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HEADACHE MANIFESTATION OF COVID-19: A CASE SERIES AND NARRATIVE REVIEW

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ABSTRACT

Despite the typical primary symptoms reported, the coronavirus disease 2019 (COVID-19) outbreak could be manifested as many symptoms. Neurological manifestations of COVID-19 are hypothesized to be caused by multiple pathophysiologies. As one of the possible prodromal symptoms in the absence of fever and respiratory symptoms, many individuals might be unaware of contracting COVID-19 infection and could possibly infect other people. This case series involved a hundred and twenty COVID-19 patients in which nine of them reported headaches as the chief complaint to provide the prevalence rate. Medical histories were assessed to provide the prevalence rate and laboratory findings of involved subjects. Narrative review of possible mechanisms of the manifestation were also denoted. To date, the proportion of non-specific manifestations as the first symptom needs to be further explored as it could be one of the initial symptoms and early manifestations of COVID-19.

Keywords: COVID-19, coronavirus, headache, neurologic manifestations, SARS-COV2

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused the COVID-19 global pandemic was initially developed in China at the end of 2019. Later on 30 January 2020, WHO declared COVID-19 a pandemic and public health emergency.[1] The data from Indonesia on 25th May 2020 showed 23.165 cases and 1.418 (6,1%) deaths.[2]

The primary symptoms of COVID-19 include fever, dry cough, and fatigue.[3] The novel data in affected areas showed that some patients diagnosed with COVID-19 had not shown typical respiratory symptoms, such as fever and coughing. There were a few groups of patients that only expressed neurological symptoms as the initial symptoms, such as the following: (1) headache, languidness, unstable walking, and malaise; (2) cerebral hemorrhage; (3) cerebral infarction; and (4) other neurological diseases. Those symptoms may be due to non-specific manifestations caused by COVID-19, but the exact proportion of non-specific manifestations as the first symptom needs to be further explored.[4]

The COVID-19 related neurological manifestation is hypothesized to be caused by multiple factors such as damage to specific receptors, secondary hypoxia, cytokine-related injury, and retrograde travel along the olfactory nerve and bulb.[12]

Even though COVID-19 is not originally neurotropic, clinical outpatient clinics must consider a group of COVID-19 patients that only expressed neurological symptoms.[5]

The mechanism by which COVID-19 could manifest in neurological symptoms, especially headache, remains unclear. It is presumed that the role of SARS-CoV-2 functional receptors (ACE2) and several biomarkers induced SARS-CoV-2 infection resulting in COVID-19.[4] The data from 214 COVID-19 showed that 78 (36·4%) patients had neurological manifestations, such as headache, dizziness, acute cerebrovascular diseases, and impaired consciousness.[4] Given its prevalence, people can transmit the disease without them knowing hence the need to study this matter further. In this case series, we report confirmed COVID-19, where the headache was the primary initial manifestation. We also perform a narrative review of the current literature.

Methods

This case series investigated patients with confirmed diagnosis of COVID-19 infection based on real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) analysis in Bethesda Hospital, Yogyakarta, Indonesia, in the period of August 2020 until January 2021. The Research Ethics Committee approved the study of Bethesda Hospital Yogyakarta, Indonesia. Every subject involved in the study gave verbal consent to the researcher.

Demographic characteristics, present symptoms, and headache data were obtained from systematic history taking. Laboratory findings were retrieved from Bethesda Hospital Yogyakarta laboratory. Trained physicians gave all interpretations.

