RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2024, DOI: 10.5603/pjnns.103063

ISSN: 0028-3843, e-ISSN: 1897-4260

Comparison of headache and facial pain prevalence and phenotype in upper respiratory tract infections of differing origins — a cross-sectional study

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ABSTRACT

Aim of study. This study aimed to compare headache and facial pain prevalence and headache phenotype among people with common upper respiratory tract infections (URTIs).

Clinical rationale for study. Headache is a common symptom in viral URTI, but its phenotyping has so far been limited to coronavirus disease 2019 (COVID-19) and influenza. Additionally, the prevalence of facial pain in URTIs has only rarely been discussed in scientific publications.

Material and methods. Patients with acute URTI symptoms were evaluated for headache phenotype using a semi-structured questionnaire. Antigen swab tests were performed in all participants.

Results. The analysis included 276 URTI/APVRS (acute post-viral rhinosinusitis) episodes in 223 patients (136 women, 60.1%) aged 18–73 [mean 41.3 / median (25th, 75th) 40 / standard deviation 15.1]. Participants were diagnosed with: COVID-19 — 107/276 (38.8%); 'common cold' — 103/276 (37.3%); influenza — 36/276 (13.0%); or APVRS — 30/276 (10.9%). Headache was present in 183/276 (66.3%) and URTIs and facial pain in 107/276 (38.8%). Predictors of headache in URTIs included sinonasal symptoms (odds ratio (OR) 10.70, $p < 0.001$) and fever (OR 2.9, $p = 0.004$). Headache more often ($p = 0.030$) had a migraine-like phenotype in COVID-19 (27.4% (20/73) vs. 9.1% (10/110) and tension-type headache (TTH)-like phenotype in 'common cold' (75.4%, 49/64 vs. 61.3%, 73/119). Previous COVID-19 immunisation (vaccination or infection) was associated ($p = 0.004$) with a lower prevalence of migraine-like headache [6.3% (1/16) vs. 32.8% (19/58)].

Conclusions and clinical implications. Headache and facial pain are prevalent during URTIs, and are associated with general and sinonasal immune response rather than virus type. Headache phenotype may depend on the causative microorganism, but it can evolve in response to previous immunisation. Our study supports vaccination against COVID-19, as people with prior immunisation are probably less likely to experience migraine-like headache.

Keywords: migraine, tension-type headache, COVID-19, SARS-CoV-2, influenza, common cold

Introduction

Headache and facial pain are highly prevalent in neurological practice. However, they are not specific to one disorder, and require differentiating between primary and secondary aetiologies. For that purpose, the phenotypes of headache attributed to different disorders should be clearly defined. The current literature provides limited data on the phenotype of headache or facial pain in upper respiratory tract infections (URTI) — one of the most prevalent secondary causes of pain

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Date submitted: 12.10.2024 Date accepted: 12.11.2024 Early publication date: 09.12.2024

in the head [1, 2]. Scientific interest in this complaint was renewed when the coronavirus 2019 (COVID-19) pandemic broke out [3]. Many publications in this area have led to the conclusion that headache is common during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [4–6]. Moreover, the available research allowed a typical headache phenotype to be described, and new classification criteria were proposed [4].

However, it should be remembered that SARS-CoV-2 is but one of many infective agents responsible for URTIs often classified under the umbrella diagnosis of 'common cold' [7]. The microorganisms that cause this disease include most often rhinoviruses, respiratory syncytial viruses (RSV), parainfluenza viruses, metapneumovirus, and other types of coronavirus [8–11]. Additionally, several infective agents cause infections with more severe disease, warranting a specific clinical approach. The most prevalent among these are influenza A and B viruses [12].

All of the above-mentioned microorganisms have been confirmed as causing headache during the acute infection phase [1]. This observation prompts the question as to whether headache in URTIs is specific to a particular virus, or is a result of pathomechanisms shared by these viral infections. Furthermore, it should be noted that both the migraine and the tension type-resembling headache phenotype have been described in COVID-19 and influenza [13, 14]. This in turn once again indicates that particular headache features might not be related to causative microorganisms, but rather to other factors modulating common pathways.

