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COVID-19 is a Real Headache!

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Abstract

After the emergence of a novel coronavirus named SARS-CoV-2, coronavirus disease 2019 (COVID-19) was initially characterized by fever, sore throat, cough and dyspnea, mainly manifestations of respiratory system. However, other manifestations such as headache, abdominal pain, diarrhea, loss of taste and smell were added to the clinical spectrum, during the course of the COVID-19 pandemic. The reports on the neurological findings are increasing rapidly and headache seems to be the leader on the symptom list. Headache was reported in 11-34% of the hospitalized COVID-19 patients, but clinical features of these headaches were totally missing in available publications. According to our initial experience, significant features of headache presentation in the symptomatic COVID-19 patients were new onset, moderate-severe, bilateral headache with pulsating or pressing quality in the temporo-parietal, forehead or periorbital region. The most striking features of the headache were sudden to gradual onset and poor response to common analgesics, or high relapse rate, that was limited to the active phase of the COVID-19. Symptomatic COVID-19 patients, around 6-10%, also reported headache as a presenting symptom. The possible pathophysiological mechanisms of headache include activation of peripheral trigeminal nerve endings by the SARS-CoV2 directly or through the vasculopathy and/or increased circulating pro-inflammatory cytokines and hypoxia. We concluded that as a common non-respiratory symptom of COVID-19, headache should not be overlooked, and its characteristics should be recorded with scrutiny.

After the emergence of a novel coronavirus named SARS-CoV-2, causing coronavirus disease 2019 (COVID-19) with a severe and deadly pneumonia in Wuhan, China, our known world has changed dramatically. COVID-19 is initially characterized by fever, sore throat, cough and dyspnea, mainly manifestations of respiratory system (1, 2). However, other manifestations such as headache, abdominal pain, diarrhea, loss of taste and smell and frost-bite like skin lesions have been added to the clinical spectrum, during the follow-up of increased number of patients within 3 months. Neurologists are involved in many places together with all other physicians and health personnel in the war against the pandemic. Nowadays, the reports on the neurological findings are increasing rapidly and headache seems to be the leader on the symptom list.

The available reports related to headache symptom in patients with COVID-19 do not contain any details about headache characteristics (Table-1) (1-13). A recent meta-analysis (n=3598 patients) and a handful of reports disclosed that headache is among the COVID-19-related symptoms with a rate mostly around 11-14%, in patients who had either died or recovered (3-5). A higher rate reported was 34% from Zhejiang province, China in a small series of 62 patients with a milder course compared to Wuhan, but no further details about the characteristics of the headache or prior headache history were given (6). In a series of 262 confirmed cases of the COVID-19 in Beijing, the most common symptoms at the onset of illness were cited as fever, cough, fatigue, dyspnea followed closely by headache with a rate of 6.5% (7). Similarly, Wuhan group also reported a headache rate of 8% as a less common symptom, among the symptoms at onset of the illness (8-9). Another study draws attention to non-classical symptoms in 74 confirmed COVID-19 cases with gastrointestinal symptoms out of 651 patients (11.4%) and

indicated that 21.62% of them had significantly higher rates of headache compared to other patients without gastrointestinal symptoms. They interpreted this finding as caused by their higher fevers and increased electrolyte imbalance, but no evidence was available in the report (10). Of the healthcare workers (n = 803) with mild symptoms, 90 were SARS-CoV-2 positive and headache was among the early symptoms associated with the positivity in the predictive statistical model together with anosmia, myalgia, ocular pain, general malaise, extreme tiredness and fever, as reported in a questionnaire. Headache was reported in 64/90 (71.1 %) health care workers with positive SARS-CoV2, while it was present in 296/713 (41.5 %) health care workers with negative SARS-CoV2 (11).

