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Views and Perspectives

Are Migraine Patients at Increased Risk for Symptomatic Coronavirus Disease 2019 Due to Shared Comorbidities?

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The coronavirus disease 2019 (COVID-19) pandemic has rapidly transformed the whole world and forced us to look through comorbid diseases and risk factors from a different perspective. COVID-19 shows some inherent risk factors like cardiovascular comorbidities independent from age, gender, and geographic location. One of the most peculiar features of the COVID-19 pandemic is that severe acute respiratory syndrome coronavirus 2 respiratory infections disproportionately impact patients with hypertension, diabetes, and other cardiovascular comorbidities rather than those with allergic respiratory diseases and immune-compromised conditions. Migraine is a complex neuro-vasculo-inflammatory disorder that is also packed frequently with certain medical conditions including vascular disorders, hypertension, allergic diseases such as asthma and systemic inflammatory disorders. Accordingly, 2 different questions arise during the pandemic: (1) Do share comorbidities of cardiovascular diseases and hypertension increase the risk of symptomatic COVID-19 for migraine patients? (2) Do comorbid allergic and atopic diseases, including asthma act as opposite influencers alongside with female gender? This paper focuses on the co-existence of comorbidities of COVID-19, in comparison with migraine, based on a wide clinical dataset and available reports. Discussed mechanisms include potential strategic roles of angiotensin-converting enzyme 2, angiotensin-II, and nucleotide oligomerization domain-like receptor family, pyrin domain containing 3 inflammasome, playing remarkable parts in the pathogenesis of COVID-19 and migraine. There are also some clues about the importance of endothelial and pericyte dysfunction and neuroinflammation in COVID-19 infection, related to complications and survival of the patients. The large epidemiological studies as well as basic research, focusing on migraine patients with COVID-19 will clarify these vital questions during the upcoming periods.

Key words: coronavirus disease 2019, migraine, comorbid disorders, nucleotide oligomerization domain-like receptor family, pyrin domain containing 3 inflammasome, pericytes

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INTRODUCTION

While severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) keeps on rapidly spreading around the world and affects more than 32 million people up to now, reports about the neurological manifestations associated with SARS-CoV-2, as a potential predictor of poor outcome are still scarce. It is reported that a variety of symptoms and syndromes such as headache, dizziness, confusion, ataxia, epilepsy, ischemic stroke, neuropathic pain, and myopathy are common especially in more severe coronavirus disease-2019 (COVID-19) patients.[1,2]

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SARS-CoV-2 may cause headache symptoms through direct or indirect mechanisms[3] and could be a new member of neuroinvasive viruses due to the complex nature of the inflammation.[1]

Surprisingly, the risk factors and comorbid disorders of COVID-19 are somewhat different from other respiratory viral illnesses. Hypertension, coronary artery disease (CAD), and cardiovascular diseases (CVD) are among the top comorbid disorders all around the world.[4-25] Other thought-provoking finding was that the male gender was reported to have an increased risk for severe COVID-19.[14,15,16,18] Moreover, several reports recently supplied evidence that allergic diseases including asthma are not risk factors for SARS-CoV-2 infection in contrast to the expectations.[11,26] This controversy drives attention to the unique pathophysiology of COVID-19 and mechanisms of underlying medical conditions inducing susceptibility for the infection.

Migraine is a complex neuro-vasculo-inflammatory disorder with various manifestations beyond headache and significantly prevalent in female gender. Growing evidence, undoubtedly, suggests that certain comorbid diseases are associated with migraine headache.[27-41] Our previous studies on a broad clinical dataset showed a high ratio of vascular diseases and allergic comorbidities including asthma in patients with migraine.[27,42-45] These comorbidities of migraine do not only affect the prognosis requiring appropriate management protocols but also provide clues about the complex nature of its pathophysiology.[42,43] Association of migraine with various diseases including atopic disorders like asthma, systemic inflammatory, rheumatologic, and vascular disorders requires a satisfactory explanation to elucidate mechanisms.

This paper mainly focuses on the potential shared pathways of migraine and COVID-19 infection, in terms of the common cardiovascular comorbidities, allergic diseases, and neuroinflammation based on available reports and our clinical experiences. This paper will also discuss whether migraine patients are more susceptible to symptomatic COVID-19 regarding shared comorbidities.

