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COVID-19-related headache and innate immune response — a narrative review

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ABSTRACT

Headache is one of the most prevalent, although often underreported, symptoms of coronavirus disease 2019 (COVID-19). It is generally accepted that this symptom is a form of secondary headache due to systemic viral infection. There are several hypotheses that try to explain its aetiopathogenesis. One of the most compelling is related to innate immune response to viral infection. This rationale is supported by similarities to other viral infections and the temporal overlap between immunological reactions and headache. Moreover, several key factors in innate immunity have been shown to facilitate headache e.g. interferons, interleukin (IL) –1-β, IL-6, and tumour necrosis factor. There is also a possibility that the virus causes headache by the direct activation of afferents through pattern recognition receptors (i.e. Toll-like receptor 7). Moreover, some data on post-COVID-19 headache and after vaccination against SARS-CoV-2 infection suggests a similar cytokine-mediated pathomechanism in these clinical situations. Future research should look for evidence of causality between particular immune response factors and headache. Identifying key molecules responsible for headache during acute viral infection would be an important step towards managing one of the most prevalent secondary headache disorders.

Key words: SARS-CoV-2, pain, innate immune response, IL-1β, IL-6, TNF, IFN, TLR-7

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic precipitated great interest in the scientific community, prompting an unparalleled development of research data. In published studies, headache has often appeared as the most prevalent neurological complaint related to different aspects of the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been named as a symptom of COVID-19 [1] or its direct and indirect sequelae [2]. Moreover, headache has been identified as a prognostic factor [3], as well as an adverse reaction to therapeutic interventions and preventive strategies [4].

However, SARS-CoV-2 is a new headache factor only to a limited degree, and the complaint had been studied decades before the current pandemic. Consequently, the purpose of this review was to critically appraise the dataset published over the last two years in this area. Furthermore, we examine the most likely explanations for phenomena described in headache-related literature during the COVID-19 pandemic in the context of evidence accumulated in the past.

Considerations for review methods

Current guidelines describe headache as one of the cardinal COVID-19 symptoms [5]. However, initial reports

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Table 1. Prevalence of headache in acute viral respiratory tract infections

Aetiology	Study	Number of participants	Headache prevalence
Viral upper respiratory infection (miscellaneous pathogens)	Liu et al. 2013 [99]	4,755	25%
Influenza virus	Yang et al. 2015 [100]	49	69%
Rhinovirus	Zlateva et al. 2020 [101]	384	68%
Respiratory syncytial virus	Widmer et al. 2014 [102]	32	66%
Metapneumovirus		33	58%
Human coronaviruses	Zeng et al. 2018 [36]	258	1%
SARS-CoV-2	Lechien et al. 2020 [1]	1,420	70%
	Pullen et al. 2020 [11]	1,252	60%
	O'Keefe et al. 2021 [9]	337	66%
	García-Azorín et al. 2021 [10]	2,194	23%
	Straburzyński et al. 2021 [8]	130	72%

indicated its low prevalence in infected subjects (11.3%) [6]. It should be underlined that this data was obtained mostly from hospital-based retrospective case series, which are prone to bias resulting from selective data collection by healthcare providers and discriminatory reporting by patients. Consequently, even recently published meta-analyses based on these studies endorse the opinion that headache is not a prevalent acute COVID-19 symptom [7]. However, the above mentioned retrospective studies were followed by prospective research based on structured questionnaires. The latter placed headache among the most prevalent symptoms of COVID-19 (22–72%) [1, 8–11], although rarely an isolated one [12]. What is more, headache may be one of the most universal complaints in SARS-CoV-2 infection, occurring regardless of virus variant [13]. To conclude, the described underreporting has had a profound impact on evidence interpretation. Consequently, studies based on structured questionnaires specifically focused on headache are the ones with lowest bias risk for the purpose of this review.

The symptoms of COVID-19-related headache have been well characterised from the clinical point of view. However, little has been published on the subject of its pathogenesis. Consequently, only hypotheses have been proposed so far. In their comprehensive review, Caronna and Pozo-Rosich proposed several such concepts [14], e.g.:

- Direct damage to peripheral and central nervous system (CNS) mediated via virus affinity to angiotensin-converting enzyme 2 (ACE2) and its ability to cross the blood-brain barrier (BBB), especially when the latter is further damaged by inflammatory and coagulopathic processes.
- Hyperinflammation and cytokine storm with the prominent role of interleukin (IL)-6.
- Trigeminal system activation resulting from overlapping pathways of COVID-19 and primary headache disorders.