The penetrance of brain parenchyma by COVID-19 is not investigated in autopsy findings, yet. Headache attributed to viral meningitis or encephalitis should be suspected, whenever headache is associated with fever, neck stiffness, light sensitivity and nausea and/or vomiting according to International Classification of Headache Disorders-III (ICHD-III) (14). While enteroviruses account for most cases of headache attributed to viral meningitis or encephalitis, a long list of other viruses may also be responsible (ICHD-III, 9.1.2)(9). However, confirmed viral central nervous system (CNS) infection accompanying COVID-19 is not that frequently observed. A suspected case with acute hemorrhagic necrotizing encephalopathy in US was reported with striking bilateral mesial temporal, and thalamic MRI findings, presenting with headache and confusion (15). Afterwards, a single case was reported diagnosed with cerebrospinal fluid (CSF) polymerase chain reaction and typical lung computerized tomography (CT), with otherwise typical clinical picture including headache (16). Thus, all reported patients with headache

symptom did not seem to be a presentation of viral CNS infection, since this complication is rare.

Headache caused by and occurring in temporal association with a systemic viral infection, in the absence of meningitis or encephalitis is well-known clinically and included in the ICHDIII classification as a separate heading (14). However, the underlying mechanisms are not elucidated yet. This headache was mostly described as diffuse pain of moderate or severe intensity, which is also the case in our anecdotal observations of COVID-19. It was noted that headache commonly coexists with fever, but headache can also occur in the absence of fever, suggesting clearly, under different circumstances the pain may have different mechanisms. Fever induced exogenously by pyrogens, such as inflammatory mediators, microorganisms, antigen-antibody complexes, complements, stimulated interleukin (IL)-1, interferon (IFN)-alpha and tumor-necrosis factor (TNF) (17).

In our experience in limited symptomatic COVID-19 patients, we have observed new onset moderate-severe bilateral headache with pulsating or pressing quality, exacerbated by bending over, in the temporo-parietal region or sometimes more anteriorly to the forehead, periorbital area and sinuses. Headache, reported by symptomatic COVID-19 patients was around 10% and headache was a predominant or primary symptom leading patients to seek medical attention. The most striking features of the headache were sudden to gradual onset and its resistance to common analgesics, or high relapse rate, that was limited to the active phase of the COVID-19. The association of COVID-19 and other primary headaches including migraine was not reported yet. In our limited experience, migraine patients easily noticed the rapid and unique onset of COVID-19 related headache, and lack of osmophobia while photophobia and phonophobia were

still distressful. Some patients described a sudden onset headache along with inflammatory findings and with or without accompanying respiratory manifestations. In a few patients, it was very intractable causing suicidal ideation. Most of these patients had no previous history of tension type or migraine headache, and they usually did not develop additional neurologic findings.

***Case Vignette**:* A sixty-five-year-old male patient admitted with severe headache and ageusia (1st April 2020). He had non-complicated diabetes mellitus for 20 years. He did not have any fever or other respiratory tract symptoms at admission, but lung CT ordered due to close contact history with family members with COVID-19 showed mild but otherwise typical ground-glass involvement pattern. Next day, his fever increased to 37.8 C, but his main complaint was still a severe headache, which he experienced for the first time in his life. The headache was bilateral and throbbing without any nausea or photophobia and accompanied by fatigue and loss of appetite. He received hydroxychloroquine, azithromycine and oseltamivir for five days according to the protocol. The severe headache persisted nine days, partly relieved with high doses of paracetamol and appeared thereafter. The patient recovered fully but lost a substantial amount of weight. His wife, aged 59 years without any prior headache history, had PCR-confirmed COVID-19 presented with fever, cough, nausea and diarrhea. She described her new-onset headache "very distressing" and reported that it lasted about 3-4 days only. This couple typically illustrated that patients without any prior headaches may present with a severe headache as an initial and the main sign of COVID-19, which lasted 3-9 days according to the COVID-19 course along with other various symptoms. If headache was ignored as a symptom of COVID-19, there will be delay in diagnosis, causing further infection in the community.

What would be the underlying mechanisms of headache in COVID-19?