It should also be noted that COVID-19 can cause headaches that last longer than the active viral infection, especially when accompanied by post-COVID (sometimes called 'long COVID') conditions [15–17]. However, prolonged post-viral complaints have also been reported in literature predating the SARS-CoV-2 pandemic. One such prolonged syndrome after acute viral infection, proposed by European experts, is acute post-viral rhinosinusitis (APVRS) [18, 19]. Facial pain and headache are common in this condition. Once again however, the literature contains little data allowing a comparison between this disorder and acute viral symptoms.

Clinical rationale for study

The purpose of this study was to compare headache and facial pain phenotype in COVID-19, 'common cold', influenza, and APVRS. We hypothesised that headache is a symptom caused by an inflammatory response rather than a causative organism. Consequently, in acute infections with more pronounced inflammatory response (e.g. COVID-19, influenza), a headache should have a different prevalence or phenotype to a headache caused by 'common cold' or APVRS. To further evaluate this concept, this study also aimed to assess whether factors indicative of a stronger innate immune response (e.g. fever) or a local response (i.e. rhinitis) are associated with a different headache phenotype. Additionally, we looked for evidence that prior SARS-CoV-2 immunisation may lead to a different headache phenotype.

Material and methods

This was a cross-sectional study set in a primary care clinic serving a population of c.10,000 people. This study recruited consecutive adult patients who attended a physician consultation for recent (< 12 weeks) onset of acute URTI symptoms (anterior/posterior nasal discharge and/or nasal congestion and/or sore throat and/or fever and/or myalgia). Consultations in the same patient for different URTIs were allowed if the patient had reported a period of at least three weeks without any symptoms from the upper respiratory tract between infections. The study was approved by the Ethical Committee of Warmia and Mazury Medical Chamber (17/2023/VIII). The trial was registered in Clinical Trials (NCT06127186). Written informed consent was obtained from all participants before inclusion.

Patients were excluded from the study if they met any of the following criteria:

- Isolated general symptoms (i.e. fever and/or myalgia) without signs of URTI on physical examination
- Recurrent URTI (> 3 episodes of URTI in 6 months prior to visit)
- Chronic or recurrent upper respiratory tract disorders (i.e. allergic and nonallergic rhinitis, chronic rhinosinusitis, neoplasms)
- Immunodeficiency disorders
- Situations that prevented the performance of an examination (i.e. neurological or psychiatric disorders which made it impossible to obtain informed consent or a reliable medical history)
- Any chronic headache or facial pain (i.e. occurring on more than 14 days per month for more than three months prior to consultation). Patients with episodic headache (e.g. episodic migraine or tension-type headache) were not excluded
- Acute bacterial URTI
- No resolution of symptoms four weeks after URTI onset or 12 weeks in APVRS.

A practice nurse assessed the patients for URTI symptoms. If any symptom was present, then on the same day the patient was examined by a general practitioner with a special interest in headache (MS). History and physical examination were collected by the investigator with the help of a semi-structured questionnaire to decrease the risk of omitting data. Patient responses were noted if a particular symptom was present in any form on the day of consultation to avoid recall bias. Questions addressed:

- URT symptoms (time from onset, nasal discharge and congestion, hyposmia/anosmia, facial pressure, cough, fever)

- Headache and facial pain (location, intensity, character, duration)
- Accompanying symptoms (nausea, vomiting, cranial autonomic symptoms (CAS) according to trigeminal autonomic cephalalgias criteria in International Classification of Headache Disorders 3 — ICHD-3 [20])
- Physical examination (body temperature, oxygen saturation, heart rate, arterial pressure, anterior rhinoscopic examination, throat inspection).