To assess data supporting these theories, our review concentrates on two major concepts: time and reference to non-COVID-19 headache scenarios. In the first, our rationale is that headache should occur simultaneously or be slightly preceded by a causal factor. As to the second concept, SARS-CoV-2 pathology shares many, mostly immune, mechanisms with disorders that have troubled humankind for millennia [5].

Headache in COVID-19 vs other viral respiratory tract infections

As mentioned above, SARS-CoV-2 causes headache in 22–72% of subjects, with the majority of prospective studies pointing to a 60–70% prevalence. These percentages are comparable to results from research on infections caused by common viruses, i.e. influenza, metapneumoviruses, respiratory syncytial viruses (RSV) and rhinoviruses (Tab. 1). However, most of these pathogens substantially differ in their biology e.g. the influenza virus can be both neurotropic and non-neurotropic [15]. It seems justified therefore to look for the source of infection-related headache in pathways that are common for all these pathogens, i.e. immune response.

SARS-CoV-2 tissue distribution

The upper respiratory tract, especially nasal ciliated cells, are the primary targets for SARS-CoV-2 in early COVID-19 stages [16]. The sinonasal mucosa is innervated by the first and second branch of the trigeminal nerve. Nerve endings of C and A-delta fibres are immersed in whatever biochemical or inflammatory processes take place in this area.

Viral sinonasal inflammation (acute rhinosinusitis) occurs in response to the replication of the virus in the nasal epithelium. Virus-derived molecules recognised by innate immune cells are referred to as pathogen-associated molecular patterns (PAMP). These structures are highly specific for given types of microorganisms (e.g. there are observations suggesting that the SARS-CoV-2 spike protein may act as a PAMP and cause neuroinflammation [17]). PAMP binding receptors are known as pattern recognition receptors (PRR). It is not

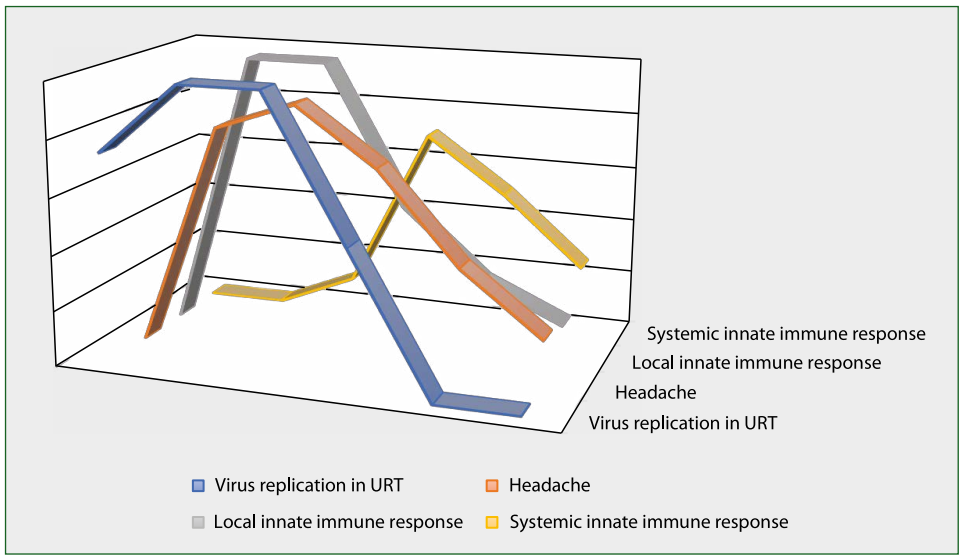

Figure 1. Schematic depiction of temporal changes in upper respiratory tract (URT) virus replication, innate immune response, and headache in mild/moderate COVID-19. Based on Schultze & Aschenbrenner 2021 [22] and O'Keefe et al. [9]

fully understood which PRRs are activated by SARS-CoV-2. However, experts suggest that the most probable targets are Toll-like receptors 3 (TLR3) and TLR7, retinoic acid-inducible gene 1 (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) [18]. These key sensors of viral infection are expressed intercellularly and respond to nucleic acids (RNA mostly), although in different ways. TLR3 and TLR7 recognise viral nucleic acid transported by the endosomal pathway (i.e. from outside the cell). RIG-1 and MDA-5 detect viruses that have entered the cell and started producing dsRNA during replication. The evidence for RIG-I and MDA5 expression in trigeminal afferents is lacking, and it seems likely that these neurons do not express TLR3 [19]. However, TLR7 is present on nasal mucosa nociceptors and, what is more, its stimulation in the nasal epithelium leads to brainstem activation [20].