Conflict of Interest: None

HIGH PREVALENCE OF VASCULAR COMORBIDITIES IN COVID-19 AND MIGRAINE

Recent reports have supported that SARS-CoV-2 provokes the well-known complex clinical pictures of the infection together with the host reaction. The viral entry route, using host angiotensin-converting enzyme 2 (ACE2) receptor seems to be the key mechanism connecting the unusual emergence of hypertension and CAD as remarkable comorbidity.[46,47] Clinical reports on COVID-19-associated vascular comorbidities and allergic diseases including asthma are summarized in Table 1. The methodologies and classifications of comorbidities are highly variable in published clinical reports. Higher prevalence of severe symptomatic COVID-19 illness in males, exceeding 75% in some case series,[14-16] is noteworthy. Hypertension is the most frequent comorbid disorder in COVID-19 patients in different countries with variable rates: 49.7-67.5% in the United States,[19,20] 36.9-54% in Europe,[22,23] and 15-34% in China.[9,13] The comorbidity rate of CAD-CVD is approximately 15%, reaching up to 44 and 48% in Italy and France, respectively.[5,14] Diabetes is observed as a comorbidity in 10-20% of the COVID-19 patients overall, but the corresponding figures are 28.3-58% in the United States.[7,20]

Moreover, allergic diseases or asthma are not investigated in most of the studies. According to a study from China, allergic disorders including asthma are reported by none of the patients,[11] whereas their frequencies are as high as 14% in France,[14] 18% in the United States,[7,20] and 22% in United Kingdom[23] (Table 1).

There is currently no reliable epidemiologic data on the possible risk of migraine for COVID-19. Scientific databases support that age and comorbidities are important factors influencing the phenotype and chronification process as well as defining the optimum algorithm of management in patients with migraine. Migraine comorbidities are more than a chance occurrence, as revealed by studies in Table 2 and Figure 1.[28,29,45] Clinical reports on vascular comorbidities associated with migraine are summarized in Table 2.

The relation between migraine and vascular comorbidity is well established as shown in Table 2.

Table 1.—Clinical Reports on COVID-19-Associated Vascular and Allergic Comorbidities

First Author Year	Country	Study Design	Sample Size	Gender % Male	Allergy Asthma %	Hyper-Tension %	CAD %	DM %
Lodigiani[5] 2020	Italy	Cohort study	388	68	NA	47.2	13.9	22.7
Zhou[6] 2020	China	Cohort study	191	62	NA	30 OR: 3.05	8 OR: 21.4	19 OR: 2.85
Bhatraju[7] 2020	USA	Hospital based	24	63	18	NA	NA	58
Mao[8] 2020	China	Hospital based	214	40.7	NA	23.8	7	14
Guan[9] 2020	China	Nation-wide	1099	58.1	NA	15	2.5	7.4
Wang[10] 2020	China	Hospital based	138	54.3	NA	31.2	14.5	10.1
Zhang[11] 2020	China	Hospital based	140	50.7	0	30	5	12.1
Mo[12] 2020	China	Hospital based	155	55.5	NA	23.9	9.7	9.7
Chen[13] 2020	China	Hospital based	274	62	NA	34	8	17
Helms[14] 2020	France	Hospital based	150	81.3	14	NA	48	20
Aggarwal[15] 2020	USA	Hospital based	16	75	NA	57	19	31
Grasselli[16] 2020	Italy	Regional network based	1591	82	4	49	21	17
Guo[17] 2020	China	Hospital based	187	48.7	2.1	32.6	11.2	15
Wu[18] 2020	China	Hospital based	201	63.7	2.5	19.4	4	10.9
Gold[19] 2020	USA	Hospital based	305	49.5	10.5	67.5	11.5	39.7
Garg[20] 2020	USA	Network based	178	NA	17	49.7	14.2	28.3
Hu[21] 2020	China	Hospital based	323	51.4	9	32.5	12.7	14.6
Lagi[22] 2020	Italy	Hospital based	84	65.5	NA	36.9	14.3	14.3
Lovell[23] 2020	UK	Hospital based	101	64	22	54	NA	36
Cui[24] 2020	China	Hospital based	81	54	NA	25	12	10
Richardson[25] 2020	USA	Hospital based	5700	60.3	9	56.6	11.1	33.8

CAD = coronary artery disease; CVD = cardiovascular disease; DM = diabetes mellitus; NA = not available; OR = odds ratio.

