Chronic facial pain: different comorbidities and characteristics between neuropathic and nonneuropathic conditions

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Objective. The aim of this study was to investigate the association between comorbidities and chronic diseases and neuropathic and nonneuropathic orofacial pain diagnoses to suggest subclassifications of disease.

Study Design. This was a cross-sectional, retrospective, case-control study. We evaluated 174 patients with orofacial pain and 132 controls by using a systematic protocol that consisted of medical history and demographic, pain, and orofacial characteristics. Patients were grouped according to their diagnosis—neuropathic or non-neuropathic pain; medical comorbidities; and exclusion criteria. Analyses included Z-score normalization, χ^2 test, Fisher's exact test, 1-way analysis of variance (ANOVA), Student *t* test, Pearson's correlation coefficient, 2-step clustering, and logistic regression at 95% confidence level.

Results. Functional chronic diseases were prevalent and correlated with pain and orofacial features. Three groups were identified in the cluster analysis: neuropathic facial pain, other orofacial pain syndromes, and fibromyalgia/temporomandibular disorders (TMDs). Logistic regression showed that hypothyroidism and gastritis were predictors for nonneuropathic orofacial conditions. Psychiatric diseases and gastritis were more prevalent among patients with generalized pain syndromes and TMDs and less prevalent among patients with neuropathic pain.

Conclusions. Functional comorbidities were associated with orofacial and dental features and may correspond to multimorbidity states in patients with chronic orofacial pain. The findings support the hypothesis that nonneuropathic orofacial pain syndromes could be functional disorders. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:273−282)

Complex chronic pain is a challenge frequently encountered in clinical practice. Despite advances in diagnosis and treatment strategies, many patients continue to experience residual and persistent symptoms. The prevalence of chronic pain ranges from 7% to 40%, and orofacial pain affects 12% to 22% of the population.[1,2] Although most painful conditions have evident signs and symptoms associated with etiologic and pathophysiologic factors, diagnosis of some of these conditions depends on exclusion criteria.[3]

The incidence of trigeminal neuralgia (TN), a paroxysmal neuropathic type of facial pain, is 4.3 per 100,000 people per year in the United States.[4,5] Its etiology and pathophysiology are not well defined. Vascular compression[4] and altered expression of sodium channels are associated features.[6] Trigeminal postherpetic neuralgia (PHN) is another neuropathic disease that affects 15% to 40% of people with a history of herpes zoster infection,[7] and posttraumatic neuropathic pain is a potential complication of oral surgeries.[8]

The diagnosis of painful orofacial diseases, including burning mouth syndrome (BMS),[9,10] atypical odontalgia, and persistent idiopathic facial pain (PIFP), depend on exclusion of other conditions.[7] Masticatory myofascial pain is associated with temporomandibular disorders (TMDs), but it can be secondary to other pain causes.[11]

Psychiatric disorders and fibromyalgia are frequent comorbidities with orofacial pain.[12,13] These conditions are often associated with functional symptoms (illnesses having unexplained signs and symptoms) and gastrointestinal disorders[12] and, to the best of our knowledge, have not been investigated in studies comparing neuropathic and nonneuropathic orofacial pain.[14-17] Moreover, other chronic diseases have only been investigated as separate conditions (and not as multimorbid states) in these patients.[18,19]

Thus, the objective of this study was to investigate neuropathic and nonneuropathic orofacial pain diagno-

Statement of Clinical Relevance

This study observed different patterns of comorbidities according to the nature of orofacial pain (neuropathic or nonneuropathic), highlighting the importance of a global clinical investigation and inclusion of psychosomatic symptoms while diagnosing and treating orofacial diseases with different etiologies.

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ses according to their association with comorbidities and chronic diseases and, on the basis of our findings, to suggest a subclassification for orofacial pain.

MATERIALS AND METHODS

Patients

In this cross-sectional case-control study, Orofacial Pain Clinic databases covering the years 2002−2012 were used to address the objectives. A total of 174 patients with orofacial pain and 132 controls participated in a detailed and systematic evaluation. The patients were consecutively evaluated during the period, and the controls were students, volunteers from the general public, and relatives or acquaintances of patients, who were included throughout the period of the study. Patients and controls were informed about the aims of the study, and informed consent was obtained. The local research ethics committee approved this study.

A trained examiner (S.R.S.) performed a comprehensive diagnostic examination on all patients. The diagnostic criteria for orofacial pain used were in accordance with the International Headache Society (IHS)[8] and the International Association for the Study of Pain (IASP) criteria.[20] Their classification was revised at the time of our analysis, taking into consideration the updates of the criteria and the most recent version of the classification. The inclusion criterion for patients was chronic orofacial pain (> 6 months' duration), and the inclusion criterion for controls was total absence of orofacial pain. The exclusion criteria for patients were acute pain (< 6 months' duration) and not agreeing to participate in the study.

