Chronic rhinitis and stress: the possible culprits of midfacial segment pain*

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Abstract

Background: Bilateral symmetrical pain in the midfacial region without evidence of sinonasal disease is termed midfacial segment pain (MSP), about which little is known. The present study explored the prevalence of facial pain and the risk factors for MSP.

Methods: We analysed cross-sectional data from the Korea National Health and Nutrition Examination Survey (KNHANES). Those who reported facial pain or pressure lasting at least three months with no evidence of a sinonasal disease on nasal endoscopy were considered to have MSP. The participants were categorised according to the presence of facial pain and chronic rhinosinusitis. Basic demographic data and medical conditions, including hypertension, diabetes mellitus, and dyslipidemia, were compared between subject groups. We also evaluated psychological stress, depressive episodes, and suicidal thoughts, as well as physician-diagnosed nasal diseases, including chronic rhinitis and symptomatic nasal septal deviation. Univariate and multivariate logistic regression analyses were performed to determine risk factors for MSP.

Results: Of 31,999 participants, the prevalence of facial pain was 0.59%. A total of 58 (0.18%) respondents had MSP, of whom 40 (73.5%) were female. On univariate analysis, female sex, chronic rhinitis, and psychological stress were more prevalent in the subjects with MSP than the control subjects. However, in the multivariate analysis, only chronic rhinitis and psychological stress remained significant, while the female sex exhibited only marginal significance.

Conclusion: Chronic rhinitis and psychological stress may be significant risk factors for MSP.

Key words: facial pain, midface, rhinitis, risk factors, stress

Introduction

Facial pain is rare, affecting approximately 4 out of 10,000 persons in the general population. However, such pain is associated with significant morbidity and negatively affects quality of life ⁽¹⁾. When pain affects the midface, patients are often misdiagnosed with sinus disease. Patients with rhinosinusitis may indeed experience facial pain. However, more than 80% of patients evidencing purulent discharge on nasal endoscopic examinations lack facial pain ⁽²⁾.

When patients with facial pain lack evidence of sinus disease, neurological causes should be considered. If the pain is bilateral, symmetrical, and localised to the midfacial region without significant nasal symptoms or signs (as revealed by normal nasal endoscopic or computed tomography [CT] findings), the pain is termed midfacial segment pain (MSP) defined as midfacial neuralgia involving the nasion, periorbital regions, or cheeks ⁽³⁾. Only the second division of the trigeminal nerve is affected, characterised by a symmetric sensation of tightness or pressure. Some patients may report nasal blockage, although the nasal airway is patent. The pain characteristics of MSP are similar to those of tension-type headache (TTH), except that the former affects the midface. TTH is often described as a sensation of a tight band around the head, while MSP is described as a similar feeling of tightness in the midface. Therefore, their underlying etiologies are assumed to be similar ⁽⁴⁾. As many otorhinolaryngologists are unfamiliar with MSP, painkillers are frequently prescribed but are not effective. The causes of TTH are not clearly understood, but psychological stress is widely accepted to be a contributory factor ⁽⁵⁾. Likewise, it could be presumed that psychological stress may also play a role in the occurrence of MSP. Over the last 2 years of the coronavirus disease 2019 (COVID-19) pandemic, the number of patients with possible MSP visiting our rhinology clinic seems to have increased. We thus hypothesised that elevated psychological stress might contribute to MSP development. To test this, we analysed the objective data (including nasal endoscopic findings) of a large, nationwide population-based study.