Headache phenotype was classified using the ICHD-3 criteria for migraine without aura (B+C+D) or infrequent TTH (B+C+D) [20]. Cases that could not be classified as either of these were labelled 'unclassifiable' even if 2/3 criteria were met. An acute viral URTI diagnosis was confirmed if the inclusion criteria were met in combination with signs of URTI on physical examination (i.e. nasal discharge anterior/posterior, nasal mucosa oedema, nasal/throat mucosa reddening) and/or a positive antigen swab test result for COVID-19, influenza A/B virus or RSV (CorDx Test COMBO: COVID-19 positive predictive value (PPV) 89.09%, negative predictive value (NPV) 100.00%, Influenza A: PPV 100.00%, NPV 99.34%, Influenza B: PPV 96.00%, NPV 99.60%, RSV: PPV 98.98%, NPV 99.21%). APVRS was diagnosed according to the European Position Paper on Rhinosinusitis (EPOS 2020) in subjects with symptoms duration of 10 or more days. Currently no validation study in Polish for EPOS criteria is available. However, English language studies have confirmed the excellent sensitivity and specificity of EPOS 2012 [19]. Previous COVID-19 immunisation (vaccination and/or infection confirmed by a polymerase chain reaction or antigen test) was verified in the national electronic database in subjects with a positive swab test result for SARS-CoV-2 infection. A follow-up telephone consultation was performed to ensure symptom remission according to the exclusion criteria (after four weeks in URTI or 12 weeks in APVRS).

The recruitment target was based on the following premises: 1. Study duration of one infective season (November 2023 to March 2024) with c.1,000 URTI cases having been seen in participating primary care practices in previous seasons; and 2. Differences in incidence of migraine-like headache phenotype based on previous observations from this research group — 29% in COVID vs. 10% in 'common cold' (the latter value was an educated guess based on the authors' experience) [5]. The sample size calculation was performed with an online tool with $p < 0.05$ and 80% power [21]. The sample size was estimated at $n \geq 67$ in COVID-19 and $n \geq 67$ in 'common cold'. The calculated sample size was considered a minimal value which could be larger if more subjects were recruited, considering that the study was to last a whole infective season.

Statistical analysis was performed in the R statistical environment ver. 3.6.0, the PSPP program and MS Office 2019. $p < 0.05$ was adopted as the level of significant relationships between analysed values. Tests based on chi-square distribution were used for data expressed at the ordinal or nominal levels. In the case of 2x2 tables, a continuity correction was used, and when the conditions for the chi-square test were not met, Fisher's exact test with expansion was used for tables larger than 2x2. Non-parametric tests (e.g. Kruskal-Wallis test) were used to analyse quantitative values presented by groups. The tests were selected based on the distribution of variables, which was verified with the Shapiro-Wilk test. The existence of a relationship between the groups was verified using logistic regression analysis.

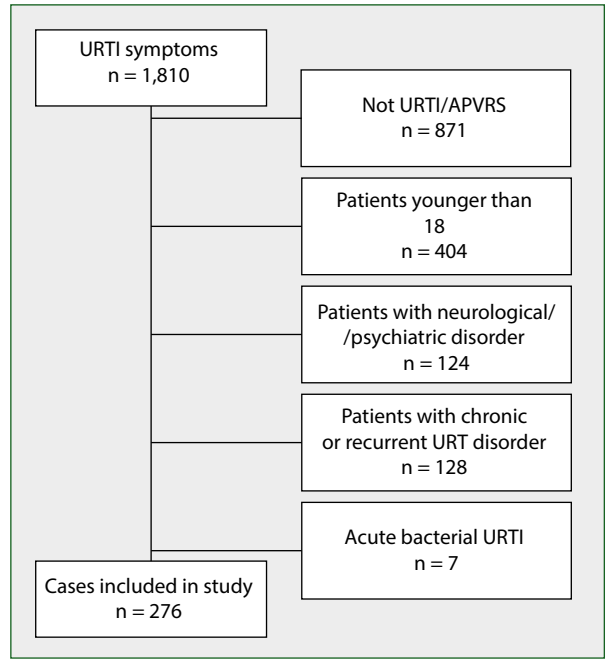

Figure 1. Selection process of patients fulfilling inclusion criteria (i.e. consultation in primary care for acute onset anterior/posterior nasal discharge and/or nasal congestion and/or sore throat and/or fever and/or myalgia). URTI — upper respiratory tract infection; APVRS — acute post-viral rhinosinusitis

Results

1,810 consultations were initially considered for inclusion in this study. The exclusion process is presented in Figure 1. The most prevalent neurological/psychiatric causes for exclusion (self-exclusion in terms of being prevented from obtaining informed consent and/or a reliable medical history) were: Alzheimer's Disease and other forms of dementia (35); the consequences of a stroke (27); an autism spectrum disorder (23); and a neurodevelopmental disorder (13). There was no missing data. In total, the analysis included 276 URTI/APVRS episodes due to the fact that consultations in the same patient for different URTIs were allowed: 26 patients were included for two separate diagnoses and 10 for three diagnoses. In accordance with the exclusion criteria, patients reporting for more than three different reasons were excluded from the study due to a recurrent URT disorder.