Medical history and clinical orofacial evaluation

Detailed medical history (chronic diseases, medication use); demographic factors (gender, age, occupation, and marital status); pain and orofacial characteristics were assessed. Specialist physicians diagnosed the medical conditions, and a single trained dentist performed the orofacial evaluation. The medical evaluation was performed by physicians from different clinics at the hospital, according to the appropriate diagnostic protocols, which included examination and other assessments, as necessary. The detailed orofacial evaluation followed the systematic protocol of the Orofacial Pain Group and included patient reported history, a clinical questionnaire, and clinical examination of the orofacial region.[21]

Chronic diseases were classified according to medical areas and as functional or nonfunctional disorders.[12,22,23] Two scores (functional and nonfunctional) were created on the basis of the number of functional and nonfunctional disorders, respectively. Medications were classified according to pharmacologic characteristics, and evaluated as 2 scores: (1) total number of medications and (2) number of medications, excluding those used in pain treatment.

Pain characteristics included pain descriptors (the main descriptor and the number of descriptors); pain intensity on a numerical scale (0−10, with 0 = no pain at all, and 10 = the worst possible pain); number of pain areas, excluding the craniofacial region pain; worsening factors (quality and quality); alleviating factors (quality and quantity); number of previous treatments; and number of previous surgeries. The orofacial characteristics included were bruxism; temporomandibular joint noises observed during the clinical examination; dental occlusion; abnormalities of the facial skin, oral mucosa, periodontal tissues, tongue, and remaining teeth (which were evaluated and counted); and the quantity of masticatory trigger points.

Classification

First, the patients were divided into groups according to the current IASP and IHS criteria.[8,20] Then, the whole sample was subjected to unsupervised clustering, and 2 other ways of classification were proposed. Finally, correlations between clinical features and the classifications were investigated. The IASP and IHS classification and the proposed classifications after clustering the whole sample are described below:

IASP criteria[20]. A.I. Relatively generalized syndromes: Fibromyalgia, complex regional pain syndrome, peripheral polyneuropathy, and Wallenberg syndrome

B.II. Relatively localized syndromes of the head and neck (neuralgias of the head and neck): TN, trigeminal posttraumatic neuropathic pain, and trigeminal PHN

B.II. Relatively localized syndromes of the head and neck (craniofacial pain of musculoskeletal origin): TMD

B.IV. Relatively localized syndromes of the head and neck (lesions of the ear, nose, and oral cavity): Tooth pain not associated with lesions (atypical odontalgia), glossodynia and sore mouth (BMS), and other and unspecified pain in the jaws (PIFP and facial palsy)

IHS criteria[8]. II.11.7 Secondary headaches (headache attributed to temporomandibular disorder: TMD)

III.13.1. Neuropathies and facial pains and other headaches (pain attributed to a lesion or disease of the trigeminal nerve): TN, trigeminal posttraumatic neuropathic pain, trigeminal PHN, painful trigeminal neuropathy attributed to other disorder (facial palsy, Wallenberg syndrome, polyneuropathy, complex regional pain syndrome)

III.13.11. Neuropathies and facial pains and other headaches: BMS

III.13.12. Neuropathies and facial pains and other headaches: PIFP and atypical odontalgia

A10.8.2. Headache attributed to other metabolic or systemic disorder: Fibromyalgia.

The following classifications, based on the neuropathic and nonneuropathic nature of the pain and the exclusion criteria, were suggested for this investigation:

Suggestion I.

1 Neuropathic facial pain (with identified etiologic cause, major neurologic signs and/or TN): TN, trigeminal posttraumatic neuropathic pain, trigeminal PHN, polyneuropathy, Wallenberg syndrome, and facial palsy
2 Other orofacial pain syndromes (with diagnosis based on exclusion, and controversies in the literature about its neuropathic nature): BMS, atypical odontalgia, PIFP, and complex regional pain syndrome
3 Masticatory myofascial pain: TMD
4 Generalized pain syndrome: Fibromyalgia

Suggestion II.

1 Facial neuropathic pain (with identified etiologic cause, neurologic signs and/or TN): TN, trigeminal posttraumatic neuropathic pain, trigeminal PHN, polyneuropathy, Wallenberg syndrome, and facial palsy
2 Other pain syndromes (with diagnosis based on exclusion, and controversies in the literature about its neuropathic nature): BMS, atypical odontalgia, PIFP, TMD, fibromyalgia, and complex regional pain syndrome

Statistical analysis

The descriptive analysis included frequencies and percentages for categorical data and means, standard deviations, and confidence intervals for quantitative data. Missing data were ages of 2 controls (1.5%) and 10 patients (5.7%); numeric pain intensity for 1 patient (0.8%); worsening factors for 4 patients (3%). Means were used for regression analysis in these cases.

