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Protocol of a cross-sectional, multicentre and multidisciplinary study describing phenotype and burden of a midfacial segment pain

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Abstract

Background: Midfacial segment pain is a term used in the past in the diagnosis of patients mainly from ear, nose and throat clinics. This type of pain cannot be attributed to other primary or secondary facial pain, but is to a large extent similar to tension-type headache with midfacial location. The purpose of this study is to describe midfacial segment pain phenotype, burden and comorbidities in a multicentre and multidisciplinary setting. The ultimate goal is a comprehensive description of this type of pain allowing for its implementation in future classifications.

Methods: This cross-sectional study is designed to describe midfacial segment pain in a clinical setting. Patients from rhinologic, headache and facial pain or oral medicine/dentistry secondary care centres will be recruited during a 1 year period. Individuals with other facial pain according to current classification such as sinonasal disorders, neoplasms, local infections, history of significant trauma associated with pain onset will be excluded. Data will be collected through a structured questionnaire covering pain characteristics, coexisting diagnoses, pain-related burden and consequences, physical examination and paranasal sinuses imaging.

Keywords

face, headache, ICOP, rhinosinusitis, tension-type headache, trigeminal nerve

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Introduction

So far, pain perceived in the middle face segment has been mentioned by few case series from mostly ENT clinics. These descriptions introduced a diagnosis of midfacial segment pain (MFSP)[1] and showed a high prevalence of this disorder in patients with suspected rhinogenic complaints.[2] MFSP was defined as symmetrical facial pain or pressure with normal sinus computed tomography and nasal endoscopic examination, and without accompanying nasal symptoms. It should be virtually identical to tension-type headache (TTH), but localised in the face. Therefore, according to the recently published classification it could be coded as tension-type orofacial pain[3] (TTOFP), except for the fact that anatomically it is not orofacial, but midfacial (i.e. located in the middle segment of the face). For the purpose of this article it can be assumed then that MFSP is probably a synonym of TTOFP. However, the authors have decided to maintain this terminology to build a continuity between historic nomenclature with scientific description (MFSP) and the disorder from ICOP-1, unconfirmed yet by studies (TTOFP).

MFSP/TTOFP by definition is a featureless pain, i.e. without accompanying autonomic or auric symptoms. It is bilateral, dull or pressing, mild or moderate and without exacerbation by physical activity.[4] These features help to differentiate it from facial migraine, in which pain is preceded by aura or accompanied by nausea/vomiting or photophonophobia. Moreover, in migraine pain is usually unilateral, pulsating, moderate or severe and aggravated by physical activity. It should be mentioned that pain in migraine may by strictly facial.[5] However, studies describing strictly facial TTH could not be identified during work on this publication. It should be also noted that MFSP featureless phenotype may be similar to persistent idiopathic facial pain. However, the latter occurs daily for over 3 months, while the former should have similar to TTH paroxysmal and non-daily nature.

There are some similarities between TTH, myofascial orofacial pain and MFSP. For example, MFSP patients may describe facial hypersensitivity to touch which could be the equivalent of myofascial tenderness. MFSP was analysed by a study from a specialised ENT clinic in Malta including 240 patients with chronic facial pain.[6] This study also described the co-existence of MFSP and facial migraine in some individuals. Another study showed that MFSP patients have more psychologic and less rhinologic burden compared to people with chronic rhinosinusitis (CRS).[7] Some case series indicate that medications effective in primary headaches and myofascial orofacial pain prevention can be also beneficial in MFSP. In one of those trials MFSP subjects received amitriptyline 10 mg (or carbamazepine in refractory cases).[6] In this case series with 3 year follow-up 46% patients had total pain remission and a further 37% at least partial pain remission, with significant reoccurrence of pain after prophylaxis withdrawal. Another study retrospectively analysed the treatment of 20 MFSP subjects.[8] Patients received amitriptyline 10–75 mg, pregabalin 150–600 mg or gabapentin 100–600 mg as a first line medication, switching between those drugs in case of treatment failure. As a third line option, authors used duloxetine 60–120 mg, carbamazepine, tramadol, buprenorphine or combinations of these drugs. Significant improvement was observed in 45% of patients at 12 months and 80% at 36 months. A combination of amitriptyline and pregabalin appeared most effective. However, RCT trials using placebo are still warranted.