It is worth noting that TLR3, TLR7, RIG-1 and MDA5 are expressed in nasal mucosa lymphoid tissue and nasal epithelial cells, leading to their activation and subsequent production of type I interferons and other pro-inflammatory cytokines [21–24]. Consequently, trigeminal afferents sustain exponential elevation of type I and III interferons (IFNs) followed by IL-1α, IL-1β, tumour necrosis factor (TNF), IL-6, C-X-C motif ligand (CXCL)-8, CXCL-10, CXCL-11, and C-C motif ligand (CCL)-5, followed by the next steps of immune response [25]. In a laboratory setting, this situation was simulated by experiments on an animal model. In that study, sinonasal stimulation with bradykinin caused the nociceptive activation of the trigeminal nucleus caudalis — a key region for headache [26]. This in turn may explain why patients with rhinosinusitis have headache and facial pain. In clinical settings, this was further supported by a study of COVID-19 patients that provided evidence for an association between acute inflammation of the sinonasal mucosa and headache/facial pain [8]. In other words, patients experiencing rhinosinusitis during COVID-19 had significantly higher odds of headache or facial pain. These correlations are multi-level and stretch beyond innate response and nasal cavity, e.g. a retrospective study found that patients experiencing headache and sinonasal symptoms have lower levels of anti-SARS-CoV2 IgG [27].

It has been confirmed that the coronavirus can penetrate different areas of the nervous system. Several mechanisms and routes to cross the BBB and spread within the CNS have been proposed, including virus affinity to ACE2 [14, 28, 29]. Some of these hypotheses assume that SARS-CoV-2 travels along the olfactory or trigeminal route [30], similarly to some neurotropic variants of the influenza virus [31]. Activation of the trigeminal ganglion, trigeminal nucleus caudalis and hypothalamus (among other regions) is considered paramount for some primary headache disorders (e.g. migraine). Consequently, this could explain headache pathomechanism occurring via a direct viral action in the trigeminal system [14, 30]. However, evidence published so far indicates moderate virus presence in the trigeminal ganglion or cranial nerve nuclei in the medulla oblongata [32, 33], and neither meningitis nor encephalitis are prevalent in COVID-19 [7, 34]. It should also be underlined that sole virus presence in CNS does not necessarily cause pain. For example, the human coronavirus is clearly neurotropic [35], and yet very seldom causes headache [36].

Molecules involved in innate immune response to SARS-CoV-2

Viral infections trigger innate and adaptive immune responses. These two reactions, although intertwined, have their own timelines, with innate being swifter and less specific. In other words, an innate reaction occurs at the same time as the

first infection symptoms, i.e. headache [8, 9, 11, 18] (Fig. 1). Studies analysing COVID-19-related headache have shed some light on its associations with innate immune response.

For example, in hospitalised patients, some infection symptoms (fever, myalgia,) have been associated with headache [37]. Fever occurs in response to, among others, endogenous pyrogens, such as IL-1, TNF or IL-6 [38]. These molecules are also part of the innate immune response in the upper respiratory tract mucosa in infections caused by the influenza virus, RSV or metapneumovirus [39, 40]. Moreover, IL-1, TNF or IL-6 contribute to calcitonin gene-related peptide (CGRP) release, although the latter phenomenon has been described only in animal cutaneous nociceptors [41].

IFNs are produced in response to SARS-CoV-2 most probably via the activation of toll-like receptors. When analysed in detail, innate immune response to SARS-CoV-2 infection is characterised by moderate levels of type I IFNs [42]. However, these molecules still play an important role in COVID-19. IFN-α (type I) and λ (type III) peak early in the disease course, especially in the nasal epithelium. A meta-analysis currently awaiting publication has shown that the application of type I IFN (β) is the cause of headache in multiple sclerosis patients [43]. IFN-α is also the cause of headache in many subjects treated with this molecule [44]. Moreover, earlier studies also pointed to possible migraine exacerbation by IFN-β therapy [45]. Type-I IFNs also activate mitogen-activated protein kinase – a pathway that is associated with pain processing in the trigeminovascular complex [46].

