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ORIGINAL RESEARCH

Correlation Between Orofacial Pain and Sensory and Autonomic Neuropathies

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Purpose: Orofacial Pain (OFP) affects 15% of the general population. OFP conditions can be myofascial, also known as temporomandibular disorders (TMDs) or neuropathic. The underlying pathophysiology in several chronic OFP conditions, is unknown. Small fiber neuropathy (SFN) is a disorder of thinly myelinated A-delta and non-myelinated C-fibers and can manifest as sensory and autonomic neuropathies. SFN has been demonstrated in some OFP conditions. Our study aims to assess the presence of OFP in patients with sensory and autonomic neuropathies and assess the correlation between OFP, skin biopsy and autonomic dysfunction.

Patients and Methods: This is a retrospective study (2018–2020) of patients from the SFN registry, Massachusetts General Hospital, Boston, USA, for the presence of OFP. All patients were included. Primary outcome: Prevalence of OFP in patients with chronic neuropathies. Secondary outcomes: Correlation between OFP and skin biopsy, dysautonomia, headaches, chronic nociceptive pain, psychological conditions, and patient factors, such as mean age and BMI.

Results: Charts of 450 patients with sensory and autonomic neuropathies were reviewed. 22.67% (n=102) had OFP. The mean (range) age at biopsy in patients with OFP was 48.36 (20–81) years, female: male ratio 3.25:1. More OFP patients had negative skin biopsy results (p value<0.05) than those with sensory neuropathies. Patients with OFP had significantly higher prevalence of psychological conditions (p value 0.000), and higher BMI >30 (p value 0.025). Dysautonomia was significantly higher in patients with TMDs when compared to the ones without TMDs (p value 0.030). There was no significant difference in mean age, gender predilection, presence of headaches, peripheral neuropathies, and nociceptive pain between patients with and without OFP.

Conclusion: OFP and sensory neuropathies can be overlapping conditions. Patients presenting with concomitant TMD and dysautonomia can be further tested for SFN. This can further help us understand a correlation if any, between idiopathic TMD/OFP conditions and SFN and further our understanding of the pathophysiology of these conditions.

Keywords: idiopathic facial pain, orofacial pain, temporomandibular disorders, skin biopsy, autonomic dysfunction, sensory neuropathic pain, dysautonomia, small fiber neuropathy

Introduction

Orofacial pain (OFP) is a term used to describe pain affecting the face and/or the oral structures.[1] The prevalence of OFP in the general population is up to 15% with a high prevalence rate among young and middle-aged women.[2] Chronic OFP conditions can be difficult to diagnose due to the varied signs and symptoms, the complex anatomy of the region and lack of objective testing in most cases.[3] OFP conditions can be categorized into myofascial, commonly known as temporomandibular disorders (TMDs) and neuropathies, which include persistent idiopathic facial pain (PIFP), persistent idiopathic dentoalveolar pain (PIDP), idiopathic burning mouth syndrome (BMS) and trigeminal neuralgia (TN) etc.[4] As the underlying etiology and pathogenesis of these conditions are mostly unknown, treatment is nonspecific and comprises management of the symptoms, rather than addressing the underlying disease process. Hence, improvement is

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not assured, and most cases will need lifetime pain management.[5] The financial burden of facial pain is approximately 2032 USD in 2017 per person per 6-month period.[6] Furthermore, patients with chronic OFP can have difficulty maintaining nutrition and social interactions. As such, OFP conditions have a huge emotional and financial impact on society and the individuals involved.