ACE is the key enzyme producing angiotensin II (Ang II) that is involved in cardiovascular disease pathogenesis, vasoconstriction, and oxidative stress (18) (Fig 1). On the contrary, ACE2 degrades Ang II to generate heptapeptide Ang 1-7 that counteracts the ACE/ Ang II/ AT1 receptor (AT1R) axis with opposite functions including cardiovascular protection, vasodilation, anti-oxidative stress, tissue protection and anti-nociception (Fig-1). Thereby ACE2 not only terminates Ang II but also generates a peptide that exerts opposite effects of Ang II/AT1R axis (19). Angiotensin-converting enzyme 2 (ACE2), a transmembrane metalloproteinase was identified as a host receptor for SARS-CoV2 entry into the cells (20). Upon SARS-CoV2 binding, internalization of ACE2 downregulates its functions, leaving Ang II/AT1R actions unbalanced.

First possibility for mechanisms of headache associated with COVID-19 could be a direct invasion of trigeminal nerve endings in the nasal cavity by the SARS-CoV-2. In the brain, ACE2 expression is detected mainly in neurons, beyond the well-known cardiovascular distribution, such as motor cortex, caudoputamen, thalamus, raphe nucleus, solitary tractus, nucleus ambiguus (21). Dysregulation of ACE2/Ang1-7/MasR axis was implicated in stroke, cognitive decline, Alzheimer's disease and Parkinson's disease and pain (22, 23). The production of Ang II locally in the neurons of rat and human dorsal root ganglia (DRG) and its co-localization with substance P and calcitonin gene related peptide (CGRP) may indicate a participation and function of Ang II in the regulation of nociception (24).

The presence of angiotensin system in the human and rat trigeminal ganglia further supports this theory (25). However, the presence of transmembrane ACE2 as a necessary component for

virus binding has not been shown in peripheral trigeminal nerve endings yet, though ACE2 expression is detected in other cranial nerves related to olfaction and gustation (21, 23). Also, Ang II increases circulating levels of CGRP (26), which is a key neuropeptide in migraine, as CGRP provokes headache and its antagonism is effective in migraine treatment (27).

Secondly, vascular pathogenesis via involvement of endothelial cells with high expression of ACE2 could play a role in the trigeminovascular activation leading to headache. SARS-CoV-2 virus enters the body through ACE2 antigen mainly expressed on respiratory epithelial cells, but this antigen has also been expressed on gastrointestinal epithelial cells as well as endothelial cells and cardiac tissues. SARS-CoV-2 virus has recently been demonstrated in the endothelial cells along with findings of diffuse endothelial inflammation (28). Increased D-dimer levels have been linked to poor prognosis of patients, and a thrombotic tendency along with the findings septic shock and multi-organ failure has been described in severe COVID-19 cases. Unbalanced vasoconstriction, oxidative stress and free radical formation upon down regulation and internalization of transmembrane ACE2 by the virus binding may lead to vasculopathy. Perivascular trigeminal nerve fibers would be stimulated sequentially in the nasal, oral cavity, around and cephalic vessels and in the dura mater. On the other hand, there is no clear findings of COVID-19 associated vasculopathy yet.

As a similar model, recent-onset intractable headache is a common feature of giant cell arteritis (GCA), and it can be seen as the initial manifestation of the disease without any other occlusive vasculopathy findings. Its immunopathology is not clearly understood as yet, but most of the genes related to GCA are involved in endothelial function, innate immunity system, cytokines and cytokine receptors (29). Interestingly, in a small proportion of GCA patients, especially in

those with negative temporal artery biopsy findings, this clinical picture has been linked to Varicella zoster associated vasculopathy, and the viral antigens could be detected in the biopsy samples, intriguingly (30, 31). Enlarging spectrum of clinical findings suggest that we need to collect more information to describe COVID-19 associated vasculopathy, which may be associated with the new-onset headache along with inflammatory findings and other clinical features.

Third option underlying headache is that the release of pro-inflammatory mediators and cytokines may trigger perivascular trigeminal nerve endings during the course of the COVID-19 infection. Neuroinflammation and various inflammatory mediators such as IL-1 beta, NFκb, PGE_2, nitric oxide (NO) are well-known to play a role in trigeminovascular activation (32-34). Prevalent headache in severe cases (17%) versus 10% in milder cases, reported by a recent study from Wuhan, could suggest the inflammation and hypoxia correlated with the disease severity may take a part (1, 4). Recently, it was also reported that compared with non-ICU COVID-19 patients, ICU patients had higher plasma levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP1, MIP1A, and TNF (8). Moreover, it is known that pyrogenic fever involves inflammatory mediators in the hypothalamus containing cytokines, glutamate, PGE_2, NO, and reactive oxygen species; besides the principal cells in this part, microglia, macrophages, astrocytes, blood brain barrier, and endothelial cells (35).