Table 1. Upper respiratory tract infections diagnosed in participants

Diagnosis	N = 276 [%]	Days from onset [median/SD]	
COVID-19	107 (38.8)	2–7 (3/1.8)	$\chi2$= 3.71
'Common cold'	103 (37.3)	2–7 (3/1.5)	*df* = 2
Influenza	36 (13.0)	2–7 (4/1.2)	p = 0.157
APVRS	30 (10.9)	10–60 (11/11.1)	NA

APVRS — acute post-viral rhinosinusitis; COVID-19 — coronavirus disease 2019; SD — standard deviation; $\chi2$ — statistical test used; *df* — degrees of freedom; p — statistical significance; NA — not applicable

Table 2. Prevalence of headache and facial pain in upper respiratory tract infections

			Diagnosis				Test result
			'Common cold' n = 103	COVID-19 n = 107	Influenza n = 36	APVRS n = 30	
Headache	NO	N	38	10	34	11	$\chi2 = 1.331$ *df* = 3 p = *0.722*
		%	36.9%	27.8%	31.8%	36.7%	
	YES	N	65	26	73	19	
		%	63.1%	72.2%	68.2%	63.3%	
Forehead pain	NO	N	12	7	18	5	$\chi2 = 1.191$ *df* = 3 p = *0.755*
		%	18.5%	26.9%	25.0%	25.0%	
	YES	N	53	19	54	15	
		%	81.5%	73.1%	75.0%	75.0%	
Facial pain	NO	N	24	14	32	6	$\chi2 = 3.539$ *df* = 3 p = *0.316*
		%	36.9%	53.8%	44.4%	30.0%	
	YES	N	41	12	40	14	
		%	63.1%	46.2%	55.6%	70.0%	
Other pain location	NO	N	39	11	40	11	$\chi2 = 2.357$ *df* = 3 p = *0.502*
		%	60.0%	42.3%	55.6%	55.0%	
	YES	N	26	15	32	9	
		%	40.0%	57.7%	44.4%	45.0%	
Isolated facial pain	NO	N	64	26	68	18	$\chi2 = 4.617$ *df* = 3 p = *0.202*
		%	98.5%	100.0%	94.4%	90.0%	
	YES	N	1	0	4	2	
		%	1.5%	0.0%	5.6%	10.0%	

COVID-19 — coronavirus disease 2019; APVRS — acute post-viral rhinosinusitis; $\chi2$ — statistical test used; df — degrees of freedom; n — number of participants; p — statistical significance

The study included 223 patients (136 women, 60.1%) aged 18-73 (mean 41.3, median [25th, 75th] 40 (standard deviation (SD) 15.1). The first patient was recruited in November 2023 and the last one in March 2024. Preexisting episodic migraine was confirmed in 45 participants (20.2%) and tension-type headache (TTH) in 56 (25.1%).

Table 1 sets out the number of consultations included for each URTI diagnosis. Days from disease onset to initial consultation did not differ between groups, although APVRS was excluded from this analysis due to the fact that it is, by definition, a disorder diagnosed after at least 10 days of symptoms.

Headache accompanied URTI in 66.3% of cases and isolated facial pain in 2.5% (Tab. 2). No significant differences in the prevalence of headache or pain location were found between different diagnoses. However, headache more often had a migraine-like phenotype in COVID-19 and a TTH-like phenotype in 'common cold' (Suppl. Tab. 1). Moreover, headache was accompanied by nausea/vomiting significantly more often in COVID-19. Previous COVID immunisation (vaccination or infection) was associated with a lower chance of migraine-like headache (Suppl. Tab. 2). However, immunisation was not associated with decreased incidence of any headache. Patients with APVRS had higher prevalence of headache phenotype that could not be classified as either migraine or TTH-like. Migraine-like headache was not associated with fever ($\chi2 = 0.950$, p = 0.330) or cough ($\chi2 = 0.895$, p = 0.639). However, patients with sinonasal symptoms during URTI had a lower chance of having a migraine-like headache

phenotype and a higher incidence of complaints that could not be classified as either migraine or TTH-like (Suppl. Tab. 3).