Table 2.—Clinical Reports of Migraine-Associated Comorbidities Based on Cohorts

First Author Year	Country	Study Design	Diagnosis	Sample Size	Gender % Female	Allergy Asthma %	HT %	CAD %	DM %
Yildirim[27] 2018	Turkey	Tertiary headache center data	ICHD-3β	2037 MwA: 225	86.9	9.9	22.9	15.8	17.0
Nuyen[28] 2006	Denmark	Primary care data setting	ICHD-II	3067 MwA: NA	78.7	8.4	10.5	1.9	1.8
McLean[29] 2017	UK	Cross-sectional primary care data	ICHD-3β	9370 MwA: NA	85	12.4	19.2 AHR: 1.18	0.7 AHR: 1.21	6.1 AHR: 1.23
Adelborg[30] 2018	Denmark	Cohort – 18 years follow-up	ICHD-3β	51,032 MwA: 13,076	70.6 71.3	NA NA	3.0 3.0	NA NA	1.4 1.2%
Gudmundsson[31] 2010	Iceland	Population based cohort study	ICHD-II	2023 MwA: 1397	71.7 68.3	NA NA	NA NA	AHR: 1.27 AHR: 1.28	NA NA
Kurth[32] 2006	USA	Cohort – 108 mos follow-up	ICHD-II	3610 MwA: 1434	100 100	NA NA	26 25.5	NA NA	1.6 1.8
Kurth[33] 2007†	USA	Cohort – 188 mos follow-up	ICHD-I	1449 MwA: NA	0	NA	34.2	AHR: 1.24	3.0
Kurth[34] 2020	USA	Cohort- 16 yrs follow-up	ICHD-3	27,858 MwA: 1435	100	NA	AHR: 2.80 AHR: 4.46	AHR: 2.11 AHR: 3.36	AHR: 4.35 AHR: 6.92
Martin[35] 2016¶	USA	Cohort	ICHD-3β	4446 MwA: NA	80.8	17	NA	NA	NA
Chen[36] 2012¶	Taiwan	Retrospective matched cohort	ICHD-II	4738 MwA: NA	78.5	3.52 AHR = 1.77	16.8 AHR: 1.64	8.37 AHR: 1.73	4.7 AHR: 1.08
Buse[37] 2020	USA	Web-based survey	ICHD-3β	15,133 MwA: NA	73	OR: 2.49	OR: 1.51	OR: 1.66	OR: 1.37
Lipton[38] 2018‡	USA	Web-based survey	ICHD-3β	12,810 MwA: NA	76	32	24	NA	9
Martin[39] 2014§	USA	Mailed questionnaire	ICHD-II	17,892 MwA: NA	77.8	OR: 3.75	OR: 1.28	NA	OR: 1.22
Mahmoud[40] 2018	USA	Meta-analysis	ICHD	394,942 MwA: NA	NA	NA	NA	AHR: 1.23 AHR: 1.56	AHR: 1.23
Bigal[41] 2010	USA	Case control	ICHD-II	6102 MwA: 270	80.3 NA	NA NA	33.1 NA	OR: 2.19 OR: 2.99	12.6 NA

†The study included only men using a multivariable model that adjusted for age, history of hypertension, diabetes mellitus, smoking status, exercise, body mass index, alcohol consumption, a high cholesterol level, parental history of MI before age 60 years, and randomized treatment assignments.
‡The cardiovascular comorbidity had more men (22%) had a later age of onset (median, 22 years), and were associated with the least severe phenotype of migraine.
§66.8% of the patients with allergic rhinitis, OR: 1.18 (0.95-1.46). The frequency and headache-related disability of migraine are higher in persons with rhinitis overall.
¶Asthma is associated with an increased risk of new-onset CM, with the highest risk being among those with the greatest number of respiratory symptoms.
††CM sufferers (n = 948) had significantly increased risks of CVD, sinusitis, asthma, gastrointestinal ulcers, vertigo, and psychiatric disorders by 1.6- to 3.9-fold.
AHR = adjusted hazard ratio; CAD = coronary artery disease; CM = chronic migraine; CVD = cardiovascular disease; DM = diabetes mellitus; HT = hypertension; MwA = migraine with aura; NA = not available; OR = odds ratio.