Small fiber neuropathy (SFN) is a disorder of thinly myelinated A-delta and non-myelinated C- fibers.[7] The clinical presentation is heterogenous and characterized by clinical signs of neuropathy with either a positive skin biopsy or positive autonomic function testing or both.[8,9] Nonspecific symptoms such as fatigue, cramps, and deep aching pain can also occur due to involvement of polymodal muscle afferents.[10] The diagnosis of SFN is based on typical complaints, combined with abnormal intraepidermal nerve fiber density in skin biopsy and/or abnormal temperature threshold testing levels, without signs of large nerve fiber involvement.[11] SFN can be length-dependent involving a typical sock and glove pattern, non-length dependent where different parts of the body can be involved in a patchy pattern or focal involving a circumscribed area only. Focal and non-length dependent (NLD) SFNs have been shown to involve the orofacial region.[12,13] For instance, reduced small fiber nerve density is an underlying cause in idiopathic burning mouth syndrome.[12,14,15] Also, association has been shown between SFN and several chronic pain conditions, such as fibromyalgia, chronic regional pain syndromes, and unexplained widespread chronic pain conditions.[16,17] Therefore, it is possible that certain patients presenting with chronic OFP conditions can also have an underlying SFN.

Our study aims to assess the prevalence of OFP in a large cohort of patients with sensory and autonomic neuropathies and assess the correlation between OFP and results of skin biopsy testing, autonomic dysfunction, primary headaches, chronic nociceptive and neuropathic pain, psychological conditions, and individual patient factors, such as BMI and mean age.

Materials and Methods

Ethics Statement

The study was performed following the standards of the Declaration of Helsinki. The study was approved by the Ethics Committee of Massachusetts General Hospital, Boston, Massachusetts (Protocol No. 2019P003169). A waiver of patient consent/authorization was approved by the Ethics Committee for this retrospective study. A waiver of consent/authorization was granted by IRB because of the difficulty in locating individuals who may have moved, the number of subjects and cost and use of limited research resources of locating individuals and sending letters and consent forms and the impact on the scientific validity of the study if only data of individuals from whom we were able to obtain informed consent was used.

The following tasks were undertaken to prevent the rights and welfare of the subjects to be adversely affected by the waiver of consent / authorization:

(1) identifiable data was stored securely with access limited to study staff.
(2) information resulting from this study would not have any important health/medical implications for subjects.

Study Design and Patient Population

This is a retrospective chart review of patients from the SFN registry, which is maintained by the Department of Neurology at Massachusetts General Hospital (MGH), Boston, USA. The registry is comprised of patients who have undergone diagnostic skin biopsy for SFN at MGH. The patients who are suspected of having small fiber neuropathy undergo work-ups with skin biopsy, electromyogram, and/or autonomic function tests and are included in this registry. The methodology of these methods is described by Zirpoli et al.[18]

All patients in this Registry from 2018–2020 present were included. The charts of these patients were retrospectively reviewed for the presence of OFP. The OFP data was evaluated by an OFP specialist (SH). OFP symptoms were divided into two categories: 1. Myofascial facial pain, which includes masticatory myalgias and/or arthralgias of the temporomandibular joint (TMJ)- collectively known as Temporomandibular Joint Disorders (TMDs), 2. Orofacial dysesthesia, which includes neuropathic pain or paresthesia or hypersensitivity in the mouth and/or face.[4]

Other data such as patient demographics-the age at biopsy, gender, patient characteristics- body mass index (BMI), history of chronic pain (neuropathic or nociceptive) in other parts of the body, history of migraines and other headaches, history of psychological conditions, such as anxiety, depression, obsessive compulsive disorder, bipolar disorder etc. were collected. Data on skin biopsy and presence of autonomic symptoms was collected and analyzed as well.

SFN data including skin biopsy and autonomic function testing were collected and analyzed.

Inclusion Criteria

Patients of all gender and ages who have undergone diagnostic skin biopsy for SFN at MGH.

Exclusion Criteria

OFP, where the underlying cause of pain was a known pathology, was not considered as OFP condition for this study.

Primary Outcome

Prevalence of OFP in patients with chronic sensory and autonomic neuropathies.

Secondary Outcome

Correlation between OFP and results of skin biopsy, presence of autonomic dysfunction, headaches, chronic nociceptive and neuropathic pain conditions, psychological conditions, age, and BMI.

Statistical Analysis

Data from the SFN registry and electronic patient records were recorded and de-identified. The results of skin biopsy, presence of autonomic dysfunction, chronic peripheral and other systemic neuropathic and nociceptive symptoms, migraines and other primary headaches, and psychological conditions were analyzed for their statistical correlation with OFP symptoms. Mean, range, frequencies were used for calculating descriptive variables. Statistical comparison was performed using Student's *t*-test for continuous variables and chi-squared test for categorical variables. Statistical significance was set at p value<0.05.