Type I IFNs initiate immune responses involving interleukin IL-1β, IL-6, TNF and some chemokines (CCL20, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL16) [18]. Consequently, these factors are more likely to participate in the origin of COVID-19-related headache than molecules that gain prominence later in COVID-19 course (CCL2, CCL3, CCL5, CXCL9, CXCL10, IL-1α, IL-17, IFN-β, IFN-γ, IL-10, IL-33) [18].

IL-6 plays an important role in the early phases of COVID-19 [18], and consequently, this particle should be considered as a possible trigger for headache in this infection. There is however contradictory evidence in this regard. On the one hand, IL-6 levels show positive linear correlation with headache intensity in COVID-19 [47]. On the other hand, headache is associated with lower, although still elevated, IL-6 levels [3]. Moreover, IL-6 is considered a key player in severe COVID-19 and cytokine storm [48] — a late complication occurring in a cohort with less prevalent headache. In reference to its nociceptive potential, it should be mentioned that patients with chronic and episodic tension-type headache (TTH) have elevated serum levels of IL-6 [49]. Moreover, this has been shown in animal migraine models to facilitate the excitability of dural afferents and allodynia [50]. It is therefore a molecule that may play an important role in triggering headache in systemic inflammation. Moreover, IL-6 receptor antagonist (tocilizumab) is a drug inducing clinical remission in giant-cell arteritis, a disease with headache as a prominent symptom [51].

TNF is an endogenous pyrogen and cytokine, playing an important role in early immune response to SARS-CoV-2 infection [18]. Moreover, it has been speculated for decades that it is a headache facilitator [52]. Four-hour TNF infusion has been associated with headache occurring in 65% of subjects [53]. Several studies have indicated that TNF may play a role in migraine pathogenesis [54]. It has also been shown to provoke the sensitisation of meningeal nociceptors [55]. Moreover, out of other cytokines analysed in one study, TNF has been most consistently associated with headache in aneurysmal subarachnoid haemorrhage [56].

As described above, time seems to be of great importance in the development of COVID-19-related headache. Since headache occurs early in the disease course, it is in this period that we should look for initiating factors. When analyses involve patients in later stages of the disease, then associations between inflammatory factors and headache are hard to find. For example, one highly comprehensive study found little association between a wide panel of cytokines and chemokines and headache [57]. The only factor associated with headache was, after adjustments, the level of IL-10. This cytokine is an important anti-inflammatory molecule targeted at the moderating effect of, among others, type I IFNs and TNF [58]. Higher levels of IL-10 may then support the hypothesis that IFNs and TNF play an important role in headache at early stages of the disease, and more IL-10 is secreted in later stages to alleviate this effect.

The above-described molecules form only a small fraction of innate immune response. Some elements have not been discussed due to little evidence allowing for their inclusion in this rationale (e.g. prostaglandins, galectins, innate immune cells including mast cells). However, other particles have been also implicated in early response to COVID-19 and associated headache. One study showed that headache in COVID-19 is associated with higher levels of NLR family pyrin domain containing 3 (NLRP3) inflammasome, and the high mobility group box 1 protein (HMGB1) [59]. The latter has been shown to be involved in trigeminal ganglion neuropathic pain [60]. Moreover, inflammasome is activated by SARS-CoV-2, which in turn leads to the activation of IL-1β and IL-18. IL-1β activates and sensitises the trigeminal ganglion [61, 62], while IL-18 may play some role in migraine [63].

In light of the described rationale, it might be surprising that COVID-19-related headache is associated with lower C-reactive protein levels [64, 65] (although these levels were still higher than in healthy subjects). However, it must be remembered that C-reactive protein is an unspecific inflammation marker rising moderately in the early phases of infection, and reaching higher levels when severe disease or complications develop. Therefore, it has probably a weaker association with processes causing headache.

Currently it is hardly possible to touch upon headache without mentioning CGRP. This molecule not only plays a pivotal role in primary headache disorders, but also participates

Table 2. Diagnostic criteria of acute headache attributed to systemic viral infection