Normal distribution was assumed by the central limit theorem. Association between variables was analyzed with the χ^2 test with Bonferroni's correction and post hoc analysis; Fisher's exact test; 1-way analysis of variance (ANOVA); and the Student *t* test. Pearson's correlation coefficient was used for correlation analysis. The significant variables from the initial analysis were considered for further investigation with classification and regression. Data were normalized with Z-score and studied with unsupervised 2-step cluster classification and logistic regression for the prediction of neuropathic and nonneuropathic conditions.

The level of significance was set at 5%, and the SPSS version 17.0 (SPSS Inc., Chicago, IL) and R studio software programs were used for statistical analysis.

RESULTS

The majority of patients with orofacial pain (83.9%) and controls (53.8%) were females ($P < .001$; Fisher's exact test), and the mean ages were 54.87 ± 15.52 and 49.09 ± 22.78 years, respectively ($P < .001$; Student *t* test). The distribution of patients, according to the main diagnosis, was TN (42 [24.1%]); BMS (36 [20.7%]); TMD (30 [17.2%]); PIFP (12 [6.9%]); trigeminal posttraumatic neuropathic pain (12 [6.9%]); atypical odontalgia (10 [5.7%]); fibromyalgia (10 [5.7%]); trigeminal PHN (7 [4%]); complex regional pain syndrome (5 [2.9%]); peripheral polyneuropathy (4 [2.3%]); facial palsy (3 [0.7%]); and Wallenberg syndrome (3 [1.7%]). Patients were classified as described below.

According to the IASP criteria

A.I. Relatively generalized syndromes (22 [7.2%])

B.II. Relatively localized syndromes of the head and neck (neuralgias of the head and neck) (61 [19.9%])

B.II. Relatively localized syndromes of the head and neck (craniofacial pain of musculoskeletal origin) (30 [9.8%]); relatively localized syndromes of the head and neck (lesions of the ear, nose, and oral cavity) (61 [19.9%]).

According to the IHS criteria

II.11.7. Secondary headaches (headache attributed to temporomandibular disorder) (30 [9.8%])

III.13.1 Neuropathies and facial pains and other headaches (pain attributed to a lesion or disease of the trigeminal nerve) (76 [24.8%])

III.13.11 Neuropathies and facial pains and other headaches (BMS) (36 [11.8%])

III.13.12 Neuropathies and facial pains and other headaches (PIFP and atypical odontalgia) (22 [7.2%]); headache attributed to other metabolic or systemic disorder (fibromyalgia) (10 [3.3%])

According to suggestion I

1 Neuropathic facial pain (71 [23.2%])
2 Other orofacial pain syndromes (63 [20.6%])
3 Masticatory myofascial pain (30 [9.8%])
4 Generalized pain syndrome (10 [3.3%])

According to suggestion II

1 Facial neuropathic pain (71 [23.2%])
2 Other pain syndromes (103 [33.7%])

There were 141 patients (81.0%) with chronic diseases ($P < .001$; Fisher's exact test), and of these, and 144

(82.8%) were taking medications ($P < .001$; Fisher's exact test) (Tables I and II). Patients with TMD, fibromyalgia, PIFP, and BMS had more chronic diseases compared with other patients with other diagnoses (in this sample), and all groups of patients (in all types of classification) showed more chronic diseases compared with controls.

There were more females in the group of patients with other pain syndromes (PIFP, atypical odontalgia, BMS, fibromyalgia, complex regional pain syndrome, TMD) compared with those with neuropathic pain diagnoses and controls ($P < .001$; χ^2 test with Bonferroni's correction and post hoc analysis), and there were age differences according to the diagnosis ($P < .001$; 1-way ANOVA). Patients with trigeminal PHN, BMS, and TN were older, and patients with trigeminal posttraumatic neuropathic pain were younger and had a higher frequency on Student t test ($P = .001$; χ^2 test with Bonferroni's correction and post hoc analysis).