Results

Charts of 450 patients who had undergone diagnostic skin biopsy to establish SFN diagnosis were reviewed. A breakdown of the patient demographics with respect to TMDs and orofacial dysesthesia is shown in Table 1.

Table 1 Prevalence of Orofacial Pain in Patients Who Underwent Skin Biopsy at MGH (Total Patients n=450)

		Myofascial Facial Pain/TMDs#	**Orofacial Dysesthesia**	**Total Patients with Orofacial Symptoms**
N		40	62	102
Gender				
	Female N (%)	32(80.0%)	46 (74.2%)	78(76.5%)
	Male N (%)	8 (20.0%)	16(25.8%)	24(23.5%)
Age at biopsy	Mean (SD*)	45.82(15.92)	47.37 (12.99)	48.36(15.91)
BMI	Mean (SD*)	26.37(5.17)	26.19(6.89)	26.28 (5.27)
Skin Biopsy	N (%)			
	Positive	5(12.5%)	11(17.7%)	16(15.7%)
	Negative	35(87.5%)	51(82.3%)	86(84.3%)

(*Continued*)

Table 1 (Continued).

		Myofascial Facial Pain/TMDs[#]	Orofacial Dysesthesia	Total Patients with Orofacial Symptoms
Autonomic Symptoms	N (%)			
	Positive	26(65%)	25(40.3%)	51(50.0%)
	Negative	14(35%)	37(59.6%)	51(50.0%)
Headaches	N (%)			
	Present	23(57.5%)	30(48.4%)	53(52.0%)
	Absent	17(42.5%)	32(51.6%)	49(48.0%)
Migraines	N (%)			
	Present	18(45.0%)	22(35.5%)	40(39.2%)
	Absent	22(55.0%)	4064.5%)	62(60.8%)
H/O Peripheral Neuropathy	N (%)			
	Present	24(60.0%)	40(64.5%)	64(62.7%)
	Absent	16(40.0%)	22(35.5%)	38(37.3%)
H/O Other Chronic nociceptive pain	N (%)			
	Present	25(62.5%)	44(71.0%)	69(67.6%)
	Absent	15(37.5%)	18(29.0%)	33(32.4%)
Psychological comorbidities (anxiety depression, other mood disorders)	N (%)			
	Present	24(60.0%)	37(59.7%)	61(59.8%)
	Absent	16(40.0%)	25(40.3%)	41(40.2%)

Notes: [#]TMDs: Temporomandibular Disorders, *SD: Standard deviation.

Tables 2–4 show the differences between patients with OFP and without OFP, with TMDs and without TMD and with and without orofacial dysesthesia, respectively.

The mean age (range, SD) of the cohort was 46.77 (18–81, 14.89) years and female: male ratio of the cohort was 2.4:1. 61.33% (n=276) of these patients had peripheral neuropathies, 69.56% (n=313) had nociceptive pain symptoms in other regions of the body, 35.11% (n=158) had migraines and 47.56% (n= 214) had other primary headaches. 24% (n=108) of these patients also had psychological comorbidities to include but not limited to depression, anxiety, panic disorder, attention deficit disorder etc.

22.67% (n=102) patients with sensory and/or autonomic neuropathic symptoms had OFP symptoms– 39.2% (n=40/102) TMDS and 60.8% (n=62/102) orofacial dysesthesia. The mean (range) age at biopsy for all patients with OFP symptoms was 48.36 (20–81) years, female: male ratio 3.25:1, mean (range) BMI 26.28 (18.42–51.57).

There was no significant difference in mean age (p value 0.822) and no gender predilection (p value 0.129) was noted between patients with OFP when compared with the ones without OFP symptoms. Most patients (73.53%) with OFP symptoms were either overweight (BMI 25.0–29.9) or obese (BMI >30) and a significantly higher number of patients with OFP symptoms had a mean BMI >30 (p value 0.025). 51.96% (n=53) patients were overweight; 21.57% (n=22) were obese. Only 26.47% (n=27) were in the normal weight range or underweight (BMI <24.9).

