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Review Paper

Transient global amnesia after COVID-19: A systematic scoping review of case reports

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Abstract
Background: Transient global amnesia (TGA) is a sudden-onset transient memory impairment along with intact neurologic examinations. Even though it is a benign neurologic condition with many differential diagnoses, the incidence rate of TGA is reported to have increased since the onset of the pandemic. Therefore, this systematic scoping review aims to investigate TGA in that context.
Methods: MEDLINE, Scopus, and Google Scholar databases were systematically searched for relevant articles with a string of specified keywords.
Results: The primary search yielded 90 studies. After all the necessary screening rounds were carried out, we were left with six included studies. One study was also identified through a search in other relatively relevant databases. Finally, seven case reports were accepted including three TGA patients with positive and one with negative test for coronavirus disease-2019 (COVID-19), respectively. COVID-19 status was unclear in the others.

Conclusion: The reported COVID-19 positive cases had presentations similar to those with TGA before the pandemic. Therefore, we think that TGA might occur concomitantly with the COVID-19 infection or due to the psychological impact of the pandemic. In the confirmed cases of TGA and COVID-19, the abnormal findings may be due to COVID-19 infection. However, the reports were not as complete as desired. Therefore, providing the readers with more detailed reports in future cases is recommended.

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Introduction

In December 2019, an unusual respiratory infection caused by a novel coronavirus emerged in Wuhan, China, and soon developed into the current coronavirus disease-2019 (COVID-19) pandemic. The symptoms of COVID-19 infection present after an approximately 5-day incubation period. Fever, cough, fatigue, dyspnea, headache, diarrhea, and lymphopenia are among the most common presentations, and death may occur in patients with more complicated involvements.[1] COVID-19 may affect other organs in a multi-organ manner and manifest as hematologic, gastrointestinal, renal, hepatic, cardiac, and neurological presentations.[2]

It has been shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can enter the central nervous system due to its neurotropic capabilities and, therefore, invade neurons.[3] Consequently, since the evolution of the COVID-19 pandemic, different neurologic manifestations, including brain fogs,[4] arterial strokes,[5,6] cerebral venous thrombosis,[7,8] cerebellitis,[9] meningitis,[10] impairments of consciousness, seizures, and various encephalopathies[11,12] have been reported.

As one of the less frequent neurologic complaints, transient global amnesia (TGA) is a sudden-onset impairment in anterograde memory which lasts up to 24 hours. Although retrograde memory may be involved in some cases, other neurologic functions stay intact.[13] People in their 50s to 70s have been found to have a higher risk of experiencing TGA.[14] Even though this condition is benign, there are differential diagnoses to consider, including transient ischemic attack,[15] strokes, seizure and post-ictal state, and metabolic and psychogenic causes.[13] Overall, three primary mechanisms contribute to the pathophysiology: migraine-related, epileptic, and vascular (i.e., hypoxia or ischemia) etiologies.[13] Although some studies report no magnetic resonance imaging (MRI) changes in patients with TGA,[16,17] other studies have made a case regarding findings in early performed imaging, often reversible.[13]

TGA is less frequently discussed in the context of the COVID-19 pandemic. In one study, a noticeable rise in the incidence of TGA since the onset of the COVID-19 pandemic has been reported.[18] Therefore, we conducted a preliminary search in the PubMed and Cochrane Library databases, looking for relevant systematic or scoping reviews, but none were found. Thus, we designed this systematic scoping review to address the increased occurrence and the possible association between TGA and the COVID-19 pandemic, since this neurological condition has been less discussed in the context of the pandemic.

Materials and Methods

This scoping review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-SCR).[16]

Databases and search strategy: We systematically searched PubMed, Scopus, and the Google Scholar databases for published studies, and the grey literature for unpublished papers from 17th to 18th July, 2021. We did not apply any restrictions on time and language. The search combined terms, keywords, and subject headings were based on the following concepts: "transient global amnesia", "TGA", "coronavirus", "COVID-19", and "SARS-CoV-2". The search strategy for PubMed was: ["Amnesia, Transient Global" (Mesh) OR "transient global amnesia" OR "TGA"] AND ["COVID-19" (Mesh) OR "coronavirus" OR "SARS-CoV-2"]. A similar search strategy was also applied to other databases. We have also done forward and backward searching of reference and citation lists of included studies to find out related papers as much as possible.

Eligibility criteria: Inclusion criteria were all types of English papers focusing on TGA in the context of the COVID-19 pandemic. We decided to exclude those that focused on other amnesia types and those whose objectives were out of the aims of the scope of the review.