Table I. Distribution of chronic diseases according to group

		Patients (N = 174)		*Controls (N = 132)*		*P*
		Frequency (N)	*Percentages (%)*	*Frequency (N)*	*Percentages (%)*	
Nephrologic disease	Yes	9	5.2	3	2.3	.160*
	No	165	94.8	129	97.7	
Gastritis	Yes	38	21.8	20	15.2	.091*
	No	136	78.2	112	84.8	
Sinusitis	Yes	29	16.7	11	8.3	.023*
	No	145	83.3	121	91.7	
Rhinitis	Yes	22	12.6	10	7.6	.105*
	No	152	87.4	122	92.4	
Asthma or bronchitis	Yes	8	4.6	2	1.5	.118*
	No	166	95.4	130	98.5	
Amygdalate	Yes	5	2.9	1	0.8	.185*
	No	169	97.1	131	99.2	
Hypertension	Yes	66	37.9	46	34.8	.332*
	No	108	62.1	86	65.2	
Heart disease	No	10	5.7	6	4.5	.422*
	Yes	164	94.3	126	95.5	
Diabetes	Yes	14	8.0	1	0.8	.002*
	No	160	92	131	99.2	
Hypothyroidism	Yes	16	9.2	4	3.0	.024*
	No	158	90.8	128	97	
Depression	Yes	36	20.7	8	6.1	< .001*
	No	138	79.3	124	93.9	
Fibromyalgia	Yes	27	15.5	0	0	< .001*
	No	147	84.5	132	100	
Rheumatoid arthritis	Yes	8	4.6	1	0.8	.046*
	No	166	95.4	131	99.2	
Hypercholesterolemia	Yes	5	2.9	7	5.3	.215*
	Yes	5	2.9	7	5.3	
Other diseases†	Yes	24	13.8	6	4.5	< .001*
	No	150	86.2	126	95.5	

	Mean ± Standard deviation (range)	*Confidence intervals (95%)*	*Mean ± Standard deviation (range)*	*Confidence intervals (95%)*	
Number of chronic diseases	1.8 ± 1.61 (0–8)	1.56–2.05	1.0 ± 1.21 (0–6)	0.82–1.24	< .001‡
Functional score	0.8 ± 0.87 (0–4)	0.65–0.91	0.2 ± 0.48 (0–2)	0.13–0.29	< .001‡
Nonfunctional score	0.9 ± 1.20 (0–6)	0.75–1.10	0.8 ± 0.99 (0–6)	0.64–0.98	.374‡
Number of neurologic diseases	0.1 ± 0.21 (0–1)	0.01–0.08	0.02 ± 0.12 (0–1)	0.00–0.04	.134‡
Number of rheumatologic diseases	0.2 ± 0.43 (0–2)	0.16–0.29	0.0 ± 0.12 (0–1)	0.00–0.04	< .001‡
Number of otorhinolaryngologic diseases	0.4 ± 0.76 (0–4)	0.25–0.48	0.2 ± 0.54 (0–4)	0.11–0.30	.037‡
Number of psychiatric diseases	0.2 ± 0.43 (0–2)	0.15–0.28	0.1 ± 0.24 (0–1)	0.02–0.10	< .001‡
Number of cardiologic diseases	0.4 ± 0.55 (0–2)	0.36–0.53	0.4 ± 0.55 (0–2)	0.30–0.49	.446‡
Number of allergies	0.2 ± 0.50 (0–2)	0.14–0.29	0.1 ± 0.36 (0–2)	0.05–0.18	.044‡
Number of infectious diseases	0.2 ± 0.52 (0–3)	0.15–0.30	0.1 ± 0.36 (0–2)	0.07–0.19	.071‡

*Fisher's exact test.
†Other diseases: Frequency less than 5.
‡Student t test.

Table II. Distribution of medications in use according to group

		Patients (N = 174)		*Controls (N = 132)*		*P*
		Frequency (N)	*Percentages (%)*	*Frequency (N)*	*Percentages (%)*	
Any antidepressant	Yes	70	40.2	3	2.3	< .001*
	No	104	59.8	129	97.7	
Tricyclic antidepressant	Yes	62	35.6	0	0	< .001*
	No	112	64.4	132	100	
Selective antidepressant	Yes	7	4.0	3	2.3	.304*
	No	167	96	129	97.7	
Anticonvulsant	Yes	79	54.6	2	1.5	< .001*
	No	95	45.4	130	98.5	
Neuroleptic	Yes	44	25.3	1	0.8	< .001*
	No	130	74.7	131	99.2	
NSAIDs and common analgesics	Yes	19	10.9	6	4.5	.033*
	No	155	89.1	126	95.5	
Opioid	Yes	9	5.2	0	0	.006*
	No	165	94.8	132	100	
Antihypertensive	Yes	42	24.1	42	31.8	.087*
	No	132	75.9	90	68.2	
Gastric protector	Yes	12	6.9	3	2.3	.053*
	No	162	93.1	129	97.7	
Benzodiazepine	Yes	8	4.6	0	0	.010*
	No	166	95.4	132	100	
Muscular relaxant	No	12	6.9	0	0	.001*
	Yes	162	93.1	132	100	
Antihypothyroidism	Yes	9	5.2	4	970	.266*
	No	165	94.8	128	3	
Statin	Yes	5	2.9	7	5.3	.215*
	No	169	97.1	125	94.7	
Vitamins	Yes	2	1.1	4	3.0	.223*
	No	172	98.9	128	97	
Other diseases†	Yes	10	5.7	5	3.8	.005‡
	No	164	94.3	127	96.2	
		Mean ± SD (range)	*Confidence intervals (95%)*	*Mean ± SD (range)*	*Confidence intervals (95%)*	
Number of medications		1.9 ± 1.49 (0-7)	1.68−2.13	0.6 ± 1.01 (0-6)	0.46−0.81	< .001‡
Number of medications (except for pain)		0.8 ± 1.07 (0-6)	0.60−0.92	0.6 ± 1.01 (0-6)	0.46−0.81	.288‡

*Fisher's exact test.
†Other medications: Frequency less than 5.
‡Student *t* test.

