Features of Neurovascular Orofacial Pain Compared to Painful Posttraumatic Trigeminal Neuropathy

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Aims: To test and re-examine the diagnostic criteria for neurovascular orofacial pain (NVOP) compared to posttraumatic trigeminal neuropathy (PTTN). **Methods:** Pain and patient characteristics were compared in patients with NVOP, PTTN, and NVOP initiated by trauma (PT-NVOP). NVOP criteria were based on prior studies, and PTTN was defined according to the International Classification of Headache Disorders, version 3 beta. **Results:** Of the 170 patients in the cohort, 90 had PTTN, 51 had NVOP, and 29 had PT-NVOP. None of the tested parameters in the NVOP and PT-NVOP patients were significantly different, and therefore these patients were combined into one group (T-NVOP). T-NVOP differed significantly from PTTN ($P < .001$) in periodic pain patterns, presence of autonomic and systemic signs, throbbing pain quality, and frequency of bilaterality. Pain quality in PTTN was more burning/stabbing than in NVOP ($P = .003$). Pain severity, waking from sleep, muscle sensitivity to palpation, and demographics were comparable. **Conclusion:** NVOP differs from PTTN in parameters essential to diagnosis: periodicity of pain, presence of autonomic and systemic accompanying signs, throbbing pain quality, and bilateral presentation. NVOP is amenable to abortive and prophylactic antimigraine therapies, distinguishing NVOP from PTTN in clinical features, treatment, and prognosis. *J Oral Facial Pain Headache 2020;34:121–128. doi: 10.11607/ofph.2448*

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When considering the differential diagnosis of migraine-like or trigemino-autonomic (TAC)–like pains in the orofacial region, a number of entities are recognized.[1] The first is a facial or orofacial equivalent to migraine without aura (MWoA), referred to in the literature as lower-half,[2] facial,[3] or orofacial[4] migraine. Indeed, the International Classification of Headache Disorders (ICHD-3) recognizes this relatively atypical presentation of migraine and specifies in the comments section that "a subset of otherwise typical patients has facial location of pain, which is called 'facial migraine' in the literature; there is no evidence that these patients form a separate subgroup of migraine patients."[5] The second possibility is a facial pain with TAC-like features, most commonly an atypically located cluster headache. This has been termed lower CH[6] or orofacial CH.[7] More recently, maxillary and mandibular presentations of short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT/SUNA) have also been described,[8,9] adding these conditions to the differential diagnosis. Because this particular location often involves dentoalveolar structures and the maxillary sinuses, these entities often cause misdiagnosis and subsequent mistreatment.[10–20] For these reasons, there has been a call for the establishment of orofacial equivalents of these well-established headache disorders.

By studying a total of 90 patients with migraine-like or TAC-like pain in the orofacial region, the present authors were able to use ICHD criteria to diagnose 38 patients, leaving 52 who did not fit the criteria for migraine or for TACs and therefore remained undiagnosable.[21,22] The authors named the disorder in these patients neurovascular orofacial pain (NVOP).[22]

The features that justify the establishment of NVOP as a distinct entity have been discussed in detail by the present author group, including the proposition of diagnostic criteria with positive (PPV) and negative predictive values (NPV).[21–24] The most prominent is oral and/or facial pain location.[3,21] Pain can be accompanied by local autonomic signs—specifically tearing, nasal congestion, or a feeling of cheek swelling or fullness[22]—and phenomena such as photo/phonophobia and nausea.[2,10,22,25] Pain is bilateral in up to a third of patients with NVOP. Although unilateral pain was initially an inclusion criterion for patient selection studies,[2,22,25] this led to biased results and limited the size of the NVOP group. In later studies, bilateral pain was included.[21] Of clinical importance is the common finding of related dentoalveolar pain with unique characteristics that mimic dental pathology. These signs and symptoms include spontaneous or evoked dentoalveolar pain (eg, cold allodynia), explaining patient reports of superimposed short pain attacks.[2,4,10,22,25,26] Additionally it has been a consistent finding that NVOP patients report a relatively late age of onset.[23] NVOP, a fairly new diagnostic entity, should be re-examined in light of new data in order to more accurately define its characteristics and avoid mistreatment. It has been the authors' experience that many of these patients undergo invasive therapies in futile attempts to treat NVOP. Whether these are dentoalveolar or otolaryngologic, the result is nerve injury that may lead to painful posttraumatic trigeminal neuropathy (PTTN). At this point, the clinical phenotype is complex, as the signs and symptoms of neuropathic pain create a complex differential diagnosis in NVOP.