A. Headache of any duration (but lasting < 3 months) fulfilling criterion C
B. Both of the following:
1. systemic viral infection has been diagnosed
2. no evidence of meningitic or encephalitic involvement
C. Evidence of causation demonstrated by at least two of the following:
1. headache has developed in temporal relation to onset of systemic viral infection
2. headache has significantly worsened in parallel with worsening of systemic viral infection
3. headache has significantly improved or resolved in parallel with improvement in, or resolution of, systemic viral infection
4. headache has one or both of following characteristics:
a. diffuse pain
b. moderate or severe intensity
D. Not better accounted for by another ICHD-3 diagnosis

in immune responses. TNF contributes to CGRP release in the trigeminal ganglion [66], while both TNF and IL-1β increase CGRP expression [67]. Moreover, nociceptive sensitisation caused by IL-6 is blocked by olcegepant, a CGRP antagonist [68]. It seems therefore justified to assume that COVID-19-related inflammation may lead to CGRP release at different levels of the trigeminal system [30]. However, in COVID-19 patients, serum levels of CGRP are lower than in healthy controls [69], while another study found no difference in CGRP levels between subjects with and without headache [59]. Finally, anti-CGRP treatments seem to have no effect on COVID-19 course [70].

Clinical features of COVID-19-related headache

Any headache should be classified according to the International Classification of Headache Disorders — 3 (ICHD-3). As regards COVID-19, it is currently diagnosed as "acute headache attributed to systemic viral infection" (Tab. 2). In some disorders, headache phenotype can contribute to identifying the pathological mechanism underlying this symptom (e.g. thunderclap headache in subarachnoid haemorrhage, postural headache in spontaneous intracranial hypotension [71]). In COVID-19 headache has however little specificity — the majority of patients appear to present symptoms similar to TTH 43–68% [8, 10, 72–75]. That is, pain is mostly bilateral, pressing and dull, and mild to moderate in intensity. This phenotype has been associated with lower C-reactive protein levels than headache with more migraine features (i.e. unilateral, pulsating, moderate to severe) [75]. Migraine phenotype is present in 25–50% of subjects [8, 73, 76], and is associated with a more severe COVID-19 course [14]. There is also some evidence that migraine-like headache in COVID-19 is associated with pre-existing migraine [74]. Accompanying autonomic symptoms (i.e. nausea or vomiting and hypersensitivity to light and sound) are not rare [64]. Non-nasal cranial autonomic symptoms (i.e. conjunctival injection and/or lacrimation, eyelid oedema, forehead and facial sweating, miosis and/or ptosis) occur rarely in the course of this infection. Naturally, nasal congestion and rhinorrhoea [8] are highly prevalent due to sinonasal inflammation. In conclusion, COVID-19-related headache may indicate a more effective and balanced immune response, especially when it resembles TTH.

Headache in COVID-19 has been associated with a better prognosis expressed as lower mortality and shorter disease duration [37, 65], although larger observations still await publication [77]. In COVID-19 α and λ IFNs peak early in a mild to moderate disease course. This might indicate that subjects able to develop this prompt immune response are apparently protected against severe COVID-19. This hypothesis is supported by experiments with rodents, where the administration of interferon I protected against cytokine storm [78]. However, it must be remembered that headache in COVID-19 is merely a symptom, and may herald serious complications e.g. cerebral venous sinus thrombosis [79] or encephalitis [80]. These conditions might be difficult to recognise during COVID-19 if headache is initially the only complaint. There is also some evidence that COVID-19 may lead to unusual changes in pre-existing migraine, e.g. there have been several case-reports of patients developing prolonged or unusual migraine aura during COVID-19 [81]. Consequently, caution is recommended, especially because many patients with COVID-19 complain of apparent 'red flags', e.g. mentioning "positional headache" or "worst headache ever" [10]. Moreover, comorbidities may have a strongly negative influence on prognosis [82].

Apart from a few case series, there is very little data on interventions effective in reducing COVID-19-related headache. In one study, paracetamol 1g iv or greater occipital nerve blocks were effective in reducing pain [47]. In another publication, indomethacin (50mg twice daily) was effective in a small case series of patients with acute (n = 21) and persistent COVID-19-related headache (n = 8) [83]. No data on preventive therapies is available, although several particles with potential simultaneously in viral infections and primary headache disorders have been proposed (e.g. low vitamin D3 levels are associated with more frequent headaches [74] and COVID-19 risk [75]).

Post-COVID-19 syndrome and headache

Headache is a common symptom of post-COVID-19 syndrome included in some diagnostic guidelines [84]. A study assessing data from 905 subjects with COVID-19-related headache showed that 31.1% of patients still had headache after one month, 16.8% after three months, and 16% after nine months [2]. These numbers were slightly lower in a recent meta-analysis: 47.1% during the acute phase, 10.6% at three

months and 8.4% after six months [85]. Nevertheless, both of these studies indicate that headache in post-COVID-19 syndrome has a poor prognosis. Approximately equal groups in post-COVID-19 headache have migraine and TTH phenotype-headache [2].