Materials and methods

Study population and data collection

We analysed the data of the Korea National Health and Nutrition Examination Survey (KNHANES) conducted from 2008 to 2012. The KNHANES is a nationwide, population-based cross-sectional study that has been conducted periodically since 1998 by the Korea Centres for Disease Control and Prevention (KCDC) to assess the health and nutritional status of the civilian, non-institutionalised Korean population ⁽⁶⁾. It is conducted annually with approximately 10,000 participants selected using multistage, clustered, stratified, and random sampling based on their age, region, and sex. The primary sample units consist of 20 households per district, and all family members over one year of age are selected to participate. The subjects are notified that they were randomly selected and asked to participate voluntarily in the survey. Upon acceptance, the participants move to specially designed and equipped mobile centres which travel to locations throughout the country, where the staffs help them fulfil health-related questionnaires and undergo tests such as body measures, blood pressure measurement, and blood tests. All the participants registered from 2008 through 2012 underwent nasal endoscopy on the same day the survey was conducted. It was performed by trained residents from the department of otorhinolaryngology. Since the presence of sinonasal diseases needed to be confirmed using the objective tests, such as nasal endoscopy or CT, we chose data from this period to test our hypothesis. The KCDC obtained written informed consent from all participants. All study protocols were approved by the KCDC Institutional Review Board. Of the 45,811 participants, 7,015 under 12 years of age and 649 for whom nasal endoscopic data were lacking were excluded. Next, 6,148 were excluded because they did not answer the questions of interest. Finally, 31,999 were included in the analysis (Figure 1).

Definitions of midfacial segment pain and sinonasal

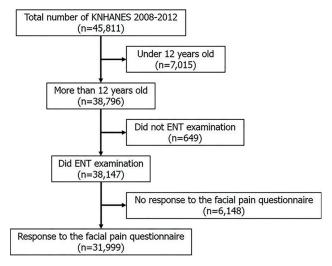


Figure 1. Study participants enrolled from the Korean National Health and Nutrition Examination Survey (KNHANES) 2008–2012.

diseases

Participants were considered to have chronic facial pain if they reported facial pain or pressure over 3 months in duration. Based on the symptoms confirmed by the participants through the questionnaire and the endoscopic findings on the same day, chronic rhinosinusitis (CRS) was diagnosed according to the European position paper on rhinosinusitis and nasal polyps (the 2020 guidelines). These require at least two of the following: anterior or posterior nasal discharge, nasal obstruction, facial pain or pressure, and olfactory dysfunction at least 3 months in duration plus purulence, nasal polyps, or mucosal oedema within the middle meatus confirmed via nasal endoscopy after nasal decongestion ⁽⁷⁾. Participants with chronic facial pain but no evidence of CRS were considered to have MSP. According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines published in 2008, chronic rhinitis (CR) was confirmed when any of four nasal symptoms, including anterior or posterior rhinorrhea, sneezing, nasal blockage, and itching of the nose, had persisted for over one month. Nasal endoscopic findings were also recorded, including a pale mucosa, mucosal swelling, and a watery or mucoid discharge. Symptomatic nasal septal deviation (NSD) was confirmed when nasal obstruction lasting more than 3 months was reported, and nasal endoscopy identified NSD after nasal decongestion.

Demographic information, basic medical conditions, and psychiatric factors

We recorded age, sex, educational level, family income, body mass index (BMI), smoking status (non-smoker, ex-smoker, or current smoker), and alcohol consumption (non-drinker, social drinker, or high-risk drinker). High-risk drinking was defined as consumption of at least seven drinks per occasion for men and at least five for women at least twice within the past 7 days. Age was classified as 12-19, 20-29, 30-39, 40-49, 50-59, 60–69, 70–79, and \geq 80 years. The educational levels comprised elementary school or below, middle school, high school, and college or higher. Family income was divided into quartiles (low, lower-middle, upper-middle, and high). BMI was calculated from height and weight and classified as < 18.5, 18.5–24.9, 25.0–29.9, and \geq 30.0 kg/m². Blood pressure (BP), blood glucose levels, and blood cholesterol levels were measured. BP was divided into normal (systolic BP < 120 mmHg, diastolic BP < 80, and the absence of diagnosed hypertension on the questionnaire), prehypertension (systolic BP of 120-139 mmHg or diastolic BP of 80–89 mmHg), and hypertension (systolic BP \geq 140 mmHg or diastolic BP \ge 90 mmHg). The blood glucose level was classified as normal (fasting blood glucose level < 100 mg/dL and the absence of diagnosed diabetes mellitus on the questionnaire), prediabetes (fasting blood glucose level of 100-125 mg/dL), or diabetes (fasting blood glucose level ≥ 126 mg/dL). The blood cholesterol level was classified as normal (< 200 mg/dL and the absence of dyslipidemia on the questionnaire), borderline (200–239 mg/dL), and high (≥ 240 mg/dL). Psychological stress, depression episodes, and suicidal thinking were all explored using a questionnaire. Psychological stress was asked, "How much stress do you usually feel in your daily life?". Answers were classified according to the degree of stress as follows: rare ("hardly any"), mild ("a little bit"), moderate ("quite"), and severe ("extremely"). Finally, it was classified into low (rare and mild) and high (moderate and severe). For evaluating depression episodes and suicidal thinking, participants were asked, "During the past 12 months, have you ever experienced a continuous feeling of sadness or despair for over two weeks that interfered with your daily activities?" and "During the past 12 months, have you ever considered committing suicide?". The following responses to the questions were used directly: "yes" or "no".