PTTN is the most recent term proposed by the International Headache Society (IHS)[5] to reflect neuropathic pain of traumatic origin affecting the trigeminal nerve and resulting in long-lasting pain. This term replaces previously used terms such as deafferentation pain, traumatic neuropathy, and phantom tooth pain, as well as early criteria of atypical odontalgia.

It is important to emphasize that this term describes a painful neuropathy in all parts of the trigeminal distribution, including the scalp, face, and oral cavity. There are a wide range of PTTN presentations due to trauma around the external parts of the head and intraorally. The extraoral presentations of PTTN are usually straightforward, with a clear history of trauma and the classical signs and symptoms of a painful traumatic neuropathy. In contrast, intraoral posttraumatic cases are complex to identify and often lack external signs (eg, a scar on the skin).[27] At present, PTTN and NVOP are diagnoses based primarily on symptoms, which are not always combined with signs of disease, structural damage, or injury.

The authors therefore consider PTTN to be a highly relevant control group when assessing the diagnostic criteria of NVOP because differentiating the two disorders is often clinically challenging. Refining these two diagnostic entities may have an additional benefit, enabling the clinician to replace the vague diagnosis of atypical facial pain or persistent idiopathic facial pain (PIFP) in some patients.[5] Furthermore, distinction between NVOP and PTTN is clinically important for therapeutic considerations, as these conditions have different therapeutic regimens and prognostic outcomes. PTTN, like other posttraumatic neuropathies, is very resistant to therapy, even when applying state-of-the-art pharmacotherapeutic protocols.[28,29] NVOP, on the other hand, is amenable to antimigraine therapy, with good prognostic outcomes.[10,24,26,30]

Previously, the authors analyzed and related the features of a number of orofacial pain syndromes and of NVOP, calculating PPV and NPV.[21] In the present study, the focus is the comparison of these features of NVOP to those of PTTN. The authors believe this to be the most clinically useful head-to-head comparison, as both conditions are associated with intraoral sources of pain. Furthermore, in earlier studies, NVOP with a history of trauma was not isolated from NVOP with no associated trauma, and the former is a relevant diagnostic entity to be compared to PTTN.

The aim of the present study was to re-examine the diagnostic criteria for NVOP compared to intraoral PTTN. Furthermore, patients with NVOP with a reported history of trauma (PT-NVOP) were separately studied, and the diagnostic features of PT-NVOP were compared to PTTN as well as to NVOP with no history of trauma. The authors' hypothesis was that PT-NVOP would acquire signs and symptoms common to both PTTN and NVOP.

Materials and Methods

Medical records of individuals diagnosed and treated between 2011 and 2015 at the Orofacial Pain Clinic, Faculty of Dentistry, Hadassah Medical Center, Hebrew University, Jerusalem, were included in this retrospective study. The Orofacial Pain Clinic serves as a secondary or tertiary center and receives patients from all over Israel. Most patients were referred from medical or dental practitioners. The Institutional Review Board approved the study, and patients consented to the use of their data for research purposes.