Table 2 Comparison of Patients with OFP Vs No OFP Symptoms

	OFP Symptoms Present (n=102)	OFP Symptoms Absent (n=348)	P value
Gender N (%)	F=78(76.50%) M=24 (23.50%)	F=239 (68.68%) M=109 (31.32%)	0.129
Mean age (SD*)	48.36 (13.71)	46.86 (15.27)	0.822
Age >50	44 (22.79%)	68 (26.45%)	0.374
Mean BMI (SD*)	26.28 (5.93)	26.36 (6.66)	0.138
BMI >30	38 (31.15%)	69 (21.03%)	0.025**
Positive Skin Biopsy n (%)	16 (15.68%)	87 (25.00%)	0.049**
Presence of Autonomic Symptoms n(%)	51(50.00%)	168(48.28%)	0.759
Peripheral neuropathies n(%)	64 (62.74%)	212((60.92%)	0.739
Chronic nociceptive pain n (%)	69 (67.60%)	244(70.11%)	0.634
Migraines n (%)	40 (39.21%)	118 (33.91%)	0.323
Other primary headaches n (%)	53 (51.96%)	161(46.26%)	0.311
Psychological comorbidities (anxiety, depression, other mood disorders)	69(67.60%)	39(11.20%)	0.000**

Notes: *SD: Standard Deviation, **p value <0.05.

Table 3 Comparison of Patients with Myofascial Symptoms/TMDs Vs No Myofascial TMD Symptoms

	TMD# Symptoms Present (n=40)	TMD# Symptoms Absent (n=410)	P value
Gender n (%)	F=32(80.0%) M=8 (20.0%)	F=285 (69.51%) M=125 (30.49%)	0.165
Mean age (SD*)	45.82 (14.97)	47.12 (14.92)	0.818
Mean BMI (SD*)	26.37 (6.24)	26.28 (6.40)	0.372
Positive Skin Biopsy n (%)	5 (12.5%)	98 (23.9%)	0.101
Presence of Autonomic Symptoms n (%)	26(65.0%)	193(47.07%)	0.030**
Peripheral neuropathies n(%)	24 (60.0%)	252((61.46%)	0.856
Chronic nociceptive pain n (%)	25 (62.5%)	288(70.24%)	0.151
Migraines n (%)	18 (45.0%)	140 (34.14%)	0.169
Other primary headaches n (%)	23 (57.5%)	191(46.59%)	0.187
Psychological comorbidities (anxiety, depression, other mood disorders)	25(62.50%)	16(3.90%)	0.000**

Notes: #TMD: Temporomandibular joint disorders. *SD: Standard Deviation. **P value <0.05.

Significant difference was noted in skin biopsy results between patients with and without OFP, with negative skin biopsy more prevalent in patients with OFP (p value=0.049). Dysautonomia symptoms were noted to be higher in patients with TMDs when compared to patients without TMDs (p value 0.030). Also, patients presenting with any type of OFP symptoms- TMDs and/or orofacial dysesthesia had significantly higher psychological comorbidities (p value 0.000). No significant correlation was

Table 4 Comparison of Patients with Orofacial Dysesthesia Vs No Orofacial Dysesthesia Symptoms

	Orofacial Dysesthesia Symptoms Present (n=62)	Orofacial Dysesthesia Symptoms Absent (n=388)	P value
Gender n (%)	F=46(74.2%) M=16 (25.8%)	F=271 (69.85%) M=117 (30.15%)	0.485
Mean age (SD)	47.37(12.94)	46.34 (15.22)	0.854
Mean BMI(SD)	26.19(5.77)	26.36 (6.47)	0.218
Positive Skin Biopsy n (%)	11(17.7%)	92 (23.71%)	0.298
Presence of Autonomic Symptoms n (%)	25(40.3%)	194(50.0%)	0.156
Peripheral neuropathies n(%)	40(64.5%)	236(60.82%)	0.579
Chronic nociceptive pain n (%)	44(71.0%)	294(75.78%)	0.416
Migraines n (%)	22(35.5%)	136 (35.05%)	0.947
Other primary headaches n (%)	30(48.4%)	184(47.42%)	0.887
Psychological comorbidities (anxiety, depression, other mood disorders)	44(71.0%)	23(5.93%)	0.000**