Patients included in the study reported sinonasal symptoms that fulfilled diagnostic criteria for acute rhinosinusitis in 212 (76.8%) cases. General symptoms included fever (n = 113, 40.9%) and cough (n = 208, 75.4%). Non-nasal CAS were reported by 53 (19.2%) participants (mostly lacrimation n = 51 or conjunctival injection n = 9). During facial palpation, 44 (15.9%) participants reported pain exacerbation. Logistic regression analysis revealed that predictors of headache in URTIs included (in order of statistical strength): sinonasal symptoms; non-nasal CAS; fever; and pain exacerbation by pressure applied over the paranasal sinuses (Suppl. Tab. 4).

Discussion

This study presents a direct comparison of headache phenotypes across URTIs of differing origins. Our results indicate that headache is common in URTIs, irrespective of the particular virus type. Also isolated facial pain may in rare cases accompany these infections. However, the phenotype of headache depends on additional factors such as the infective agent, previous immunisation, and sinonasal involvement. Overall, these results provide an insight into headache phenotype and facial pain prevalence in some of the most prevalent diseases worldwide.

Only a few studies have so far phenotyped headache in patients with SARS-CoV-2 infection and influenza [5, 13, 14]. Additionally, several other authors have provided evidence for headache-related complaints in COVID-19 [3, 5, 22, 23]. Most of this data indicates that migraine-like phenotype can occur not only in SARS-CoV-2, but also in influenza infections, in 25% and 43% of cases respectively [13, 14]. The results presented in these two studies were comparable to our research in regard to COVID-19 (27.4%), but differed in terms of influenza (15.4%). This latter variation may be due to differing study designs or to the small number of influenza patients in our current research. However, as the present study shows, headache phenotype may have been conditioned by other factors.

We hypothesised that patients with COVID-19 or influenza may have a different headache phenotype than do those with a 'common cold'. This hypothesis would appear to be at least partly correct, as migraine-like phenotype has been found to be more prevalent in COVID-19. It should be noted that both COVID-19 and influenza are considered to have a worse prognosis and more pronounced general symptoms (i.e. fever, myalgia) than 'common cold' [8, 24]. It has been previously proposed that this might be the result of stronger innate immune response activation manifesting with general symptoms (i.e. fever, myalgia) [1, 25]. The current study does not confirm that migraine-like headache phenotype is associated with fever independently of the infective agent. However, factors associated with a milder disease course (e.g. previous immunisation) reduce the odds of this headache phenotype appearing. Previous immunisation might have also contributed to the lower prevalence of migraine-like headache phenotype among influenza participants in this study, although the data that would confirm this was unavailable to us.

It should also be noted that fever, sinonasal symptoms or facial hypersensitivity to touch are predictors of any headache, independently of a potential causative virus. These observations further support the notion that headache during URTIs is secondary to immune response, especially when trigeminal afferents are directly exposed to inflammation (i.e. during sinonasal inflammation). Similar observations were made in a previous study by our group [5]. The association between sinonasal inflammation and headache might be explained by direct trigeminal C and A-δ fibre exposure to inflammatory mediators during local response to virus [1]. Moreover, a systemic inflammatory response accompanies URTIs. In this situation, the trigeminal ganglion or dura mater may be reached by the biochemical components of immune reaction (e.g. interferons, chemokines, prostaglandins), which in turn can contribute to headache [1]. Finally, a direct effect of viruses on the central nervous system has been postulated as a possible cause of headache during URTIs [4].