Inclusion criteria for NVOP were based on the criteria established in prior studies.[21,22,24,31] The criteria for PTTN were adopted from ICHD-3.[5] Exclusion criteria were: pain due to local pathology (eg, dental, masticatory muscles, TMJ, salivary glands, maxillary

sinus); clear migraine symptomatology fulfilling ICHD criteria for MWoA; and/or suspected TACs or intracranial pathology. Primary and resultant data were recorded on an intake form. Demographic data included gender and age. Unilateral vs bilateral pain, dominant pain side, and the occurrence of migratory pain were documented. Patients were asked to report whether the pain was constant, came as an acute attack, or both (ie, constant background pain with periods of more severe pain). Frequency of attacks was recorded and characterized as follows: several per day; once a day; several per week; several per month; or several per year. Attack duration was documented in minutes, hours, days, or as relentless pain (constant). Patients were asked to rate pain quality and pain intensity. Pain quality was assessed with the following descriptive terms: burning, electrical, pressure, throbbing, and stabbing (including sharp).[31–33] Pain intensity was rated by employing an 11-point verbal pain scale (VPS), where 0 was no pain and 10 was the worst imaginable pain.[31] The presence of accompanying signs and symptoms was documented. General symptoms included photophobia, phonophobia, nausea, or vomiting. Local autonomic signs included lacrimation, conjunctival injection, nasal congestion, rhinorrhea, or cheek flushing. Patients were specifically asked whether the pain woke them from sleep.

Clinical Examination

All patients underwent a thorough extraoral examination, including cranial nerve examination. The TMJs and masticatory muscles were examined bilaterally with about 2 kg of digital pressure.[34] The presence of tenderness to palpation was recorded. An intraoral examination was performed to exclude dental, periodontal, and mucosal pathology. Radiographs of teeth and jaws were obtained as needed to exclude any dental or jaw pathology. Brain and brainstem imaging were performed if brain pathology (eg, tumor) was suspected. Whenever pathology of the sinuses, ears, or nasopharynx was suspected, the patient was referred to an otolaryngology specialist.

Statistical Analyses

Numeric variables were descriptively presented as means and standard deviations (SDs), and categorical variables as frequencies and percentages. Differences between independent variables (univariate) were analyzed using analysis of variance (ANOVA), *t* test, and chi-square test, as appropriate. In order to identify independent multivariate influences on the results, multiple logistic regression analysis was used. The statistical processing was performed using SPSS 22.0. Statistical level of significance (alpha) was set at $P < .05$.

Table 1 Demographic and Pain Characteristics Divided According to Group

	Total mean	Group	Mean	*P*
Age (y)	45 ± 15.1	NVOP	40.96 ± 15.2	NS
		PT-NVOP	39.8 ± 12.6	
		PTTN	49 ± 14.9	
VPS (0–10)	7.8 ± 1.7	NVOP	8.0 ± 1.7	NS
		PT-NVOP	8.1 ± 1.5	
		PTTN	7.7 ± 1.8	
Onset of pain (mo)	35.2 ± 53.2	NVOP	26.6 ± 41.7	NS
		PT-NVOP	29.4 ± 29.6	
		PTTN	37.9 ± 61.7	

VPS = visual pain scale; NVOP = neurovascular orofacial pain; PT-NVOP = neurovascular orofacial pain with history of trauma; PTTN = posttraumatic trigeminal neuropathy; NS = not significant.

Results

A total of 170 patients were included in the study, 51 who were defined as NVOP, 29 who also met the criteria for NVOP but reported a traumatic event related to the initiation of pain (PT-NVOP), and 90 who were defined as PTTN.

Patient demographics are presented in Table 1: age, VPS, and onset of pain were similar for all three groups. Table 2 summarizes the signs and symptoms, as well as gender, associated with NVOP compared to PT-NVOP and PTTN. From Table 2, it is evident that there were no differences between NVOP and PT-NVOP. Based on the similarities between these two groups, they were combined into one group called Total NVOP (T-NVOP) (n = 80). T-NVOP was then analyzed compared to the PTTN group (Table 3).