Notes: *SD: Standard Deviation, **P value <0.05.

noted between OFP and presence of other chronic pain conditions, such as, peripheral neuropathies (p value 0.739), nociceptive pain (p value 0.634), migraines (p value 0.323), and other primary headaches (p value 0.311).

When the patients with OFP symptoms were compared to the overall cohort, it was noted that autonomic symptoms were present in 50% (51/102) patients with OFP, which was comparable to the overall cohort 48.7% (219/450). Similarly, peripheral neuropathies were present in 62.7% (64/102) of OFP patients, which was comparable to the cohort 61.3% (276/450), migraines were present in 39.2% (40/102) of OFP patients as compared to 35.1% (158/450), other headaches in 52% (53/102) of OFP patients as compared to 47.5% (214/450) in overall cohort. Chronic nociceptive pain was present in 67.6% (69/102) patients with OFP, like the overall cohort where 69.6% (313/450) patients had chronic nociceptive pain conditions. Skin Biopsy results were positive in 15.7% (16/102) patients with OFP as compared to 22.9% (103/450) in the overall cohort.

Discussion

In this study, we aimed to assess the prevalence of OFP in a large cohort of patients with sensory and/or autonomic neuropathies and found that more than 20% (n=102) of these patients had OFP. We speculate these numbers to be higher because this study has several limitations, which are mentioned below. Also, in this study, patients who had OFP symptoms presented with a high number of other chronic overlapping pain conditions, like migraines, which were present in 39.2% (n=40) patients, and other primary headaches and chronic nociceptive and neuropathic pain, in more than half the patients with OFP. This aligns with the concept of coexisting pain conditions, or chronic overlapping pain conditions (COPCs),[19,20] a concept that has been recognized by the National Institutes of Health and the US Congress as a set of disorders that can occur simultaneously in patients and include, but should not be limited to, temporomandibular disorder (TMD), fibromyalgia (FM), irritable bowel syndrome (IBS), vulvodynia, chronic tension-type headache, migraine headaches to name a few. Collectively, these conditions are increasingly referred to.[19,20] Most of these conditions are defined as idiopathic, 'as not being able to be explained by injury or pathology in the tissues from which the pain originates'.[21]

The clinical presentation of SFN is heterogeneous, with no single clinical pattern fitting all presentations.[7] SFN was thought to be rare, but an epidemiological study in the Netherlands reported an incidence of 12 cases per 100 000 inhabitants per year and a prevalence of 53 cases per 100,000.[22] In the past few decades, an increasing number of studies widened the spectrum of diseases associated with small nerve fiber degeneration,[23] such as fibromyalgia,[24] chronic regional pain syndrome,[25] painful erythromelalgia,[26] burning mouth syndrome,[12] etc.—conditions that are increasingly

recognized to fall under COPC spectrum. A recent systematic review and meta-analysis showed fibromyalgia to be complicated by SFN in 49% of cases.[24] Is it possible that the other conditions that overlap with fibromyalgia but are idiopathic, for example, TMDs and BMS, are also complicated by SFN?

Skin biopsy, which allows reliable quantification of intraepidermal nerve fiber density, has been a milestone for the diagnosis of SFN[27] and is widely acknowledged as confirmatory diagnostic test with high diagnostic accuracy (sensitivity 94.35, specificity 91.9%)[27] when combined with clinical symptoms. In this study, abnormal skin biopsy was noted in more than 1/5th of the total patients (22.9%, n=103) and in about 1/6th of the patients with OFP −15.7% (n=16) - signifying the presence of underlying SFN in this group of patients. SFN has been noted as an underlying cause in idiopathic BMS,[12] where biopsy specimens were taken from the region of pain, that is, the tongue, to assess for the damage of peripheral nerve fibers. It is possible that a more localized biopsy specimen will be more specific and diagnostic when assessing SFN as the underlying cause of idiopathic OFP, especially when other peripheral symptoms are absent. Therefore, in our opinion, the statistical analysis showing a lower prevalence of OFP in abnormal skin biopsy patients is not meaningful. More biopsy techniques and local sites such as oral mucosa should be explored to assess for intraepidermal nerve fiber density in non-length dependent or focal SFN cases.