In general terms, the definition and classification of trigeminal pain syndromes follows the distribution of the three branches of the trigeminal nerve: pain of the ophthalmic nerve is treated by ophthalmologists in the case of eye-pain, and neurologists in the case of headaches. Pain of the mandibular and maxillary nerve are treated by ENT specialists in case of nasal symptoms, or oral medicine specialists/dentists in case of orofacial symptoms. There is notable overlap of idiopathic pain syndromes in the face, and such a black-and-white anatomical attribution is certainly oversimplistic.[9] Headaches are classified by ICHD-3[4] and orofacial pain by ICOP.[3] Both approach overlapping syndromes similarly, i.e. are compatible in cases where more than one medical speciality is involved (e.g. trigeminal neuralgia). However, ENT, pain and headache specialists treat many patients with idiopathic facial pain syndromes which are not rhinogenic, although they may show a significant overlap with syndromes already classified in ICHD-3 and ICOP. It is also possible that some may well be specific to ENT and overlooked so far by the above named classification systems. What is needed is a better description of these ENT-specific syndromes called midfacial segment pain with the aim to describe it for the purposes of clinical application, education and research, with the ultimate goal to integrate MFSP in ICHD-3 and ICOP. The purpose of the current study is to provide a comprehensive description of MFSP. We hypothesise that:

1. A group of patients with midfacial pain that cannot be attributed to other ICOP or ICHD-3 diagnoses will be evaluated in participating centres. The data obtained should also allow to indicate how often rhinologists, headache and facial pain specialists and oral medicine specialists/dentists in secondary care consult these patients.
2. Common pain features can be identified among MFSP subjects (i.e. pain location, intensity, quality, frequency and accompanying symptoms). This hypothesis assumes that MFSP will have a phenotype that is similar to TTH, but located mostly within the second division of the trigeminal nerve. This data should allow to propose diagnostic criteria for MFSP that can be implemented into ICOP and ICHD.
3. MFSP associated burden and comorbidities can be described on the basis of obtained responses.

Methods

Recruitment

Patients will be recruited from clinical settings in:

- rhinologic clinics,
- headache and/or facial pain clinics,
- oral medicine/dentistry clinics.

Retrospective analysis of patients' charts, followed by contacting eligible subjects and prospective filling out of the questionnaire will be accepted.

The study is time limited to 12 months in each participating centre and aims at a minimum number of 200 cases (i.e. on average 20 cases from each participating centre). However, smaller numbers can be accepted if the disorder proves to have low prevalence in participating centres during 1 year of study duration, especially that both our experience and recent insurance registry data[10] suggest that MFSP might be a rare disorder.

Inclusion criteria

The study will include patients consulting rhinologic, oral medicine/dentistry, headache or pain specialists because of facial pain with the following features:

- located at least partially within an area innervated by the second or third division of the trigeminal nerve (both bilateral and unilateral),
- duration of attacks of >5 minutes and <1 month,
- attacks recur for >1 month,
- at least one pain-free day per month (this pain-free day must be unrelated to the use of abortive or prophylactic treatment modalities).

Exclusion criteria

a. Facial pain can be attributed to other ICOP-1 diagnosis, apart from tension-type orofacial pain. This means that investigators should exclude especially:
   - facial migraine by ensuring that facial pain is not accompanied by either migraine aura AND/OR nausea/vomiting AND/OR photo- and phonophobia,
   - persistent idiopathic facial pain by ensuring that the patient experienced a pain-free day or days in the last month (this day or days must be unrelated to use of abortive or prophylactic treatment modalities),
   - stomatognathic disorders incl. myofascial orofacial pain (Chapter 1–3 of ICOP-1) by ensuring that pain is neither related to jaw motion, function or parafunction nor that signs of temporomandibular disorders are present on physical examination.

b. Facial pain with clear rhinogenic cause, such as acute and chronic rhinosinusitis fulfilling both clinical and endoscopic/imaging diagnostic criteria according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020).
c. Facial pain that can be attributed to neoplasms.
d. Facial pain that can be attributed to local infection including post-herpetic neuralgia.
e. History of significant trauma associated with pain onset (pain developed within 7 days from trauma).