Recent large-scale genome-wide association studies (GWAS) in migraine have identified over 40 common DNA sequence variants, showing robust association with migraine, mostly related with vascular and neuronal mechanisms, but also with “metal ion homeostasis”, surprisingly (36). This rather unexpected finding implements the hypothesis that disturbances of metal ion

homeostasis might contribute to migraine susceptibility. Given the fact, that ACE2 is one of metalloproteinases, and also that ACE inhibitors can be effective prophylactic agents for reduction of migraine frequency, it seems worth to plan further studies on the role of ACE2 in headache pathophysiology. Angiotensin-I-converting enzyme (ACE) inhibitors and AT1R blockers are effective in migraine prophylaxis (36). In humans, serum ACE levels are strongly genetically determined. ACE insertion (I)/deletion (D) genotypes of migraine patients showed the higher incidence of the D/D genotype in migraine with aura patients. ACE-DD gene polymorphism was also suggested in determining the migraine attack frequency pattern (38). Interestingly, the ACE-DD genotype frequency was increased in the patients with acute respiratory distress syndrome (ARDS), and this genotype was significantly associated with mortality in the ARDS group (39). It is important to note that human ACE2 gene, mapped to the X chromosome, may also have a role in significant male preponderance in COVID-19 mortality.

We appreciate that the headache type of COVID-19, being a secondary complaint of a common primary disorder, is somewhat nonspecific and diverse. We have nevertheless should attempt to identify its characteristics and underlying associations with growing clinical experience and new research technology.

It should also be emphasized that management of preexisting migraine with avoidance of in-person clinic and emergency department visits is important in terms of current societal goal of maintaining social distance during the COVID-19 pandemic (40). Furthermore, a recent study highlighted that, healthcare workers in Singapore, mandated to wear personal protective equipment (PPE) such as N95 face mask and protective eyewear develop de novo PPE-associated headaches or exacerbation of their pre-existing headache disorders (41).

There is also the possibility that COVID-19 as a trigger for headache may induce chronic headache disorders such as new daily persistent headache. Therefore, the careful follow-up the COVID-19 patients will be more important in the next months.

In conclusion, as a common non-respiratory symptom of COVID-19, headache should not be overlooked, and its characteristics should be recorded with scrutiny. After defeating the pandemic well-recorded large clinical repository may revolutionize our understanding of triggering in pain matrix by viral antigens.