Despite these hypotheses, the authors of a recent systematic review on headache in COVID-19 stated that "there is no good documentation for any pathogenesis for headache in the context of COVID-19" [4]. A recent review by experts from the European Academy of Neurology and the European Headache Federation did not find evidence that facial pain accompanies COVID-19 [4], although some data from the past had suggested that this might be the case [5, 26]. The current study suggests that facial pain accompanies c.40% of URTIs including COVID-19. Moreover, in rare cases (2.5%), patients may complain of isolated facial pain without an accompanying headache. This finding might prove instrumental in the development of future editions of the International Classification of Orofacial Pain [27].

Rhinosinusitis is associated with a higher incidence of headache during COVID-19 and influenza [5, 28]. This is why APVRS has several features that made it especially interesting as a comparator in this study. On the one hand, it is a disease with prominent sinonasal inflammation. On the other hand, it is a sequel to viral infection with little systemic inflammatory response [19]. In other words, headache in APVRS could be promoted to a larger extent by rhinosinusitis than by systemic inflammatory factors. These mechanisms seem to result in a change in headache phenotype, as more often it is neither migraine nor TTH-like. Future studies on URTI-headache should take into account that both systemic (viral) and sinonasal factors contribute to this symptom and determine its final phenotype. As a footnote, it should be mentioned that non-nasal CAS observed in this study

were limited to lacrimation and conjunctival injection. Both these symptoms are highly prevalent in rhinitis, but are also reported by patients with different primary headache disorders [29].

This study is limited by several factors. Firstly, sampling was limited to patients actively seeking medical help. As a result, people who decided to treat their symptoms at home or via another healthcare provider (e.g. hospital A&E) were not included in the study. Some studies have shown that only 5–22% of people with RTI symptoms seek medical consultation, with high variability between countries and studies [30]. Secondly, the diagnostic process did not try to diagnose the particular viruses causing 'common cold'. The most important limitation associated with this might be the result of misdiagnosing other disorders with URTI symptoms (e.g. allergic rhinitis) as 'common cold'. In order to limit this possibility, strict exclusion criteria were applied, especially with regard to recurrent or chronic URT conditions. Moreover, a follow-up assessment helped to reduce the risk of this type of bias. It should also be noted that this study did not collect information about medications used by participants. Consequently, symptomatic URTI treatment that preceded their consultation or medications used for chronic disorders might have influenced the results. And finally, this study did not analyse the seroconversion status of participants. Therefore, data on immunisation is only valid in respect of registered COVID-19 cases or vaccinations. Thus patients who achieved immunity via other measures (e.g. unreported or subclinical disease), or patients immune to other virus variants, may have limited the strength of the observed associations.

In conclusion, not only headache, but also facial pain, seem to be prevalent during URTIs, and to be associated with general and sinonasal immune response rather than virus type. However, headache phenotype to some extent depends on causative microorganisms. This may not mean that viruses have a unique pain pattern, as this study suggests a change in headache phenotype in people who have been previously immunised against COVID-19. In other words, the symptomatology may evolve over time.

Clinical implications/future directions

Our observations may be relevant to ongoing scientific efforts to establish diagnostic criteria for acute headache attributable to COVID-19. Classification committees should consider the pros and cons involved in isolating different entities according to microorganisms because this may lead to a multiplication of classification entities — each for a different virus, but with similar symptoms.

In addition, this research indicates that prior immunisation against COVID-19, and possibly other URTIs also, may protect against migraine-like infection-related headache, although this is an observation requiring further scientific confirmation.

Article information

Acknowledgements: *The authors would like to thank Mrs Joanna Straburzyńska for her linguistic proofreading.*

Funding: *This study was supported by statutory financing from University of Warmia and Mazury, Olsztyn, Poland and Wroclaw Medical University, Wroclaw, Poland.*

Conflicts of interest: *MS: no conflict of interest; MW-P is an editorial board member of the Polish Journal of Neurology and Neurosurgery. She was not involved in the journal's peer review process of, or decisions related to, this manuscript.*

Authors' contributions: *MS: conceptualisation, data curation, formal analysis, investigation, project administration, visualisation, draft preparation, review and editing; MW-P: supervision, validation, review and editing.*

Availability of data and materials: *A dataset supporting the conclusions of this article is available in the Figshare repository, unique persistent identifier and hyperlink to dataset(s) in: https://doi.org/10.6084/m9.figshare.25751748.v1.*

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