Statistical analysis

The KNHANES data were subjected to two-stage, stratified cluster sampling to improve accuracy and representativeness. We calculated the pooled weights of the data for each of the 5 years (2008, 2009, 2010, 2011, and 2012) and then merged them using the appropriate guideline ⁽⁸⁾. We applied the pooled weights in all analyses with the exception of the number of participants. Categorical variables are presented as numbers with weighted proportions and continuous variables as means with standard errors. All subjects were categorised into three groups according to their CRS and chronic facial pain status: controls (those having neither CRS nor facial pain), CRS patients with facial pain (CRSFP), and MSP patients. CRS patients lacking facial pain (n = 1,051) were not included in the final analysis. The differences between the MSP and non-MSP subjects in terms of demographic data, sinonasal diseases, and psychiatric factors were explored using the chi-squared test and regression analysis (for

categorical and continuous variables, respectively). The Benjamini–Hochberg method was used to control the family-wise error rate during multiple comparisons. We performed univariate logistic regression analysis to evaluate the associations between MSP and all factors. Next, we adjusted the MSP covariates via multivariate logistic regression. We selected covariates with p-values < 0.05 on univariate analysis (Model 1) and additionally all psychological factors (Model 2). All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA), and a two-tailed p-value < 0.05 was considered significant.

Results

Of the 31,999 participants, there were 30,809 (96.3%), 132 (0.41%), and 58 (0.18%) in the control, CRSFP, and MSP groups, respectively (Table 1). In the global group comparison, the mean age did not differ among the groups, but the gender distribution appeared different with marginal significance (p = 0.054) among the groups. In addition, there were significant differences in the prevalence of prediabetes or diabetes, CR, and symptomatic NSD among the groups. When it comes to the psychological factors, psychological stress was significantly different among the groups, while depression episodes or suicidal thinking did not. However, BMI, education level, income level, smoking status, alcohol consumption, blood pressure, and blood cholesterol level did not differ among the groups (Table 1). Then, the risk factors for MSP were explored by comparing the covariates between the MSP and the control groups. In the univariate logistic regression analysis, female sex, CR, and psychological stress were more prevalent in the MSP group. However, the prevalence of prediabetes and diabetes, one of the factors showing significant difference in the global group comparison, did not differ between the two groups. Moreover, there was no case of symptomatic NSD in the MSP group (Table 2). Next, the multivariate analysis was performed to confirm the risk factors for MSP. Among the covariates having statistical significance in the univariate analysis, only CR and psychological stress remained significant on multivariate analysis while female sex exhibited only marginal significance (Model 1; Table 3). Likewise, when depression episodes and suicidal thinking were added as covariates in the analysis, only CR and psychological stress showed significant difference between the two groups (Model 2; Table 3).

Discussion

Facial pain can be caused by numerous conditions: temporomandibular joint disease, sinonasal diseases, primary headache syndromes, primary headache syndromes, trigeminal neuralgia, or infected diseases. As the cause may not be simple, diagnosis and management can be challenging ⁽⁹⁾. In particular, distinguishing sinogenic and non-sinogenic causes of midfacial pain is difficult. Sinogenic pain is often unilateral and accompanied

Table 1. Participant characteristics.