A secondary pain diagnosis was present in 64 patients (36.8%). TMD was the most common secondary diagnosis affecting 41 patients, including 9 (75%) with trigeminal posttraumatic neuropathic pain; 9 (25%) with BMS; 7 (16.7%) with TN; 7 (58.3%) with PIFP; 2 with complex regional pain syndrome; 2 with trigeminal PHN (28.6%); 2 with atypical odontalgia (20.0%); and 1 each with facial palsy, polyneuropathy, and Wallenberg syndrome. In addition, among patients with TN, 1 (2.4%) had cervical myofascial pain, and among patients with BMS, 2 (5.6%) had fibromyalgia. Among patients with TMD, 16 (53.3%) had fibromyalgia, and 2 (6.7%) had cervical myofascial pain. And, last, 2 patients with complex regional pain syndrome had fibromyalgia.

The distribution of patients according to pain and orofacial characteristics is outlined in Table III. Mostly, among the study patients, there were multiple pain descriptors (32.2%). The most common were "burning" (14.1%); "shock-like" (15%); and "throbbing" (4.6%). The main worsening factors were emotional distress (12.4%); cold (11.8%); and chewing (9.5%). The main alleviating factors were medication (21.6%); rest (6.5%); and physiotherapy/massage (4.2%).

Pain and orofacial characteristics were not correlated with the classifications, except for the number of pain areas outside the craniofacial region; higher prevalence among patients with TMD and fibromyalgia; worsening factors (correlated with BMS); alleviating factors (correlated with TMD); number of remaining teeth (correlated with TN); and number of trigger points (more prevalent in patients with TMD and fibromyalgia). Besides, the number of chronic functional diseases (functional score)

Table III. Distribution of pain and orofacial characteristics according to group

		Patients (N = 174)		*Controls (N = 132)*		*P*
		Frequency (N)	*Percentages (%)*	*Frequency (N)*	*Percentages (%)*	
Bruxism	Yes	86	49.4	18	13.6	< .001*
	No	49	28.2	108	81.8	
	Doesnt know	39	22.4	6	4.5	
Temporomandibular joint noises	Yes	66	37.9	40	30.3	.183†
	No	108	62.1	92	69.7	
Occlusal abnormality	Yes	55	31.6	28	78.8	.051†
	No	119	68.4	104	21.2	
Facial skin abnormality	Yes	29	16.7	21	15.9	.877†
	No	145	83.3	111	84.1	
Oral mucosa abnormality	Yes	24	13.8	8	6.1	.037†
	No	150	86.2	124	93.9	
Tongue abnormality	Yes	78	44.8	57	43.2	.817†
	No	96	55.2	75	56.8	
Periodontal disease	None	125	71.8	105	79.5	.486*
	Gingivitis	12	6.9	6	4.5	
	Mild periodontitis	12	6.9	5	3.8	
	Moderate periodontitis	17	9.8	9	6.8	
	Severe periodontitis	8	4.6	7	5.3	
Dental abnormality	Yes	39	22.4	39	29.5	.185†
	No	135	77.6	93	70.5	
		Mean ± SD (range)	*Confidence intervals (95%)*	*Mean ± SD (range)*	*Confidence intervals (95%)*	
Number of pain descriptors		1.8 ± 1.06 (0–5)	1.60–1.92	0	0.0–0.0	< .001‡
Numeric pain intensity		7.9 ± 2.57 (0–10)	7.55–8.32	0.08 ± 0.870 (0–10)	−0.07–0.23	< .001‡
Number of pain areas (except craniofacial)		0.95 ± 0.74 (0–2)	0.84–1.07	0.42 ± 0.55 (0–2)	0.33–0.52	< .001‡
Number of worsening factors		1.04 ± 0.75 (0–3)	0.92–1.15	0	0.0–0.0	< .001‡
Number of alleviating factors		0.76 ± 0.61 (0–3)	0.67–0.86	0	0.0–0.0	< .001‡
Number of previous treatments for pain		1.28 ± 0.93 (0–4)	1.14–1.42	1.28 ± 0.92 (0–4)	1.14–1.42	< .001‡
Number of previous surgeries		0.21 ± 0.48 (0–3)	0.14–0.28	0.01 ± 0.09 (0–1)	0.00–0.02	< .001‡
Number of remaining teeth		15.6 ± 10.97 (0–28)	13.90–17.23	18.4 ± 10.73 (0–28)	16.53 -20.25	.024‡
Number trigger points		2.69 ± 2.38 (0–6)	2.33–3.05	0.25 ± 0.65 (0–4)	0.14–0.37	< .001‡

*χ^2 with Bonferroni's correction and post hoc analysis.
†Fisher's exact test.
‡Student *t* test.

was correlated with most orofacial features (number of pain descriptors, pain intensity, number of pain areas outside the craniofacial region, worsening and alleviating factors, previous treatments, number of remaining teeth, and number of trigger points).