Table 1. Summary of Cases

Case	Age (Sex)	Symptoms	Laboratory Findings					Status
			Leukocyte (thousand/mm³)	Total Lymphocyte (10³/μL)	NLR	CRP	O₂ Saturation	
1	41 (F)	Headache, diarrhea, bronchopneumonia	24·50 (H)	1·2 (L)	2·75	66·56 (H)	98	Alive
2	31 (M)	Headache, fever, sore throat	32·80 (H)	2·6	1·73	2·06	94	Alive
3	31 (F)	Headache, fever	25·40 (H)	2·7	2·37	4·8	94	Alive
4	25 (F)	Headache, fever	17·00 (H)	1·8	4·44 (H)	24·96 (H)	97	Alive
5	34 (F)	Headache, fever	32·10 (H)	1·7	1·88	1·04	97	Alive
6	35 (F)	Headache, fever	36·40 (H)	1·3 (L)	1·31	7·25	96	Alive
7	35 (F)	Headache, fever	34·40 (H)	3·3	1·76	3·23	97	Alive
8	34 (M)	Headache, fever, pneumonia	24·4 (H)	2·4	2·67	21·7 (H)	95	Alive
9	48 (M)	Headache, shortness of breath, pneumonia	10·4	1·1 (L)	8·27 (H)	228·46 (H)	62·4	Dead

Notes: CRP: C-Reactive Protein; F: Female; M: Male; NLR: Neutrophil-to-Lymphocyte Ratio
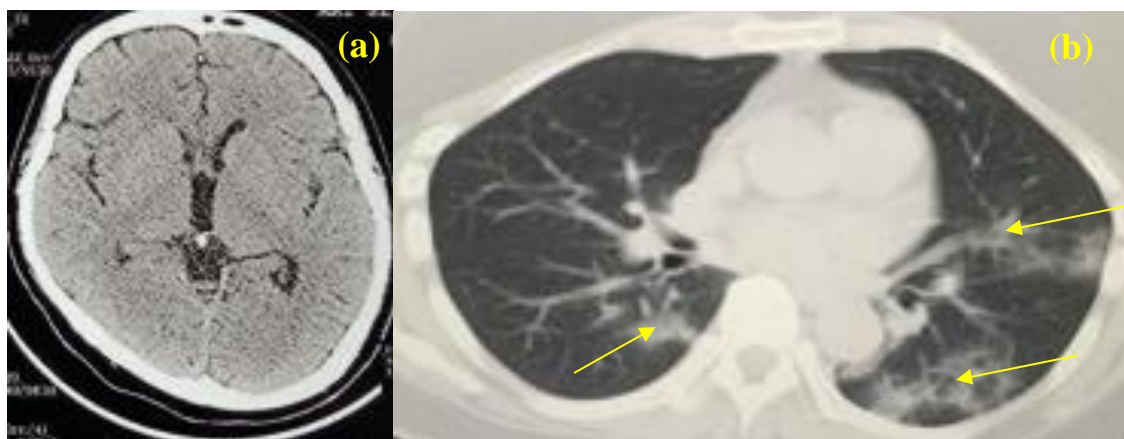
Figure 1. Head and Lung Computed Tomography Scan of Case 9; a 48-years-old male with COVID-19 confirmed and severe headache at presentation denoting (a) Normal brain, and (b) Ground-glass opacity in the chest (yellow arrow).

Discussion

Neurologists and general practitioners are involved with all other physicians and health personnel to deal with the pandemic. This report presented an interesting case due to the lack of clear and specific clinical symptoms in the patients with COVID-19. This type of case is challenging, leading to missed or erroneous diagnoses that may increase the chance of transmitting the infection. In addition, due to the absence of fever and respiratory symptoms as the chief complaints, such patients with COVID-19 might be unaware of being infected. The reports on the neurological findings are increasing rapidly, and headache seems to be the most prevalent symptom among the other neurological manifestations.[4,6] In this study, out of 120 patients, 9 patients (7.5%) complained of some type of headache. The data from the Indonesian task force for COVID-19 showed that headache present in 23.7% of cases.[2] Still, the available reports related to headache symptoms in patients with COVID-19 do not contain any details about headache characteristics.[2,7] Recent systematic review showed that headache is among the COVID-19-related signs with a rate mostly around 11-14%, in patients who had either died or recovered.[8]