In the PTTN group, pain was mostly unilateral (90% of patients) compared to 67.5% of T-NVOP patients ($P < .0001$, $c^2 = 13.114$, df = 1). The two groups differed significantly in their temporal pain characteristics. If only the discrete attack characteristics were considered, the difference was pronounced; 16.7% in PTTN vs 55% in T-NVOP. Thus, T-NVOP was characterized by its attack nature, while PTTN was more continuous in nature ($P < .0001$, $c^2 = 29.154$, df = 3). The two groups also differed in pain quality: While PTTN patients complained mainly of burning (42.2%) or electrical (40%) pain, T-NVOP patients reported significantly less burning and electrical sensation (respectively: 20%, $P = .002$, $c^2 = 9.339$, df = 1; and 28.8%, $P = .01$, $c^2 = 6.688$, df = 1). On the other hand, T-NVOP patients complained significantly more of pressure (60%, $P = .002$, $c^2 = 9.785a$, df = 1) and throbbing (53.8%, $P < .00001$, $c^2 = 18.666$, df = 1) pain. Pain frequency was significantly more periodic in the T-NVOP group than in the PTTN group, which was very obvious when several per week, month, or year were combined (50.1% in the T-NVOP group and 14.5% in the

Table 2 Comparison of Parameters Among Groups

		Groups			*P* value		
		PTTN, n (%)	NVOP, n (%)	PT-NVOP, n (%)	PTTN/ NVOP	PTTN/ PT-NVOP	NVOP/ PT-NVOP
Gender	M	34 (37.8)	15 (29.4)	6 (20.7)	NS	NS	NS
	F	56 (62.2)	36 (70.6)	23 (79.3)			
Laterality	Unilateral	81 (90)	37 (72.5)	17 (58.6)	.007	< .0001	NS
	Bilateral	9 (10)	14 (27.5)	12 (41.4)			
Location	Perioral	76 (84.4)	41 (80.4)	19 (65.5)	NS	NS	NS
	Oral	14 (15.6)	10 (19.6)	10 (34.5)			
Temporal pain characteristics	Attack	15 (16.7)	29 (56.9)	15 (51.7)	< .0001	.001	NS
	Persistent	31 (34.4)	7 (13.7)	5 (17.2)			
	Both	44 (48.9)	15 (29.4)	9 (31.1)			
Pain quality	Pressure	33 (36.7)	32 (62.7)	16 (57.1)	.003	.055	NS
	Throbbing	20 (22.2)	26 (51)	17 (60.7)	< .0001	< .0001	NS
	Burning	38 (42.2)	10 (19.6)	6 (21.4)	.06	.047	NS
	Electrical	18 (20)	5 (9.8)	0	NS	.01	NS
	Stabbing	36 (40)	16 (31.4)	7 (25)	NS	NS	NS
Frequency	Constant	35 (38.9)	11 (21.6)	8 (27.6)	< .0001	< .0001	NS
	Several per day	30 (33.3)	7 (13.7)	7 (24.1)			
	Once a day	12 (13.4)	6 (11.8)	1 (3.4)			
	Several per week	5 (5.6)	14 (27.5)	7 (24.1)			
	Several per month	8 (8.9)	12 (23.5)	5 (17.2)			
	Several per year	0	1 (2)	1 (3.4)			
Duration	Minutes	32 (35.6)	1 (2.1)	3 (10.7)	< .0001	< .0001	NS
	Hours	26 (28.9)	22 (45.8)	11 (39.3)			
	Days	3 (15)	17 (35.47)	7 (25)			
	Continuous pain	29 (32.2)	8 (16.7)	7 (25)			
Accompanying signs	Systemic	2 (2.2)	22 (43.1)	9 (31)	< .001	< .0001	NS
	Autonomic	11 (12.2)	22 (43.1)	9 (31)	< .0001	NS	NS

NVOP = neurovascular orofacial pain; PT-NVOP = neurovascular orofacial pain with history of trauma; PTTN = posttraumatic trigeminal neuropathy; NS = not significant.
T-NVOP = total neurovascular orofacial pain group; PTTN = posttraumatic trigeminal neuralgia.