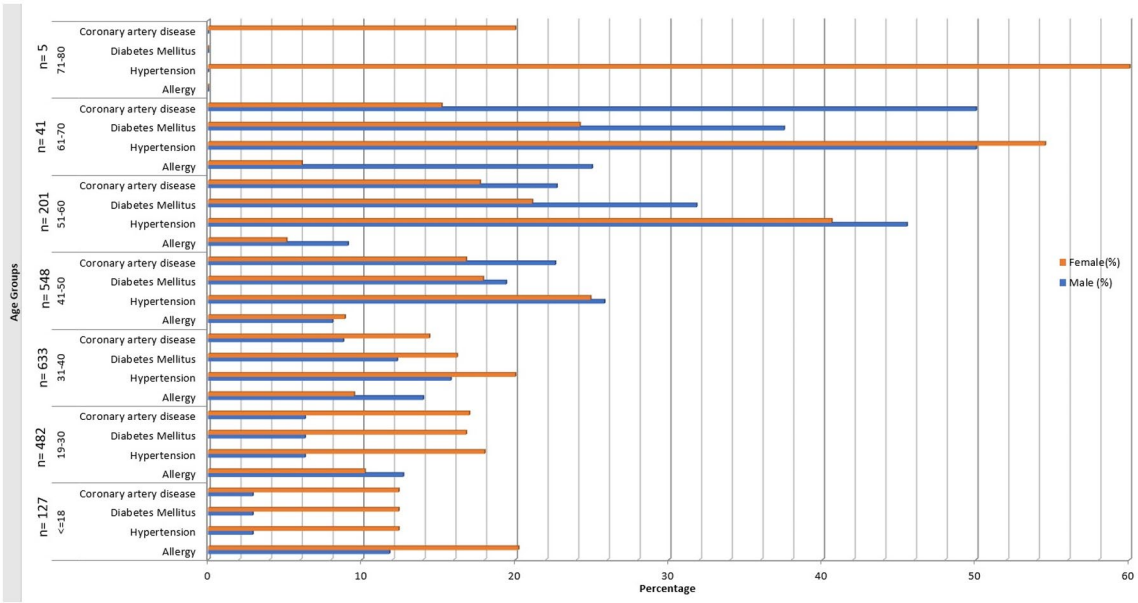

Fig. 1.—The prospective large clinical dataset of a total of 2037 patients with migraine from a tertiary headache center shows female preponderance and high comorbidity rates of hypertension, diabetes mellitus, coronary artery diseases (CADs), and allergic diseases including asthma in patients with migraine.[27] It is notable that the frequency of allergic diseases including asthma is reduced after the age of 50 years, while vascular comorbidities are strikingly increased particularly in women with migraine. Hypertension is more frequent in women and CAD is more frequent in men after age 60.

Regarding increased CVD risk, migraine with aura needs particular attention. A meta-analysis suggested an increased vascular risk only in patients with migraine with aura but not in patients without aura.[48] The risk of ischemic stroke is doubled in migraine with aura, whereas it is uncertain in migraine without aura.[49] Other studies noted that the association of CVD was stronger in patients with aura than in those without aura.[31,40] According to the recent population study, women with migraine with aura had a higher adjusted incidence rate of CVD compared with women with migraine without aura or no migraine[34] (Table 2).

A prospective large clinical dataset of 2037 patients with migraine from a tertiary headache center highlighted the well-known female preponderance and high comorbidity rates of hypertension, diabetes mellitus, CAD, and allergic diseases including asthma in patients with migraine.[27] Some comorbidities were more evident in migraine prognosis, with an impact on the headache frequency and risk of chronic migraine. In this study, Yildirim and colleagues developed a Migraine Comorbidity Index (MigCI) Score[27] in order to determine the potential effect of the recorded comorbidities on migraine attack frequency and an "e-Migraine" application, which is a validated tool to estimate the severity of headache based on MigCI. By the same published methodology,[27] we re-analyzed the dataset, as presented in Figure 1 to show age- and gender-based differences in migraine comorbidities. It is notable that the frequency of allergic diseases including asthma is reduced after 50 years of age, while vascular comorbidities are strikingly increased particularly in women with migraine. The frequency of hypertension is higher in women and CAD is more frequent in men after the age of 60 seconds (Fig. 1). Atherothrombotic risk factors (including hypertension, diabetes mellitus, CAD), and intriguingly, allergies and atopic disorders show significant association with migraine (Fig. 1). High cardiovascular comorbidity in our study is consistent with recent large genome-wide association studies showing the involvement of variants related to vascular gene functions.[50] The distributions of these 4 migraine comorbidities, seen in Figure 1 according to age also imply that especially those migraine patients over 50 seconds may be susceptible to COVID-19.

PUZZLING REVERSE ASSOCIATIONS OF ALLERGIC COMORBIDITIES

Intriguingly, allergic diseases and asthma have been reported as low-risk factors for developing COVID-19 in recent epidemiologic studies, in contrast to other respiratory conditions.[11,26] To tackle this dilemma, Jackson et al. studied ACE2 expression in the upper and lower respiratory tract epithelium following allergen challenge in 3 different cohorts with allergic diseases.[51] They identified a significant reduction in the ACE2 expression in the airway epithelium in patients with allergic rhinitis and asthma. Notably, the lowest ACE2 levels were detected in patients with asthma and highest levels of immunoglobulin E (IgE). Reduced ACE2 expression in patients with allergy and asthma, upon allergen exposure may be related to this decreased risk of severe COVID-19.

A recent study investigated COVID-19 susceptibility in several asthma subgroups. Peters and colleagues examined ACE2 and transmembrane serine protease 2 (TMPRSS2) expression in the sputum cells of 300 patients with asthma. Higher expression of ACE2 and TMPRSS2 was detected in male gender, African Americans, and patients with diabetes mellitus.[52] This result is line with the fact that the presence of other comorbidities and male gender are increased risks for COVID-19.[25] Further research on allergic disorders, respiratory allergy, and asthma is needed to understand the real impact of underlying type 2 inflammatory processes on COVID-19 susceptibility and disease severity.