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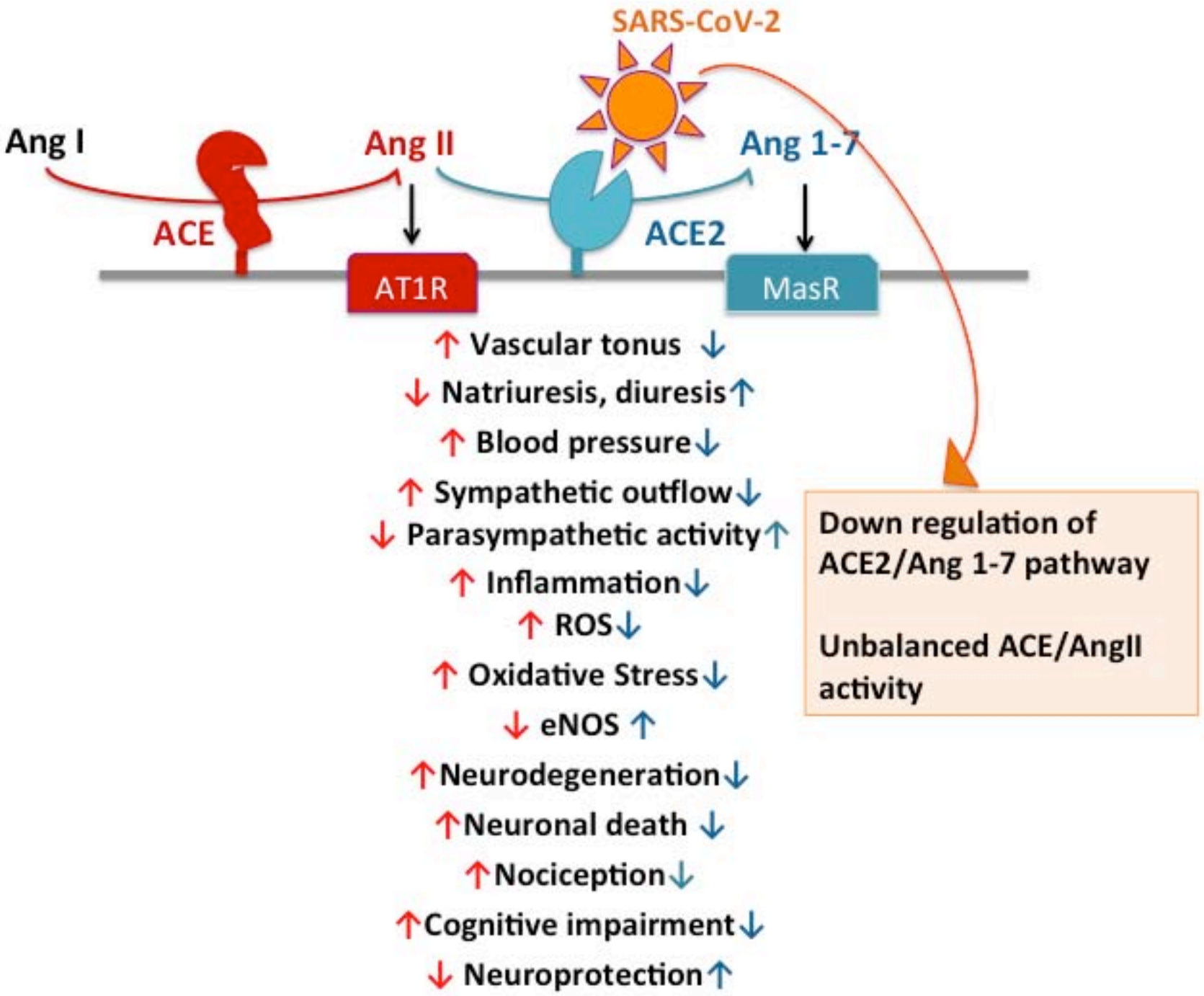
Figure Legend: Schematic diagram of pathophysiological role of Angiotensin-converting enzyme 2 (ACE2) in COVID-19. Angiotensin II (Ang II), produced by ACE, acts through AT1 receptor (AT1R) and mediates various functions all around the body including peripheral and central nervous system (red arrows). On the contrary, Ang 1-7 generated by cleavage of Ang II by ACE2, acts through Mas receptor (MasR) and exert opposite functions (green arrows). Thereby, ACE2 not only terminates Ang II but also generates a peptide, counterbalancing the effects of Ang II/AT1R axis. Upon SARS-CoV2 binding, internalization of ACE2 downregulates its protective functions, leaving pathogenic Ang II/AT1R actions unbalanced.


SARS-CoV-2
Ang I
Ang II
Ang 1-7
ACE
ACE2
AT1R
MasR
↑ Vascular tonus ↓
↓ Natriuresis, diuresis ↑
↑ Blood pressure ↓
↑ Sympathetic outflow ↓
↓ Parasympathetic activity ↑
↑ Inflammation ↓
↑ ROS ↓
↑ Oxidative Stress ↓
↓ eNOS ↑
↑ Neurodegeneration ↓
↑ Neuronal death ↓
↑ Nociception ↓
↑ Cognitive impairment ↓
↓ Neuroprotection ↑
Down regulation of ACE2/Ang 1-7 pathway
Unbalanced ACE/AngII activity