Table 3 T-NVOP Group Compared to PTTN Group

		Total, n (%)	T-NVOP, n (%)	PTTN, n (%)	*P* value (T-NVOP/PTTN)
Laterality	Unilateral	135 (79.4)	54 (67.5)	81 (90)	< .001
	Bilateral	35 (20.6)	26 (32.5)	9 (10)	
Temporal pain characteristics %	Attack	59 (34.7)	44 (55)	15 (16.7)	< .0001
	Persistent	43 (25.1)	12 (15)	31 (34.4)	
	Both	68 (40)	24 (30)	44 (48.9)	
Pain quality[a]	Pressure	81 (47.6)	48 (60)	33 (36.7)	.001
	Throbbing	63 (37.1)	43 (53.8)	20 (22.2)	< .0001
	Burning	54 (31.8)	16 (20)	38 (42.2)	.002
	Electrical	23 (13.5)	5 (6.3)	18 (20)	.01
	Stabbing	59 (34.7)	23 (28.8)	36 (40)	.139
Frequency	Constant	54 (31.8)	19 (23.8)	35 (38.9)	< .001
	Several per day	44 (25.9)	14 (17.5)	30 (33.3)	
	Once a day	19 (11.1)	7 (8.8)	12 (13.3)	
	Several per week	26 (15.3)	21 (26.3)	5 (5.6)	
	Several per month	25 (14.1)	17 (21.3)	8 (8.9)	
	Several per year	2 (1.1)	2 (2.5)	0	
Duration[b]	Minutes	36 (21.2)	4 (5)	32 (35.6)	< .001
	Hours	59 (35.3)	33 (41.3)	26 (8.9)	
	Days	27 (15.9)	24 (30)	3 (3.3)	
	Continuous pain	44 (25.9)	15 (18.8)	29 (32.2)	
Accompanying signs[a]	Systemic	33 (20)	31 (38.8)	2 (2.2)	< .0001
	Autonomic	43 (25.3)	31 (38.8)	11 (12.2)	< .0001

T-NVOP = total neurovascular orofacial pain group; PTTN = posttraumatic trigeminal neuralgia.
[a]More than one pain quality or accompanying sign could be used in description.
[b]Absolute numbers could be lower than number of patients in the cohort if some answers were missing or ambiguous.

PTTN group) ($P < .001$, $c^2 = 26.464$, df = 5). T-NVOP differed from PTTN in the pattern of pain duration ($P < .001$, $c^2 = 42.518$, df = 3), as PTTN-typical pain was either very short (minutes, 35.6%) or of a continuous nature (32.2%), while T-NVOP pain duration was typically hours (41.3%) or days (30%).

Systemic symptoms (usually nausea) were reported significantly more in the T-NVOP than in the PTTN group (38.8% and 2.2%, respectively, $P < .00001$, $c^2 = 36.689$, df = 1), which was also true for autonomic signs, mostly tearing (38.8% and 12.2%, respectively; $P < .0001$, $c^2 = 16.444$, df = 1). According to the regression model (Table 4), the variables that reached statistical significance as predictors of the T-NVOP diagnosis were bilateral pain ($P = .012$), throbbing quality ($P = .027$), presence of autonomic or systemic signs ($P = .001$, $P = .007$, respectively), and a higher frequency of pain attacks when once a day or several per day were grouped with constant pain ($P = .004$). Of note is that waking from sleep, which was present in about 50% of patients (not shown in tables), did not differ between T-NVOP and PTTN ($P > 0.1$).

A diagram of pain characteristics of T-NVOP compared to PTTN is summarized in Box 1.