Patients who additionally and independently suffer from primary headaches whose midfacial pain cannot be explained as orofacial headaches are explicitly not excluded. In other words, patients with migraine are not excluded, as long as their facial pain has no typical migraine features (i.e. nausea/vomiting, photo- AND phonophobia or aura) and facial pain attacks occur independently of headache episodes.

Also, patients showing signs of mucosal contact points or deviated nasal septum will be included, but the presence of these conditions should be noted in the patients' history. Moreover, patients with Lund-Mackay score of 4 or less can be included in the study, unless any singular sinus can be scored with 2 points.

Data collection

A structured questionnaire (see supplementary materials for details) will be filled out during patient consultation in participating centres and submitted online to the central database after anonymisation. Parts of the questionnaire will be filled out by the patient under the investigator's supervision. The clinical observation chart including the questionnaire is included in the supplementary materials. The questions cover the following areas:

- Pain characteristics (i.e. location, frequency, duration, quality, intensity, accompanying symptoms, provoking/relieving factors).
- Coexisting diagnoses (i.e. other headache/pain-related disorders).
- Pain-related burden and consequences (i.e. medications used and their efficacy, consultations in the past, surgical procedures in the past, cost of treatment).
- Physical examination.
- Paranasal sinuses imaging.

To achieve homogeneity of data in this multicentre and multidisciplinary study:

1. All the investigators participating in the study discussed with the study coordinator any anticipated problems with recruitment, with focus on areas less familiar to a particular centre (e.g. neurological disorders in an ENT setting).

2. A structured questionnaire was designed to identify participants fulfilling exclusion criteria. The major part of this questionnaire was designed to be filled out by the patient, to avoid investigator-related bias.
3. The study coordinator will ad hoc reanalyse data submitted by particular centres to identify any problems related to recruitment. If such issues are identified, a reassessment will be undertaken to achieve good quality of submitted data.

Ethical approval

Prior to study initiation each participating centre will obtain approval from the appropriate ethical board (if required by local regulations). Investigators will obtain written informed consent from all eligible participants prior to starting study procedures. All the non-anonymised data will remain in the participating centres. Only data without personal information (i.e. name, surname) will be submitted to the central database. The data will be coded in a way that would allow the principal investigator in each centre (but not investigators from other centres) to identify subjects when needed.

Study registration

The study will be registered in ClinicalTrials.gov after protocol publication and prior to recruitment initiation.

Study duration

Twelve months from the study onset.

Statistical analysis

Due to the exploratory character of the study and lack of comparators, only basic descriptive analyses are planned:

- medians in case of age, attack duration,
- percentages in case of gender, pain laterality, location (see supplementary 'Clinical observation form' for all assessed parameters).

If the results allow for a more robust analysis, comparisons between subgroups will be employed. In that case, patients will be divided into subgroups based on the presence of primary headache diagnosis, sinonasal symptoms. In that case analysis will include associations between the presence of co-occurring migraine/TTH or nasal discharge/congestion with pain characteristics (laterality, duration, location, intensity, character). The goal would be to identify factors associated with MFSP severity, as we hypothesise that people with:

- coexisting primary headache disorder or sinonasal symptoms may be associated with more severe or frequent MFSP,
- MFSP in people with migraine may have more prevalent features typical to that type of headache.

If these associations are found, they may suggest an overlap in aetiopathogenesis between MFSP and primary headache disorders, as well as the presence of cranial autonomic symptoms also in this type of facial pain.

A power analysis indicated that 200 patients would give >80% power to detect a difference of 15% in incidence between the above mentioned subgroups. The verification of differences between groups will be based on the significance level of $p < 0.05$. We will use a chi-square test to analyse variables expressed at ordinal or nominal level. The continuity correction will be applied for 2×2 tables, and Fisher's exact test for tables larger than 2×2, when the conditions for the chi-square test will not be met. Quantitative variables broken down into groups will be calculated with Mann–Whitney–Wilcoxon test. Furthermore, a cluster analysis with an internal cluster assessment for participant demographics, pain features and associated symptoms is planned (Davies–Bouldin index, measuring similarity/distance between clusters, Dunn's index). The aim of the latter calculations is to identify potential subgroups of MFSP indicating possible distinct diagnostic entities in this group.

Article highlights

- Midfacial segment pain/tension-type orofacial pain requires scientific description.
- We propose a cross-sectional study that will characterise this type of pain in multicentre and multidisciplinary setting.

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