Patients with migraine show a high ratio of allergic disorders as comorbidity. Furthermore, atopic disorders including seasonal rhinitis, conjunctivitis, and asthma are frequently associated with migraine than tension-type headache (21.6% vs 6.4%).[53] The results of a web-based survey in 15,133 participants showed that increased migraine headache frequency was associated with higher risk of allergic comorbidities such as asthma and hay fever.[37]

At least one atopic disorder was reported by 41.4% of migraine patients. The relative risks for allergic asthma and allergic contact dermatitis were calculated as 1.87 and 1.67, respectively.[54] The latter finding was also recognized in children with migraine, and approximately 1/3 of the children manifested with at least one allergic disorder, including asthma, rhinitis, conjunctivitis, and dermatitis.[42] Complementary to these studies, increased inflammatory cytokine levels were detected in the plasma of migraine patients without any known allergic disorders.[42-44] Furthermore, a clear correlation was noticed between the frequency of migraine attacks and the increased IgE levels indicating the severity of atopic disorders.[42,44]

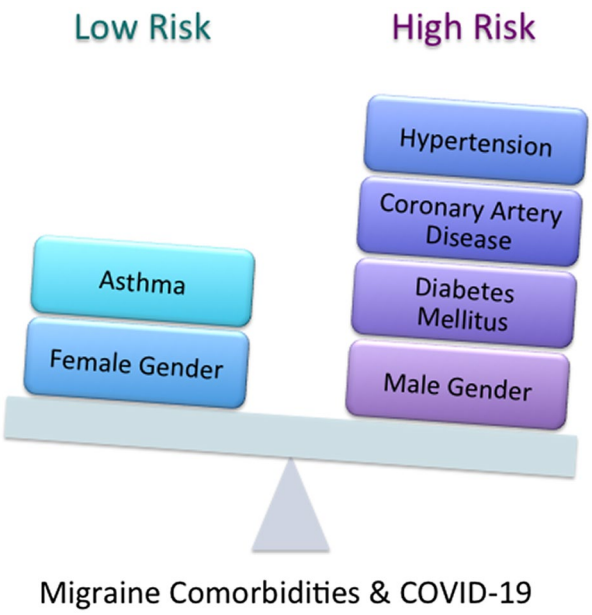

Fig. 2.—Relative frequencies of vascular risk factors, gender, and allergic asthma reported in symptomatic COVID-19 patients. These disorders are all frequent comorbidities with migraine headache.

THE INTERSECTION OF VASCULAR COMORBIDITIES IN COVID-19 AND MIGRAINE

The peculiar feature of the COVID-19 pandemic is that SARS-CoV-2 infections disproportionately impacts on patients with hypertension, cardiovascular comorbidities, compared to patients with respiratory disorders including asthma (Table 1, Fig. 2). The mechanisms of the vasculature-associated manifestations of COVID-19 are poorly understood. However, the identification of transmembrane ACE2 receptor as a key molecule for SARS-CoV-2 virulence brings the angiotensin system into focus.[46,55] Angiotensin II (Ang II) produced by ACE is a key player involved in CVD pathogenesis, hypertension, vasoconstriction, oxidative stress, and nociception through its AT1 receptor (AT1R).[3,55] ACE2 cleaves Ang II into angiotensin 1-7

(Ang 1-7), which decreases the detrimental effects of Ang II/AT1 receptor (AT1R). Ang 1-7 mediates vasodilatation, decrease in blood pressure, vascular and tissue protection, anti-nociception, and anti-inflammatory properties via mitochondrial assembly receptor (MasR) (Fig. 3). Thus, ACE2 exerts synergistic protective effects by both terminating Ang II and also converting Ang II to Ang 1-7, which activates vasodilatatory and anti-inflammatory signals. ACE2 is down-regulated upon SARS-CoV-2 binding, accompanied by reduced Ang 1-7/MasR actions and augmented Ang II/AT1R functions.[3,55]

SARS-CoV-2 entry using ACE2 receptor expressing epithelial cells in the upper and lower respiratory system provides the rationale for common COVID-19 symptoms. Widely distributed vascular cells that express ACE2 may play a role in systemic inflammation, vascular complications, and coagulopathy associated with COVID-19 infection.[56,57] Identification of the cellular targets in the vasculature is important to understand the vascular entry points of the SARS-CoV-2 during viremia. In a post-mortem study, SARS-CoV-2 was detected within vascular cells with diffuse endothelial inflammation.[56] Endotheliitis as a result of the