Table 4 Multiple Regression Models by Odds Ratios (ORs) for all Variables Differentiating Between Total Neurovascular Orofacial Pain and Posttraumatic Trigeminal Neuropathy Groups

				95% CI for OR	
	B	P[c]	OR**	Upper	Lower
Laterality[a]	1.460	.015	5.242	1.513	18.168
Attack/persist[b]	0.172	.407	1.271	0.832	1.940
Throbbing	0.980	.037	1.184	0.478	2.937
Pressure	0.585	.206	2.288	0.846	6.187
Burning	−0.854	.098	3.322	1.250	8.825
Electrical	−1.720	.032	0.495	0.179	1.367
Frequency	1.755	.001	0.235	0.052	1.062
Duration units	−0.307	.050	1.167	0.409	3.336
Systemic	2.644	.002	7.957	3.011	21.027
Autonomic	1.537	.005	0.726	0.532	0.991
Constant	−2.269	.053	6.488	2.223	18.939

CI = confidence interval.
[a]Unilateral versus bilateral.
[b]Constant pain, attacks once a day or several times per day vs other attack durations/forms.
[c]Two-tailed statistical significance.

Pain characteristics	T-NVOP	PTTN
Bilateral	frequent	rare
Throbbing	common	rare
Burning	rare	common
Electrical	very rare	not frequent
Periodic frequency	very common	rare
Duration characteristics	most common: hours to days	most common: minutes or continuous
Systemic/autonomic	very common	rare

Box 1 Diagram of Pain Characteristics of Neurovascular Orofacial Pain (T-NVOP) Compared to Painful Posttraumatic Trigeminal Neuropathy (PTTN)

Discussion

The features of NVOP vis-à-vis other chronic oral and facial pains were analyzed in a previous study[21] and can be differentiated by calculating PPV and NPV. In the present study, the features of NVOP were compared to those of PTTN, which has significant clinical relevance, especially when there is a history of multiple and repeated consultations with different specialists resulting in various treatments, including repeated invasive procedures. Distinction between NVOP and PTTN is clinically important for appropriate therapeutic strategies, as these conditions have different therapeutic protocols and prognostic outcomes. PTTN, like other posttraumatic neuropathies, is very resistant to therapy, even when using relevant evidence-based pharmacotherapeutic protocols.[28,29] NVOP, on the other hand, is amenable to antimigraine therapy, with good prognostic outcomes.[10,24,26,30]

While it was hypothesized that PT-NVOP may display signs and symptoms common to both PTTN and NVOP, the data showed that PT-NVOP was similar to NVOP and the two differed significantly from PTTN. This phenomenon of intraoral migraine-like pain induced by trauma has been described, and posttraumatic migraine is a well-known entity. The similarity in the diagnostic characteristics of NVOP and PT-NVOP is significant. This means that even in cases when NVOP patients undergo inappropriate dental treatment, they still maintain the same diagnostic features of NVOP and can be treated accordingly. The authors suggest that in cases of NVOP where invasive therapy resulted in additional PTTN, both diagnoses should be assigned. While PT-NVOP has the same diagnostic features as NVOP, it has been the authors' experience that in some cases, anti-neuropathic medications must be added to the antimigraine treatment for better results. However, since treatment results were not recorded systematically in the present study (discussed under Study Limitations), the authors are unable at this stage to identify what proportion of patients needs add-on therapy. Of note is that waking from sleep did not distinguish between T-NVOP and PTTN patients. Waking from sleep is a characteristic of migraine[35,36]

and was therefore included in the present definition of NVOP.[24] In light of the present study findings, the authors suggest that waking be removed from the original diagnostic criteria of NVOP.[22] Similarly, waking from sleep also did not differentiate between other acute[37] or chronic[31] facial pain conditions.