The pathomechanism of post-COVD-19 headache is unknown, although there is some evidence that patients with post-COVID may have increased IL-6 levels [86, 87]. Another study indicated elevated levels of IFN-α, TNF, G-CSF, IL-17A, IL-6, IL-1β, while IL-13 and CXCL-10 were decreased [88]. Although no clear association with pre-existing primary headache disorder has been confirmed, several scenarios are possible:

- persistent secondary headache due to COVID-19
- first manifestation of previous asymptomatic primary headache disorder
- exacerbation of previous low-grade primary headache disorder.

Post-vaccination headache

The COVID-19 pandemic has provided further data in the area of headache related to innate immune response, albeit not directly related to infection, but rather to vaccination. A recent meta-analysis including 83 studies of 1.57 million subjects revealed that headache occurs after the first and second COVID-19-vaccination dose in 22% and 29% of patients respectively [4]. Patterns similar to COVID-19 can be observed in cases of vaccine-related headache. Headache occurs early after vaccination [89–92] and is often accompanied by other systemic symptoms (i.e. myalgia and fever [91]). Similarly to COVID-19, headache after vaccination has more often a TTH phenotype, with migraine-like features present in one third of cases. Post-vaccination headache is not vaccine- or even pathogen-specific, i.e. it is present after vector and mRNA vaccinations. Moreover, immunisation against other types of viruses (e.g. influenza [93], human papillomavirus [94], Ebola [95]) is also commonly associated with headache. The risk of headache after COVID-19 vaccination is doubled by a pre-existing primary headache disorder (e.g. migraine) [91, 92].

The above observations may point to a common mechanism of vaccination- and COVID-19-related headache, with the only common denominator being immune response. One study showed that SARS-CoV-2 spike protein, a major antigen in vaccines, may act as a PAMP and cause neuroinflammation [17]. However, pain should be less prevalent after a second vaccine dose, if this mechanism is responsible for headache (when humoral immunity leads to faster spike protein elimination). Another study showed that after the first dose of SARS-CoV-2 mRNA vaccine (BNT162b2) a prompt release of IFN-γ, CXCL-10, IL-6, IL-8, IL-15, CCL-3, CCL-4 is observed, with some changes lasting for more than one week [96]. After the second dose IFN-γ, CXCL-10, IL-15 and IL-6 were elevated to levels several times higher than after the first dose. This pattern is mirrored by headache, which usually occurs within the first 24 hours, remits after a couple of days after the first vaccination [89–92], and is more prevalent after the second dose [4]. As a side issue, it should be mentioned that CCL-2 and IL-3 were not significantly increased throughout the study, TNF concentrations were only slightly higher, and type I and III IFNs were not analysed at all in this study [96].

It is important to remember that headache might be a primary complaint in patients presenting with vaccination complications. Probably the most widely cited source of post-vaccination headache is vector-vaccine-induced immune thrombotic thrombocytopenia (VITT), [4] although even less prevalent complications have been described (e.g. Tolosa-Hunt syndrome [97]). The major difference between headache in VITT and after vaccination is time. Post-vaccination headache occurs in the first 24 hours, while in VITT it occurs after several (7–10) days [98].

Conclusions and future research

Probably the most important question about COVID-19-related headache remains unanswered. It seems that the pandemic has run its primary course and will recur as a milder disease. Reduction in interest from the scientific community will follow. Meanwhile, the mechanism of headache in COVID-19 and the common pathways for other viral infections and primary headache disorders remain unknown.

Our rationale indicates that elements of innate immune response can trigger headache, peak early in COVID-19 alongside headache, and play an important role in protecting against severe disease course, allowing for a better prognosis in subjects with COVID-19-related headache. Consequently, it seems likely that interactions between innate immune response (especially in the sinonasal area) and trigeminal system play a crucial role in the aetiopathogenesis of headache secondary to COVID-19.

Moreover, if innate immune reaction to SARS-CoV-2 can trigger headache, then probably similar pathways are activated in other clinical situations (e.g. infections, immunisation, immunomodulatory treatment, autoimmune disorders). Future research should look for evidence of causality between particular immune response factors and headache. If found, such a correlation could have important clinical consequences for diagnosis and treatment strategies in a wide variety of disorders with prominent immune response.

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