Characteristics	Control (n = 31,809)	CRSFP (n = 132)	MSP (n = 58)	P-value
Age (mean, SE)	42 (0.2)	40.6 (1.9)	44.3 (2.3)	0.45
Gender, n (%)				
Male	13957 (43.9)	54 (40.9)	18 (31)	0.054
Female	17852 (56.1)	78 (59.1)	40 (69)	
3MI (kg/m2), n (%)				
Underweight (<18.5)	2252 (7.1)	9 (6.8)	4 (6.9)	0.87
Normal (18.5≤, <25)	20046 (63.3)	77 (58.3)	34 (58.6)	
Overweight (25≤, <30)	8227 (26)	35 (26.5)	17 (29.3)	
Obesity (\geq 30)	1121 (3.5)	11 (8.3)	3 (5.2)	
Education level, n (%)				
≤ Primary school	9443 (30.2)	36 (27.7)	20 (35.7)	0.78
Middle school	4339 (13.9)	14 (10.7)	7 (12.5)	
High school	9622 (30.8)	47 (36.2)	18 (32.1)	
≥ College	7838 (25.1)	33 (25.4)	11 (19.6)	
income level, n (%)				
Low	7700 (24.5)	37 (28.7)	21 (37.5)	0.62
Lower-middle	7891 (25.2)	26 (20.2)	10 (17.9)	
Upper-middle	7879 (25.1)	34 (26.4)	14 (25)	
High	7903 (25.2)	32 (24.8)	11 (19.6)	
Smoking status, n (%)				
Non-smoker	20146 (63.7)	88 (67.2)	36 (62.1)	0.072
Ex-smoker	3523 (11.1)	9 (6.9)	9 (15.5)	
Current smoker	7969 (25.2)	34 (26)	13 (22.4)	
Alcohol consumption, n (%)				
Non-drinker	15781 (51.4)	71 (55.5)	26 (47.3)	0.39
Social drinker	11890 (38.7)	40 (31.3)	24 (43.6)	
High-risk drinker	3024 (9.9)	17 (13.3)	5 (9.1)	
Blood pressure, n (%)				
Normal	14438 (46.9)	66 (51.6)	23 (41.8)	0.83
Prehypertension	7293 (23.7)	26 (20.3)	12 (21.8)	
Hypertension	9061 (29.4)	36 (28.1)	20 (36.4)	
Blood glucose, n (%)				
Normal	20934 (73.1)	91 (73.4)	40 (78.4)	0.0005*
Prediabetes	4869 (17)	24 (19.4)	3 (5.9)	
Diabetes	2853 (10)	9 (7.3)	8 (15.7)	
Blood cholesterol (mg/dL), n (%)				
< 200	18181 (63.4)	85 (68.5)	28 (53.8)	0.59
200≤, <240	7006 (24.4)	23 (18.5)	13 (25)	
≥ 240	3508 (12.2)	16 (12.9)	11 (21.2)	
Chronic rhinitis, n (%)	2145 (7.3)	71 (53.8)	8 (13.8)	<.0001*
Symptomatic NSD, n (%)	943 (3.6)	52 (39.4)	0 (0.0)	<.0001*
Psychological stress, n (%)	7810 (28.3)	49 (37.1)	22 (37.9)	0.025*
Depression episodes, n (%)	4041 (13.4)	26 (19.7)	13 (22.4)	0.19
Suicidal thinking, n (%)	4586 (14.8)	38 (28.8)	11 (19)	0.11

* A chi-square test and regression analysis were used to analyze the categorical and continuous variables, respectively, with significance set at P < 0.05. CRSFP, chronic rhinosinusitis with facial pain; MSP, midfacial segment pain; SE, standard error; BMI, body mass index; NSD, nasal septal deviation.