The temporal periodic pattern in NVOP in the present study is characteristic of migraine at large and supports the authors' previous findings.[22,38] Periodicity is a feature that differentiates NVOP from PTTN; the latter is usually described as a daily constant pain.[33] Most important, this temporal characteristic of NVOP did not change when PT-NVOP was compared to the PTTN group, maintaining the "original" periodic nature of NVOP. However, while periodic migraine is usually treated in an abortive manner, NVOP is treated in a prophylactic manner because it often occurs daily (in 50.1% of the present sample), is often aggravated by food ingestion, and interferes with daily living.[24] Another pain characteristic in NVOP but not present in PTTN is the throbbing quality, which is usually described as burning or stabbing.[39,40] This is not surprising, since throbbing pain is also common in migraine.[41,42] Yet, throbbing pain is also common in dental pulp inflammation (reversible/irreversible pulpitis),[37] leading to diagnostic confusion and often unnecessary dental treatments. Finally, the NVOP patients had a high rate of general (eg, photo/phonophobia, nausea) and autonomic signs not present in the PTTN group (Table 3).

The discrimination of NVOP from PTTN has additional diagnostic advantages considering the similarity of PTTN to PIFP,[43] especially as pain in PIFP may occasionally be similar to NVOP: it is bilateral in up to 40% of cases, and most PIFP patients are women with a mean age of onset in the mid-40s. Additionally, some PIFP patients responded partially to triptans, suggesting possible neurovascular mechanisms[44] or more likely misdiagnosis. It is therefore suspected that some patients of this heterogenous PIFP population should have been diagnosed as NVOP. While the major aim of this study was to characterize the features of NVOP that segregate it from PTTN, these 80 NVOP subjects, in addition to those from previous studies,[21,22] give the chance of a better representation of NVOP as a unique form of orofacial neurovascular disorder. The unique features of NVOP have been previously reported.[10,21,22] The overall "character" is more similar to migraine than to one of the TACs. It is acknowledged that facial pain during a migraine attack is not uncommon, yet isolated facial migraine located mainly in the lower half of the face seems extremely rare.[45] However, as discussed by Yoon et al,[45] their sampling method did not allow for the collection of data on isolated facial migraine, an entity that seems to be underdiagnosed.[12,13,15–17,23,26] However, these isolated facial migraine patients meet all criteria for migraine and are different from those with NVOP.

These findings present sufficient specific features that enable the classification of NVOP as a distinctive form of orofacial pain. Most prominent is the orofacial location sometimes being accompanied by a diffuse dentoalveolar pain with specific features reminiscent of pulpitis; ie, pain evoked by thermal stimuli. This type of evoked pain in NVOP explains the short duration. In 5% of NVOP patients, reported pain duration is only minutes, which is characteristic of dental pain. On the whole, 46.3% of NVOP patients report attack durations of minutes to hours, a very different time range relative to most patients with MWoA (4 to 72 hours). Also, 17.5% of NVOP patients described several attacks per day, a feature not usually observed in migraine patients.

Although migraine is classified as unilateral,[5] it can appear bilaterally in up to 40% of cases.[46–48] Similarly, NVOP has a relatively high frequency of bilateral pain (32.5%). Additionally, 23.8% of NVOP patients have constant chronic pain, in contrast to the lower prevalence of chronic migraine (7.7%) among migraineurs.[49] Of interest, NVOP patients have a mean age of onset of 40.9 years,[23] which is comparable to the present study (40.5 years of age). This is significantly older than typically reported in migraine, where 50% of patients suffer their first headache before the age of 25 years and 75% are affected by the age of 35 years.[50] Aggravating factors reported by migraineurs, such as routine physical activity, were not observed in this cohort of NVOP patients. These differences allow the distinct classification of NVOP from migraine, orofacial migraine, and TAC,[21] but, due to the similarities between NVOP and migraine, there is a need to examine inclusion criteria for NVOP and to determine the key differences from the IHS classification of MWoA, which is defined as "recurrent headache disorder manifesting in attacks lasting 4–72 hours." Typical characteristics of MWoA are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.[5] Location—except for laterality—is not specified in the ICHD criteria for migraine, and in this respect facial location does not exclude migraine; hence, facial or orofacial migraine remain in the diagnostic umbrella of the migraines. Autonomic signs are mentioned in the notes for migraine: "Migraine attacks can be associated with cranial autonomic symptoms and symptoms of cutaneous allodynia."[5] Autonomic signs are much more prevalent when migraine pain spreads to the facial area (47.8%),[45] an occurrence that was comparable to the present results (38.8%). Once autonomic signs have become