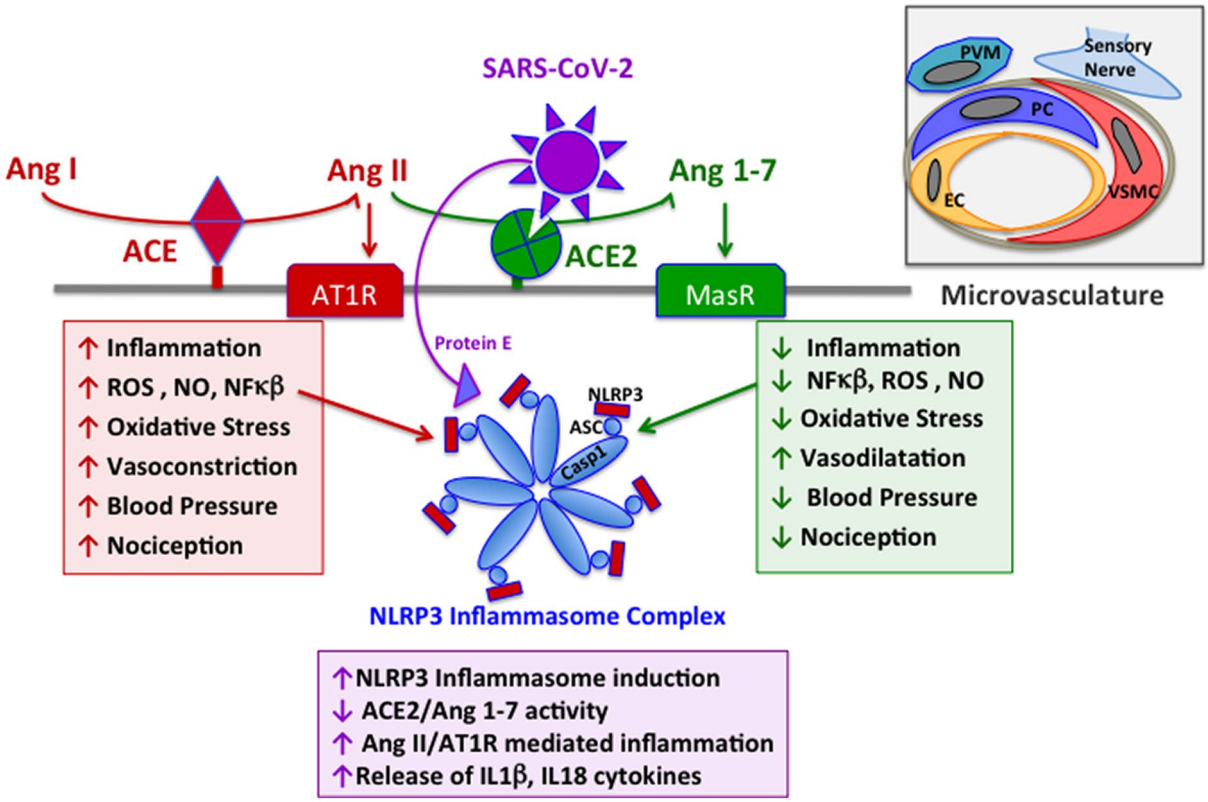

Fig. 3.—The diagram summarizing the hypothetical mechanisms of the inflammatory activation in the microvasculature in COVID-19. Vascular cells involved in regulating microvascular circulation and inflammatory responses are shown in the upper right part; endothelial cells (EC), pericytes (PC), vascular smooth muscle cell (VSMC), perivascular macrophages (PVM), and sensory nerve ending. Angiotensin II/(Ang II) that is produced by angiotensin-converting enzyme (ACE), and its downstream effect via AT1 receptor (AT1R) are the main players in the pathogenesis of hypertension, cardiovascular diseases, and inflammation, tissue damage, and nociception. Conversion of Ang II by ACE2 into Ang 1-7 yields protective functions via Mas receptor (MasR) against detrimental effects of Ang II/AT1R, including vasodilation, blood pressure decrease, vascular and tissue protection, anti-nociception, and anti-inflammatory properties. SARS-CoV binding to the ACE2 and internalization of the complex is the entry route for the virus, which leads to exaggerated inflammatory responses not only through the unbalanced AT1R pathway, but also via direct impact of virus protein E on inflammasome complex. Functional NLRP3 inflammasome complex consists of caspase 1, ASD (apoptosis-associated speck-like protein containing a caspase-recruitment domain), and NLRP3 primed by NF-κβ. The important key regulator of the suggested pathogenesis is the activation of the NLRP3 inflammasome complex, which leads to the release of proinflammatory cytokines of IL-1β, IL-18 recruiting other immune-competent cells and cell injury implicated in a variety of disorders.

synergistic interaction of viral invasion and the host inflammatory response may play a role in the impairment of microcirculatory function in systemic organs. When ACE2-related pathway is discarded upon SARS-CoV-2 binding, several downstream events occur such as unbalanced inflammatory signals, increased production of reactive oxygen species, activation of nuclear factor-kappa beta (NF-κβ), and subsequent NLRP3 (nucleotide oligomerization domain-like receptor family, pyrin domain containing 3) inflammasome. As a result of these processes, proinflammatory cytokines are released causing vasculopathy, circulation, and coagulation problems.[3,55-58]

Chen and colleagues demonstrated that ACE2 was highly expressed in pericytes, suggesting a type of perivascular mural cell may be the actual target in the vasculature for SARS-CoV-2.[57] Any injury to pericytes may lead to the endothelial and vascular dysfunction.[57] The dysfunctions of pericytes, expressing contractile properties, are linked to many microvascular diseases, including hypertension, diabetes, fibrosis, and inflammation. A study posted in bioRxiv stated that ACE2 was specifically expressed in microvascular pericytes, but absent in the endothelial cells and perivascular macrophages.[58] It is intriguing to pinpoint pericytes as the main ACE2-expressing cells in the vasculature. Disrupted barrier function of the endothelium with increased permeability has been associated with hypertension, ischemic heart disease, diabetes, obesity, and aging, which are all risk factors for severe COVID-19 patients.[59,60] Thereby, endothelial barrier breakdown already present in those disorders, may leave pericytes exposed directly to SARS-CoV-2 during viremia and induce complications and adverse outcomes easily in COVID-19. Alternatively, pericytes could also take a role during the CNS entry of SARS-CoV-2 in a similar manner shown for another neurotropic virus recently.[61]