Factors	Crude OR [95% CI]	P- value
Age	1.01 [0.99 - 1.03]	0.33
Female sex	2.44 [1.07 - 5.56]	0.035*
BMI (kg/m²)		
Underweight (<18.5)	0.4 [0.05 - 3.06]	0.38
Overweight (25≤, <30)	1.35 [0.61 - 3.02]	0.46
Obesity (30≤)	0.7 [0.14 - 3.54]	0.67
Education level		
Middle school	0.77 [0.29 - 2.04]	0.60
High school	0.75 [0.31 - 1.82]	0.52
≥ College	0.76 [0.28 - 2.11]	0.60
Income level		
Lower-middle	0.61 [0.25 - 1.51]	0.28
Upper-middle	0.52 [0.18 - 1.52]	0.23
High	0.52 [0.2 - 1.3]	0.16
Smoking status		
Ex-smoker	1.18 [0.45 - 3.13]	0.74
Current smoker	1.03 [0.43 - 2.47]	0.96
Alcohol consumption		
Social drinker	1.58 [0.8 - 3.12]	0.19
High-risk drinker	1.43 [0.45 - 4.57]	0.54
Blood pressure		
Prehypertension & hypertension	1.09 [0.52 - 2.26]	0.83
Blood glucose		
Prediabetes & diabetes	0.55 [0.26 - 1.19]	0.13
Blood cholesterol		
Above normal (≥200 mg/dL)	1.57 [0.75 - 3.29]	0.23
Chronic rhinitis	3.61 [1.37 - 9.56]	0.010*
Symptomatic NSD	NA	NA
Psychological stress	2.31 [1.14 - 4.7]	0.021*
Depression episodes, n (%)	2.16 [0.92 - 5.07]	0.077
Suicidal thinking, n (%)	1.24 [0.52 - 2.95]	0.62

Table 2. Univariate analysis of risk factors of midfacial segment pain compared with the control subjects.

*Significance was set at P < 0.05. Reference for the education and income levels are primary school and low income, respectively. OR, odds ratio; BMI, body mass index; NSD, nasal septal deviation.

by nasal symptoms such as obstruction and mucopurulent rhinorrhea and a sensation of pressure or congestion. Non-sinogenic pain can be bilateral and is often pulsatile or "tight" ⁽¹⁰⁾. MSP characteristically involves the bilateral midface in a symmetrical manner. If a patient presents with bilateral midfacial pain lasting more than 3 months in duration without evidence of sinonasal disease, MSP should be considered.

A few hypotheses have been advanced to explain the mechanism of non-sinogenic pain, but the mechanism remains elusive. For example, the vacuum theory suggests that negative pressure induced within a blocked sinus causes pain. However, as many patients with diffuse nasal polyposis lack facial pain, convincing evidence is needed ⁽¹¹⁾. The contact point theory suggests that contact among sinonasal structures might induce pain. However, the contact points did not differ between asymptomatic and symptomatic populations. Moreover, contacts were found on the contralateral side in half of all symptomatic patients with unilateral facial pain ⁽¹²⁾. Anatomical variations such as NSD, septal spurs, conchae bullosa, infraorbital cells, a lateralized uncinate process, and a paradoxical middle turbinate were previously suggested to cause MSP, but no associations were found ⁽¹³⁾. Our results are similar; no MSP patient had symptomatic NSD. It is widely accepted that chronic facial pain is associated with stress ⁽¹⁴⁾. Stress and pain share neural and endocrine pathways. Noxious signals, such as stress, not only enhance the sensitivity of the peripheral myofascial receptors but also downregulate the central inhibition of supraspinal impulses ⁽¹⁵⁾. Tension-type facial pain, such as MSP, is thought to be caused by central sensitisation of the second-order neurons of the trigeminal caudal nucleus (the principal relay nucleus for facial pain) caused by prolonged nociceptive input from peripheral injuries including psychological stress or emotional disturbance. Thus, MSP is believed to reflect trigeminal neuronal hypersensitivity ⁽³⁾. The word "tension" was not used when the term MSP was coined, to avoid lengthy and unproductive conversations with patients about the role played by stress ⁽³⁾. However, we found that psychological stress was clearly associated with MSP after adjusting for other risk factors. Psychological stress needs to be considered when treating such patients. In addition, a previous study found that 30%–60% of patients with chronic facial pain were depressed ⁽¹⁴⁾. In the present study, both depression episodes and suicidal thinking were included as covariates in the multivariate analysis (Model 2, Table 3). However, neither depression episodes nor suicidal thinking was significantly associated with MSP. Regarding sex, prior studies reported a female preponderance in MSP ^(13,16-18). In our study, 73.5% of MSP subjects were female, thus a significantly larger proportion than that in the control or CRSFP group on univariate analysis. The difference was only marginally significant on multivariate analysis, presumably because of the small number of MSP subjects. Notably, we found that CR was significantly associated with MSP. Stress is a well-known risk factor for allergic rhinitis and is associated with a decreased quality of life ^(19,20). However, to the best of our knowledge, we are the first to show that CR is an independent risk factor for MSP (after adjusting for psychological stress). All sinonasal diseases were confirmed by nasal endoscopy, with high diagnostic accuracy. Most epidemiologic repositories lack nasal endoscopic data and CT images; our study was uniquely positioned to yield firm evidence on the association between sinonasal diseases and MSP. In terms of the mechanism by which CR elicits or aggravates

Table 3. Risk factors for midfacial segment pain.