part of the NVOP inclusion criteria, cluster headache located orally cannot be completely ruled out in some patients. Yet, orofacial cluster headache is rather rare and attacks are mostly nocturnal, with an agitated behavioral pattern typical for cluster headache.[7] None of the NVOP patients presented with these behavioral patterns.

Of note, NVOP is readily responsive to both abortive and prophylactic antimigraine medications, and this is often utilized as a diagnostic tool.[10,24,25,30] The time duration of 4 to 72 hours specified for migraine does not concur with the duration of NVOP; typically, very short bouts of pain were associated with tooth sensitivity to cold ingestion. Other durations of attack—minutes to hours—were usually shorter than the lower limits of MWoA (4 hours), but so is abdominal migraine, with an inclusion criterion of 2- to 72-hour duration.[5] The need to challenge classification definitions, such as the time course of craniofacial pain syndromes, was discussed in a previous study on trigeminal neuralgia,[51] and the accumulation of new data often results in the extension of boundaries of previous classifications. Whether NVOP "belongs" to the migraine "family" and can be considered a distinct form of this disorder or as a unique entity separated from migraine and orofacial migraine is unclear at this point. There is a need for more widespread collection of clinical data and possibly the use of triptans as a diagnostic marker. Such issues were historically debated when cluster headache was identified and separated from migraine. Paroxysmal hemicrania was subsequently defined and had until that moment been diagnosed as cluster headache. The authors suggest, until it is otherwise refuted, that NVOP be considered a unique form of orofacial pain due to its specific features stated above.

Future studies comparing the three related entities—isolated facial migraine, MWoA with facial spread, and NVOP—are needed in order to detect specific signs, symptoms, and treatment responses in each. It should be noted that the first branch of the trigeminal nerve has some specific features and may explain some of the differences between the characteristics of headache and facial pain. The ophthalmic branch is most often involved in all primary headache types and is the least reported in trigeminal neuralgia. Underlying these differences may be specific central processing that differs between the first and second/third branches. For example, painful stimuli in the dermatomes of the maxillary and mandibular branches do not induce lacrimation as in the first division. Also, activation of 5-HT1B/1D receptors by local injection of naratriptans into the ventrolateral periaqueductal gray produced selective inhibition of trigemino-vascular nociceptive afferent input, but not of facial afferents.[52] Thus, NVOP seems to be associated with central activation of the second and third divisions, whereas MWoA is mainly associated with the first division. However, the dural innervation by the second and third divisions, which has been clearly demonstrated, makes this distinction less clear.[53]

Study Limitations and Suggestions for Future Research

The present study is limited by its retrospective nature, and prospective studies are needed for further distinction between NVOP, orofacial migraine, and MWoA with facial pain spread. Regrettably, another limitation is the lack of recorded history regarding the past or present typical migraine headaches of the patients and their relatives. Also, pharmacologic treatment outcomes that could have further confirmed the diagnoses were not always obtained.

Follow-up studies of the therapeutic responses of NVOP patients to specific antimigraine abortive (eg, triptans) and prophylactic (eg, beta-blockers) medications are clearly needed. Likewise, the responses of PT-NVOP patients to anti-migraine in addition to anti-neuropathic medications should be studied. Finally, this study is mostly based on qualitative data, and future quantitative measures—such as multicenter studies—are needed, preferably done including tests such as quantitative sensory testing, thermography, local anesthetic blocks, and biomarkers such as substance P, calcitonin gene-related peptide, and other peptides.

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