Unsupervised cluster analysis was performed with the diagnostic classifications and the significant variables (after initial description): functional score; otorhinolaryngologic diseases; medications; number of pain areas (beyond the craniofacial region); trigger points; and worsening and alleviating factors. Only 1 case was excluded by the analysis as an outlier (0.6%). Masticatory myofascial pain and generalized pain syndromes (fibromyalgia) were combined in cluster 1, and other orofacial pain syndromes and neuropathic facial pain were distributed in clusters 2 and 3, respectively (Table IV). A comparison of the characteristics of these groups is provided in Figure 1.

Logistic regression was performed to predict neuropathic or nonneuropathic pain in the orofacial region, only with patients who did not have generalized pain complaints. The best-fitting model was chosen on the basis of the lower Akaike information criterion, and it included the following independent features: hypothyroidism, gastritis, and trigger points (Akaike information criterion = 208.35). Functional scores and psychiatric diseases were not associated with facial pain subtypes in the regression but were associated with generalized pain symptoms and fibromyalgia. The coefficients, confidence intervals, and significance are shown in Table V.

Table IV. Distribution of features according to clusters of patients

		Cluster 1 (45; 26.0%)		*Cluster 2 (58; 33.5%)*		*Cluster 3 (70; 40.5%)*		P
IASP classification*	A.I. Relatively generalized syndromes	15	68.2%	0	0%	7	31.8%	< .001†
	B.II. Neuralgia of head and neck	0	0%	0	0%	60	100%	
	B.II. Craniofacial pain of musculoskeletal origin	30	100%	0	0%	0	0%	
	B.IV. Lesions of ear, nose, and oral cavity	0	0%	58	95.1%	3	4.9%	
IHS classification*	II.11.7. Temporomandibular disorder	30	100%	0	0%	0	0%	< .001†
	III.13.1. Lesion or disease of the trigeminal nerve	5	6.7%	0	0%	70	93.3%	
	III.13.11. BMS	0	0%	36	100%	0	0%	
	III.13.12. PIFP and atypical odontalgia	0	0%	22	100%	0	00%	
	A10.8.2. Fibromyalgia	10	100%	0	0%	0	0%	
Suggestion I*	Facial neuropathic pain	0	0%	0	0%	70	100%	< .001†
	Other orofacial pain syndromes	5	7.9%	58	92.1%	0	0%	
	Masticatory myofascial pain	30	100%	0	0%	0	0%	
	Generalized pain syndrome	10	100%	0	0%	0	0%	
Suggestion II*	Facial neuropathic pain	0	0%	0	00%	70	100%	< .001†
	Other pain syndromes	45	43.7%	58	56.3%	0	0%	
Functional score‡	Mean ± SD	1.1 ± 0.93		0.8 ± 0.92		0.5 ± 0.72		.003§
	95% confidence interval	0.81−1.37		0.59−1.07		0.37−0.71		
Otorhinolaryngologic diseases	Mean ± SD	0.5 ± 0.92		0.4 ± 0.70		0.3 ± 0.70		.209§
	95% confidence interval	0.23−0.79		0.21−0.58		0.09−0.42		
Medication‖	Mean ± SD	2.6 ± 1.55		1.8 ± 1.64		1.6 ± 1.20		.003§
	95% confidence interval	2.09−3.02		1.34−2.21		1.33−1.90		
Number of pain areas (except craniofacial region)‖	Mean ± SD	1.3 ± 0.63		0.9 ± 0.80		0.8 ± 0.71		.001§
	95% confidence interval	1.10−1.48		0.72−1.14		0.60−0.94		
Worsening factors*	Mean ± SD	1.1 ± 0.62		0.8 ± 0.73		1.2 ± 0.84		.003§
	95% confidence interval	0.88−1.25		0.58−0.97		1.03−1.43		
Alleviating factors‖	Mean ± SD	1.1 ± 0.65		0.7 ± 0.58		0.7 ± 0.60		.001§
	95% confidence interval	0.87−1.26		0.50−0.81		0.56−0.84		
Number of trigger points‖	Mean ± SD	4.0 ± 1.91		2.3 ± 2.45		2.1 ± 2.37		< .001§
	95% confidence interval	3.40−4.55		1.68−2.97		1.56−2.64		

*All groups were different.
†χ^2 with post hoc analysis and Bonferroni's correction.
‡Difference between groups 1 and 3.
§One-way analysis of variance (ANOVA).
‖Difference between group 1 and groups 2 and 3.Cluster 1: Masticatory myofascial pain and generalized pain syndrome (fibromyalgia).Cluster 2: Other orofacial pain syndromes.Cluster 3: Neuropathic facial pain.*BMS,* burning mouth syndrome; *IASP,* International Association for the Study of Pain; *IHS,* International Headache Society; *PIFP,* persistent idiopathic facial pain; *SD,* standard deviation.