	Multivariate analysis (Model 1)		Multivariate analysis (Model 2)	
	Adjusted OR [95% CI]	P-value	Adjusted OR [95% CI]	P-value
Female sex	2.13 [0.92 - 4.94]	0.079	2.11 [0.91 - 4.86]	0.080
Chronic rhinitis	3.47 [1.3 - 9.28]	0.013*	3.46 [1.3 - 9.2]	0.013*
Psychological stress	2.2 [1.07 - 4.53]	0.033*	2.12 [1.02 - 4.41]	0.046*
Depression episodes			1.71 [0.72 - 4.05]	0.23
Suicidal thinking			0.65 [0.26 - 1.59]	0.34

* A logistic regression model was used to analyze risk factors. Control group values were used as a reference. The association between each risk factor and midfacial segment pain was analysed using an adjusted logistic regression model. Significance was set at P < 0.05. OR, odds ratio; CI, confidence interval.

MSP, inflammation-induced hypersensitisation of the peripheral sensory receptors might play a role, although further studies are required.

MSP management remains challenging for patients and clinicians. Amitriptyline (a tricyclic antidepressant that effectively treats TTH) is also effective in patients with MSP ^(3,16). MSP patients frequently respond to low-dose amitriptyline (10 mg daily). If amitriptyline is not effective, neurontin, propranolol, or carbamazepine can be prescribed; the combination of amitriptyline and pindolol may be better than amitriptyline alone ⁽¹⁶⁾. Medications prescribed to treat neuropathy (pregabalin, gabapentin, and carbamazepine) can also be used. Long-term therapy (1-2 years) may be required, depending on the response. The success rate during long-term follow-up was as high as 70% (18). Our work had several limitations. First, participants did not undergo CT, and therefore hidden pathologies cannot be excluded. However, as common sinonasal diseases (CRS, NSD, and CR) were confirmed by nasal endoscopy, it is unlikely that the midfacial pain was caused by hidden (rare) sinonasal pathologies. Second, the prevalence of MSP might have been underestimated since the information on facial pain was collected using questionnaires with no detailed interview of the participants by the researchers. In prior studies, the prevalence of facial pain was reported as 1.87% - 25.79% of the general population, whereas it was 0.59% (190 out of 31,999) in the present study (21, ²²⁾. In addition, because the detailed history of the pain characteristics and locations was lacking, some patients considered to have MSP might have had other causes of facial pain. Third, since the number of the MSP group was small, overfitting of the data and subsequently reduced generalisability can be caused, particularly in the multivariate analysis. However, it is less likely that the overfitting issue exists in the present study because the number of selected covariates was also small (e.g. three

in Model 2). Fourth, the data on psychological stress, depression episodes, and suicidal thinking was obtained by a simple questionnaire, not a structured and validated one. They are currently collected using a validated questionnaire. However, the KNHANES data from 2008 through 2012 were chosen for the present study because they contained nasal endoscopy data. Finally, data were not collected during the COVID-19 pandemic. Thus, our hypothesis cannot be proven directly. Nevertheless, given that psychological stress is the key factor of interest, not the pandemic per se, this does not compromise our finding. A strength of our study is that we evaluated nasal status objectively.

Conclusion

MSP appears to exhibit a female preponderance. CR and psychological stress seem to be the major risk factors for MSP.

Authorship contribution

Each of the authors contributed to, read, and approved this manuscript. SWK and YHJ designed the study and wrote and revised the manuscript. HJC and RBK contributed to data collection and provided statistical expertise. HJC and YJJ contributed to data interpretation and participated in critical revision of the manuscript.

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Conflict of interest

No conflict of interest.

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