The available reports on COVID-19 have not emphasized the nature of headaches. A meta-analysis of 3598 patients has shown headaches present in 10-14% of patients infected with COVID-19.[9] In a series of 262 confirmed cases of the COVID-19 in Beijing, the most common symptoms at the onset of illness was cited as fever, cough, fatigue, and dyspnoea, followed closely by headache with a rate of 6.5%.[10] Similarly, a study from Wuhan reported headaches as a less common symptom, present in 8% of cases.[3] In a study by Mannan et al. among 50 pediatric patients, the headache was present in only 3 cases. Most of them had encephalopathy, brainstem, cerebellar signs, and muscle weakness.[11]

The mean age of the subjects in this study was relatively young (34.8 years old) and dominated by females (66.6% or

6 out of 9), consistent with the previous study.[12] The reason behind this is unknown, but it is assumed that the younger population has higher mobility and is thus susceptible to infection. The gender difference was analyzed previously but provided no potential mechanism. Higher intensity of headache and its phenotype were hypothesized to be related to a higher prevalence of migraine.[13]

The mechanism of headache in COVID-19 could be via direct invasion of trigeminal nerve endings in the nasal cavity by the SARS-CoV-2.[14] The vascular pathogenesis via involvement of endothelial cells with high expression of ACE2 could play a role in the trigeminovascular activation that causes headache.[15] The release of pro-inflammatory cytokines may trigger perivascular trigeminal nerve endings. The inflammatory mediators such as IL-1 beta (Interleukin-1 beta), NFκb (nuclear factor kappa-light-chain-enhancer of activated B cells), PGE2 (Prostaglandin E2), NO (Nitric Oxide) are well-known to play a role in trigeminovascular activation.[14,16] The activation and overproduction of inflammatory cytokines could also be linked to fever reported by all subjects and elevated CRP reported by 4 out of 13 subjects (>10 mg/ L), indicating a systemic infection process. Elevated CRP was reported in case 1, case 4, case 8, and especially in case 9 (44.4%) indicating a prominent inflammatory process. Elevated CRP may be a valuable early marker in predicting the progression of the disease in COVID-19 patients.[9] However, specifically, Trigo et al. stated that subjects complaining of headaches were not likely to have elevated CRP[12] even though no known theory supported this topic. Alongside CRP, total leukocyte, lymphocyte count, and NLR were independent predictors of COVID-19 mortality.[9,17] A normal range of leukocytes was found in only 1 patient (case 9). A previous study noted a higher amount of leukocytes to be the predictor of mortality, but most severe cases also present normal leukocytes.[3,17]

Lymphopenia was found in 2 recovered patients (case 1 and case 6) and 1 dead patient (case 9). Previous studies stated that low lymphocyte count ought to be the predictor of poor prognosis, as the damage to the immune system extends.[9,18] The falling of lymphocyte count coincides with raising the neutrophil count could indicate the cytokine storm of SARS-CoV-2-infected patients.[18]

Since infected patients are contagious during the incubation period, these patients with atypical presentations represent an important hidden source of the spread of the virus. Physicians should inquire about the detailed medical history of each patient in more detail. In this atypical case, routine blood tests, and chest CT should be considered.[6]

This case series ought to shed pioneer for other researchers studying the same topic, especially in Indonesia However, there are a few limitations in this study. We could not obtain the patient's history regarding vaccination against COVID-19. The characteristics of headaches were also not included in this study.

Conclusion

We concluded that headaches could be associated with COVID-19 signs and symptoms based on their pathophysiology relating to the angiotensin system, inflammatory cytokine, and trigeminovascular activation.

Headache might be an isolated symptom of COVID-19, which could not be reckoned in asymptomatic patients, thus provoking dire needs for quick and reliable pathogen tests.

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Conflict of Interest

The author reports no conflicts of interest in this work.

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