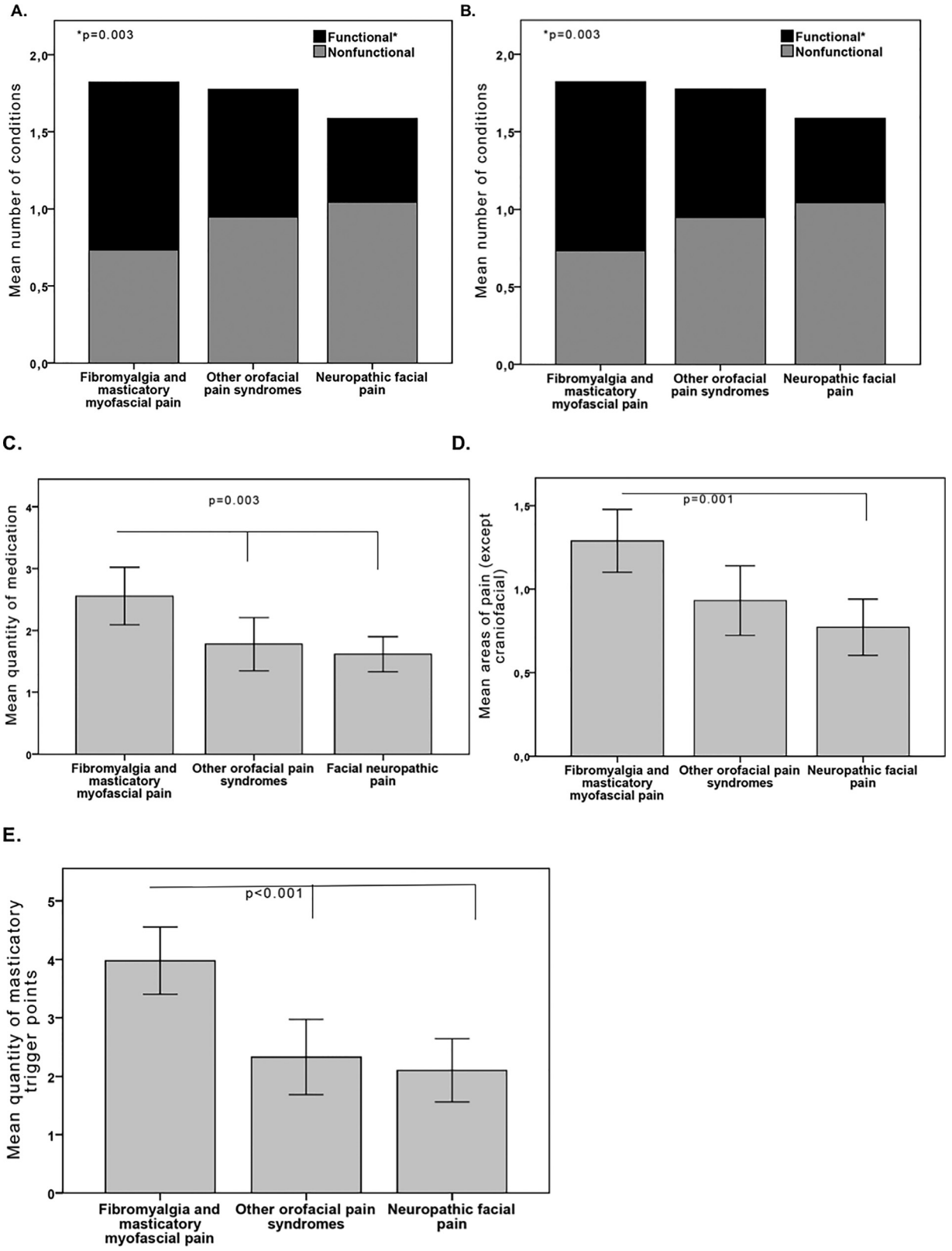

Fig. 1. Distribution of features according to the suggested classification. **A**, Functional and nonfunctional disorders. **B**, Distribution of diseases. **C**, Quantity of medications (error bars 95% confidence interval [CI]). **D**, Quantity of areas with pain (except craniofacial) (error bars 95% CI). **E**, Quantity of trigger points (error bars 95% CI).

