±SE	0.37±0.13	0.24±0.09	0.39
	Affective	Tiring-exhausting, mean±SE	1.41±0.18	1.56±0.13	0.502
		Sickening, mean±SE	0.74±0.15	1.09±0.13	0.083
		Fearful, mean±SE	0.46±0.14	0.73±0.12	0.147
		Punishing-cruel, mean±SE	0.72±0.15	0.86±0.12	0.438

Statistical analysis was performed using the Student t test.

NVC = neurovascular compression; SF-MPQ = Short-Form McGill Pain Questionnaire.

(Table 1), and psychosomatic complaints compared with the group with NVC (Figures 2 and 3). Until now, subtypes of PIFP patients have not been described in terms of presence or absence of accompanying NVC. Our findings may enable a more detailed understanding of the relationship between PIFP, psychiatric comorbidity, functional somatic symptoms, and NVC.

NVC has been reported to be associated with TN [23–25]. In recent years, it has been reported that severe NVC is present more in the symptomatic side than in the asymptomatic side of TN patients [9]. On the other hand, in a similar study of PIFP patients, it has been reported that there was no difference between the symptomatic side and asymptomatic side [10]. These reports examined the severity of NVC. With respect to mild NVC, it has been suggested that there is no impact on these symptoms. Although in this study we did not examine severity of NVC, differences in the characteristics of PIFP patients with or without NVC were demonstrated. Our findings suggest that mild NVC, excluding the condition TN, can be a predisposition to one of the subtypes of PIFP.

A lack of association between PIFP and NVC has been reported [10,26,27]. These reports have suggested that there is no association between the presence or absence of PIFP symptoms and the presence or absence of NVC. However, our results suggest that there are some characteristic differences between PIFP patients with and without NVC. Therefore, our results are not inconsistent with these reports.

Our previous studies have shown that pain might have a larger emotional component than a sensory one in AO (a subtype of PIFP) patients with comorbid psychiatric disorders [6]. In this study, we showed that PIFP patients without NVC were more prone to have psychiatric comorbidity than patients with NVC. Moreover, the group without NVC tended to have "heavy" pain compared with the group with NVC. Although patients without NVC tend to have psychiatric comorbidities, there was no difference in the emotional component of the SF-MPQ between the two groups (Table 2). The difference in the characteristics of PIFP patients with or without NVC is not only in psychiatric history but also in other several factors. Our results suggest that these other

several factors may affect the quality of the pain of PIFP patients without NVC.

Tricyclic antidepressants (TCAs) such as amitriptyline are known to be effective for chronic pain in the orofacial region [28–31]. However, the therapeutic response to a TCA is known to be limited [32]. One possible cause of the limited efficacy of antidepressants is the heterogeneity of the PIFP patient population [33]. The current study highlights the differences in the characteristics of PIFP patients in the presence or absence of NVC. However, we have yet to examine differences in treatment response between patients with and without NVC. Although there is no correlation between the response of TCA and NVC, neuropathic medication is likely to be effective in patients with NVC. There is a need to examine the pharmacologic response of PIFP patients with or without NVC. It may be possible to select a more appropriate medication for PIFP patients by understanding the underlying pathophysiology in cases with or without NVC.

Conclusions

It has been suggested that there are some differences in the characteristics of PIFP patients with or without NVC, such as psychiatric morbidity and severity of somatic symptoms. Our findings may further our understanding of the pathophysiology of PIFP and eventually lead to improved treatment options.

Acknowledgments

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