The key role of the angiotensin system in cephalic nociception and the migraine has also been implicated previously.[3,62,63] The expression of Ang II in the neurons of human and rat trigeminal system infers its function in the regulation of cephalic nociception.[63] Ang II is found primarily in small- and medium-sized neurons in the trigeminal ganglia, and majority of Ang II immunoreactivity is co-localized with substance P.[63] Angiotensinergic processes detected in the rat spinal trigeminal tract suggested its role as a neurotransmitter. Ang II leads to increased levels of calcitonin gene-related peptide (CGRP), a key neuropeptide provoking migraine headache as well as the target for effective novel migraine treatment.[64] Moreover, strategies of inhibiting ACE or blocking AT1R are both clinically utilized treatments in preventing migraine attacks.[65] Also, ACE insertion/(I)/deletion (D) gene polymorphism was implicated in migraine headache frequency. ACE-DD genotype was associated with migraine with aura.[66] Remarkably, the ACE-DD gene polymorphism was also implicated in the mortality in acute respiratory distress syndrome.[67,68] Thus, it is tempting to speculate that the ACE genotypes could play a role in both migraine phenotype and COVID-19 illness severity.[3] Taking into account that ACE is a transmembrane metalloproteinase, identification of genes linked to metal ion homeostasis, in addition to the neuronal and vascular genes in large genome-wide association studies in migraine is imperative.[69]

As a complex "neuro-vasculo-inflammatory" disease, vasodilatation in cephalic vasculature and inflammatory process following the sensitization/activation of the trigeminovascular system and CGRP along with other neuropeptide releases are the central mechanisms of migraine attacks.[70,71]

Endothelial cells play a crucial role in the control of vascular signaling process, maintenance of vascular barrier, blood coagulation, and also mediate immune signaling pathways. Intraparenchymal brain vasculature is privileged with the highest ratio of pericytes to endothelial cells. Pericytes, as a key element of the neurovascular unit, participated in microcirculation, cerebral blood flow regulation, and neuroinflammatory response.[72] Dysfunction of pericytes may induce a proinflammatory state, disrupt vasculature exposing perivascular trigeminal nerve endings to inflammatory triggers, and alter homeostasis predisposing vascular events. Some reports support a close correlation between migraine and ischemic vascular events including small lesions or silent deep white matter changes, albeit with the absence of stroke symptomatology,[73] although there have been some inconsistencies in results. The latter data may suggest an increased cerebral vulnerability to ischemia in migraine-susceptible brains especially in migraine patients with aura.[49]

INFLAMMATION AS A SHARED PATHWAY IN MIGRAINE AND COVID-19

Inflammation takes a central role in COVID-19 infection following post-receptor events activated by ACE2 upon viral binding.[74,75] SARS-CoV encoded protein E, necessary for viral virulence, activates the innate immune signaling receptor NLRP3 inflammasome, as well as other inflammatory pathways such as NF-κβ and p38MAPK (mitogen-activated protein kinase).[76,77] The NLRP3 inflammasome is a crucial part of the innate immune defense system (Fig. 3).[74,75] The activation of NLRP3 produces proinflammatory cytokines such as interleukin 1β (IL-1β), IL-18, IL-6, tumor necrosis factor, prostaglandins, and leukotrienes amplify tissue inflammation during COVID-19.[74,75,78] This was confirmed by the finding that IL-1β and other inflammatory cytokines were detected in ACE2-positive, viral receptor-expressing epithelial cells in the respiratory tissues infected by SARS-CoV.[78]

In terms of COVID-19 illness, it is also important to note that the "hyperinflammatory response" induced by SARS-CoV is the main cause of disease severity and death. Deregulation of macrophage reaction may induce damage to the host as evidenced in the case of macrophage activation syndrome or so-called cytokine storm associated with SARS-CoV2. NLRP3 has been shown to be associated with inflammation induced by various factors including viruses.[74-77] It is remarkable that NLRP3 activation was significantly diminished in bat immune cells compared to humans,[79] which may justify the lack of SARS-CoV-2-related disease in these animals. As a flying mammal enduring high metabolic rate, bat is considered to host SARS-CoV2. In line with this, the impact of SARS-CoV occurs either direct by cytotoxic effects of the virus itself or its deviant activation of intrinsic defense response in relation to NLRP3 inflammasomes.[80,81]