Table V. Coefficients, confidence intervals, and significance from logistic regression of facial pain patients (neuropathic and nonneuropathic conditions)

	Coefficients	*Confidence interval*	*P*
Intercept (α)	0.52	$0.44 \leq \alpha \leq 0.61$	< .001
Hypothyroidism (β_1)	−0.08	$-0.14 \leq \beta_1 \leq -0.01$	.0313
Gastritis (β_2)	−0.07	$-0.15 \leq \beta_2 \leq 0.01$	.0770
Trigger points (β_3)	−0.04	$-0.11 \leq \beta_3 \leq 0.04$	.3141

DISCUSSION

This study showed that there is an association between comorbid chronic diseases and chronic orofacial pain. Functional disorders, especially psychiatric diseases and gastritis, were more prevalent in patients with TMD and fibromyalgia and less prevalent in patients with neuropathic facial pain. These comorbidities were correlated with orofacial and pain features, such as number of remaining teeth, trigger points, number of pain descriptors, and number of pain areas beyond the craniofacial region. Moreover, nonfunctional illnesses tended to be more prevalent in patients with neuropathic facial pain.

There is evidence to support the association between TMD and fibromyalgia as comorbidities.[24] Besides, chronic diseases, such as depression and gastrointestinal functional disorders, are prevalent in patients with fibromyalgia.[12,13,25-28] Thus, it was not a surprise that unsupervised classification analysis resulted in both TMD and fibromyalgia being included in the same group, as associated illnesses.

At the other extreme, the group with neuropathic facial conditions had the lowest quantity of chronic diseases, especially functional disorders, and the lowest quantity of pain in areas of the body other than the craniofacial region. Particularly, gastritis and hypothyroidism were predictors of nonneuropathic orofacial conditions, supporting the fact that PIFP, BMS, atypical odontalgia, complex regional pain syndrome, and TMD are more often associated with chronic comorbidities compared with neuropathic illnesses. Most of these diagnoses are based on exclusion of other pain conditions and can be interpreted as somatoform symptoms that do not have an organic cause, thus being classified as functional disorders.[23,29] Although part of the scientific community assumes that some of these conditions are neuropathic,[10] there is no consensus regarding this notion; this was considered in this study to remain impartial for the analysis. The recognition of this aspect may allow more effective assessment options that consider comorbidities and would help determine which conditions would be more neuropathic in nature, although in others, such as BMS and PIFP,[10] other underlying mechanisms play a major role and need to be further investigated. These findings might help with the differential diagnosis, contributing to the identification of these patients on the basis of positive signs of comorbid conditions; however, their diagnosis is still based on exclusion.[30]

Besides, facial pain could be a symptom of a systemic illness, or a chronic condition may change the orofacial clinical features; therefore, further investigation is necessary to understand the mechanisms underlying this association. Functional disorders seem to activate the neuroimmune system,[31] promoting systemic and neural inflammatory changes that lead to peripheral and/or central sensitization.

The group of patients with other chronic orofacial pain syndromes included those with chronic facial pain diagnoses that have a clinical presentation in common—spreading pain not restricted to a neural branch—and controversial diagnostic criteria. The suggestion of the classification used in this study opens the way to future investigations regarding the mechanisms of sensitization involved in chronic neuropathic and nonneuropathic pain, as well as in the delineation of precise diagnostic criteria that would consider the clinical aspects of the patient's general health.

There is a high convergence from the various cranial nerves that innervate the face and parts of the skull, including nasal and buccal mucosae, paranasal sinuses, bones and muscles of the face, teeth, cornea, and dura mater,[32] and areas up to the upper part of the digestive system.[33] Otorhinolaryngologic diseases and dental problems are commonly chronic infections and inflammatory processes that sensitize the trigeminal system and provoke hyperalgesia,[34] inducing facial pain. In this study, we found a higher prevalence of facial pain in the group of patients with fibromyalgia and TMD. The correlation between hypothyroidism and facial pain may be related to the neurotrophic and inflammatory roles of hormones.[35,36]

It is important to emphasize that for a broad analysis of variables in this study, it was necessary to include patients with different diagnoses in the groups studied. Although this heterogeneity is a limitation of the study, the novel evaluation of this complex sample makes the findings valid, and this study may be useful as a precursor of further research on the subject. The profiles of morbidities evaluated varied, depending on the type of chronic pain, and this needs to be taken into account in the diagnosis and treatment of these facial conditions.

CONCLUSIONS

Psychiatric diseases and gastritis were more prevalent in patients with generalized pain syndromes and TMD and less prevalent in patients with neuropathic pains. Functional comorbidities were associated with orofacial and dental features of pain. Our findings support that chronic

orofacial pain syndromes, such as PIFP, atypical odontalgia, BMS, TMD, and complex regional pain syndrome, could be considered functional disorders.

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