It is worth noting that half the patients in this study with OFP had dysautonomia, with significantly higher number of these patients being the ones with TMDs. It is possible that this could be due to a more centralized pain phenomenon in these patients rather than just a peripheral insult. In a study done by Durham et al, a high prevalence of painful temporomandibular joint disorders was noted in patients with autonomic dysfunction and Postural Orthostatic Hypotension.[25,28] It is important to note that the correlation between OFP and autonomic dysfunction has not been studied widely. Very few studies exist that correlate facial pain with autonomic dysfunction. In another case-control study conducted by Leonard et al in patients with trigeminal neuralgia (TN), it was noted that patients with TN had autonomic nervous system dysfunction (tested with cardiac reactivity to cold pressor test) when compared to healthy controls.[29] Systematic studies to further evaluate the existence of autonomic symptoms in patients with OFP are needed. Functional MRI studies can help us understand these central pain conditions.

OFP and TMDs have been associated with psychological comorbidities in many studies. In a large prospective case-control study, Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), psychological comorbidities were found to be causal determinants of TMD pain.[30] Psychological comorbidities were noted to be significantly higher in patients with OFP symptoms in this cohort across all OFP diagnoses—TMD and/or orofacial dysesthesia.

Obesity and chronic pain have been associated, but the correlation is understudied and remains largely unknown.[31] How obesity affects the trigeminal nociceptive system in humans, which is central to OFP conditions, remains unknown. Animal studies have shown that the trigeminal nociceptive processing, is abnormal in mice with obesity.[32,33] Our study shows a significant correlation between chronic OFP and obesity. Considering a high burden of these conditions on both individuals and society, this correlation needs further investigations.

Limitations

This is a retrospective study, and some data could not be interpreted. The cohort was not specifically focused on studying the OFP conditions. Therefore, there is a possibility that this study underestimates the prevalence of OFP in this cohort who underwent a work-up for SFN due to the following reasons—most SFN questionnaires, like the Small Fiber Neuropathy and Symptoms Inventory Questionnaire (SFN SIQ) that was used in this cohort, are designed to assess distal neuropathies and autonomic symptoms, hence patients do not tend to mention facial pain unless prompted or specifically questioned by their provider. The biopsy specimens were not taken from the region of orofacial pain. It is possible that a more localized biopsy specimen will be more specific for clarifying the condition of SFN. Patients with jaw pain and OFP consult their dentists for these symptoms and do not necessarily discuss them with their neurologists or primary care physicians unless specifically asked. Similarly, due to a lack of data on the characterization of this patient group, many patients with OFP do not undergo work-up for SFN and hence the data can be skewed due to more patients with typical length-dependent neuropathic symptoms in this cohort.

Conclusions

OFP and sensory and autonomic neuropathies can be overlapping conditions. The study shows a significant correlation between TMD and dysautonomia, which has not been studied before. Hence, patients presenting with concomitant TMD and dysautonomia can be further tested for SFN. This can further help us understand a correlation, if any, between idiopathic TMD/OFP conditions and SFN and further our understanding of the pathophysiology of these conditions. To further our understanding of the correlation between OFP/TMD conditions and SFN, more structured studies focusing on OFP, neuropathies, and dysautonomia will be needed. Presence of psychological comorbidities in these patients warrants a multidisciplinary team, to include neurologist, OFP specialist, and psychologist/psychiatrist in appropriate management of these patients. One cannot ignore the correlation between obesity and presence of OFP in this cohort. Well-designed studies to understand the relation between these two chronic conditions, obesity, and OFP, are needed.

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Disclosure

The authors report no conflicts of interest in this work.

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