Recent evidence implies that NLRP3 inflammasome, by activating proinflammatory cytokines of IL-1β and IL-18, contributes to the pathogenesis of CVDs and hypertension via vascular inflammation.[82,83] The demonstration of NLRP3 activation by Ang II via AT1R ascertains the important association between the angiotensin system and inflammasome complex (Fig. 3).[82,83] Furthermore, microvascular mural cells, pericytes, and brain microglia were reported to induce NLRP3 inflammasome in response to tissue injury and release inflammatory mediators like IL-1β and IL-18.[84,85] NLRP3 inflammasome was also detected in cardiac microvascular endothelial cells following myocardial ischemia/reperfusion injury.[86] The activation of NLRP3 inflammasome has been associated with various pathological processes and disorders including obesity and diabetes.[87] Thus, Ang II and inflammasome activation likely link vascular comorbidities to both COVID-19 and migraine.

The NLRP3 inflammasome may be involved in several neuroinflammatory processes but the exact mechanisms of how an inflammation impact on migraine is ill defined. As a complex neuro-vasculo-inflammatory disease, there is also robust evidence on the roles of various inflammatory players in migraine.[57,71,88,89] Upon induction, trigeminal nerve axons that densely enveloping meningeal vessels, provoke the release of CGRP and other neuropeptides from perivascular terminals, causing vasodilatation, leakage, and inflammation dominated by the activation of perivascular macrophages and mast cells.[57,88] In experimental migraine models, glyceryl trinitrate (GTN)-induced NF-κβ activation and inducible nitric oxide synthase expression in perivascular macrophages in dura mater and NO and proinflammatory cytokines of IL1 β, IL6 release were detected.[88,89] Consistently, GTN-induced hyperalgesia was associated with NLRP3 inflammasome activation and IL-1β expression in microglia in the brainstem trigeminal nucleus.[85] All these studies provide significant proof demonstrating the complex interactions of sensory neurons with vascular and immune-competent cells mediating inflammation, vascular reactivity, and pain response.

In line with this, many studies have underscored that headache occurs more frequently compared to the general population in patients with various types of inflammatory disorders. Migraine without aura is among the most common headache types affecting more than 50% of multiple sclerosis patients.[90] Headache is a remarkable symptom of patients with other systemic inflammatory disorders like systemic lupus erythematosus and Behçet's Disease. However, the association between the headache and various autoantibodies, cytokines, vascular injury, neuronal damage, or a medication-related effect has not been proven yet, to elucidate

the underlying mechanism of these comorbidities. In Behçet's disease, migraine attacks are closely associated with exacerbations of systemic inflammatory findings.[91]

Central as well as systemic inflammatory processes linked to neurological disorders suggest the contribution of complex neuroimmune interplay in the brain across multiple temporal and spatial scales. Growing evidence indicates that common risk factors such as hypertension, atherosclerosis, diabetes, or infections induce the innate inflammasome complex that is also related to neurological disorders.[75,82,83,86,87] Thus, it is tempting to speculate that the inflammasomes triggered by either intrinsic events or external SARS-CoV-2 could be the functional link between migraine and COVID-19.[92] Research is needed to elucidate this hypothetical point to find out promising therapeutic targets.

OPPOSITE INFLUENCE OF GENDER IN COVID-19 AND MIGRAINE

It is well demonstrated that migraine is more prevalent in women and its clinical features are more robust in female gender (Table 2).[93,94] Studies suggest that the effect is predominantly associated with female sex hormonal influence.[93-95] Instead, higher prevalence of severe symptomatic COVID-19 illness was reported in male gender in several series (Table 1).[14-16] In addition, COVID-19 illness is associated with more severe pulmonary involvement and higher mortality rate in men, compared to women.[18,25,96,97] Recent findings of higher sputum cell expression of ACE2 and TMPRSS2 detected in males are also in line with the latter notion.[52] The identification of ACE2 gene mapped to the X-chromosome may provide some clarification to gender susceptibility. Additionally, the regulation of vascular endothelial cell functions by estrogens[98] may also play a role in different CVD risk in women. Another interesting point is that estrogens and progesterone interact with the inflammasome activation and attenuate proinflammatory cytokine activity in several disease models including ischemic vascular diseases.[99] Therefore, female sex hormones may exert anti-inflammatory actions partially through inflammasome activation.

CONCLUSION

We posit that migraine patients are exposed to increased risk for COVID-19 due to angiotensin system and NLRP3 inflammasome-mediated mechanisms associated with vascular and inflammatory comorbid disorders, especially in relation to advancing age. Participations of NLRP3 inflammasome complex and pericyte dysfunction, also important in SARS-Cov-2-related pathophysiology, may contribute to the neuro-vasculo-inflammatory mechanisms of migraine. Yet, the female preponderance of migraine and type-2 allergic response may act in the opposite direction counterbalancing the increased risk for COVID-19. The clinical research focusing on migraine and COVID-19 patients will clarify this dilemma.

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