Furthermore, we selected the eligible articles based on the population, intervention, comparator, and outcome (PICO) tool.[19]

Population: Cases who had experienced TGA were of interest. We applied no limits regarding the age, sex, past medical history, and other demographic factors.

Intervention (exposure): We only included studies which had happened during the COVID-19 pandemic. However, we did not apply any limitations on the result of diagnostic measures for COVID-19.

Comparator: We considered no limitation regarding the presence of a control group.

Outcome: Diagnosis of COVID-19 in the cases was our primary outcome. In addition, outcomes of secondary interest were the clinical and para-clinical findings in the cases.

Study selection: Two independent authors

assessed the search strategy's title and abstract screening of the retrieved papers. Then, the same authors did the full-text screening for inclusion and exclusion criteria.

Data extraction: Two authors separately and independently did the data extraction of the included studies, retrieving data consisting of the first author's name, study design, the summary of case presentation (in case reports), and the primary outcomes. Furthermore, all discrepancies were resolved through the senior author's counseling.

Synthesis of results: As for the presentation of the results, publications and the data items mentioned were summarized and categorized, and the quantitative data have been synthesized using summarized descriptive numerical reporting.

Results

The primary search in three databases yielded 90 results, of which sixty-five duplicates were removed. The other 25 studies were screened, and 19 were excluded based on their titles and abstracts. Other six remnant studies were assessed for eligibility, all meeting the inclusion criteria. One study was identified via searching reference and citation lists and met the inclusion criteria. Ultimately, seven studies were included for this systematic scoping review. Five studies were case reports (including 6 cases), and two were letters to the editors (one case was presented in one of them) (Figure 1).

In the seven included studies, seven patients had been reported to have TGA in the COVID-19 context. The mean age of the reported cases was approximately 60.8 years, ranging from 48 to 86. Among them, two were men, and five were women. Asthma and obstructive sleep apnea were identified simultaneously in one case. Hypertension was also observed in two. Body mass index (BMI) exceeded the normal range in two individuals. One patient suffered from debilitating migraine, dyslipidemia, and diabetes mellitus (DM). In addition, Takotsubo cardiomyopathy was reported in one of the cases.

The history of taking any drug or substances was unclear and not reported in five cases. A patient with asthma was consuming beta-agonists and steroid inhalers in addition to the occasional use of alcoholic drinks. Another patient was on Zomig (zolmitriptan) nasal spray due to her migraine. Three patients subjectively reported experiencing emotional stress near the course of TGA, including the fear of infection, fear of losing the job, and the stress induced by the nasopharyngeal swab test. Although there were no reports of any physical stressors in five patients, the head and neck massage (to alleviate headache) and the swab test mentioned by the other two cases can be considered physical stressors. The duration of amnesia was reported in 5 patients, with a mean of 15 hours, ranging from 2 to 24. Six patients had an amnestic gap concerning the events near the TGA episode. The presence of an amnestic gap period was unclear in one patient (not reported).

One patient was reported to have normal findings in the physical examination. Elevated blood pressure had been reported in 3 cases; disorientation to time and date and fever was reported in a single patient. One patient had a headache and vomiting in the course of the disease, and one patient had become anxious in the course of TGA. Chest pain was presented in the patient with coincident TGA and Takotsubo cardiomyopathy. Brain MRI returned with no abnormal findings in two patients, and four patients had abnormal findings in brain imaging, as shown in table 1. D-dimer was slightly higher in one patient, and abnormally low or high serum sodium, calcium, and glucose levels were reported in another. Three patients had tested positive for COVID-19, while the test had returned negative in one, with the other three's COVID-19 status unknown (Table 1).

Discussion

In the era of the COVID-19 pandemic, an alarming increase (over 50%) in the number of cases presenting to the neurological care centers with TGA has been reported.[18] This sudden trend ignited our curiosity in the overall situation regarding the subject at hand and its possible correlation to the viral cause of the pandemic itself.

Overall, three were confirmed to have COVID-19 infection among the seven investigated individuals. One case had a negative test, and the COVID-19 infection status was not reported in the other three.

Migraine-related complaints as a significant risk factor associated with TGA have also been notably affected since the onset of the pandemic.[25,26] Presumably, in one of the 7 cases, the presence of an underlying migraine disorder further fueled our suspicions. Furthermore, the presumed COVID-19-related onset of cerebrovascular events and seizures, as the other two possibly effective underlying TGA etiologies, can also be hypothesized to play a part.[12,27]
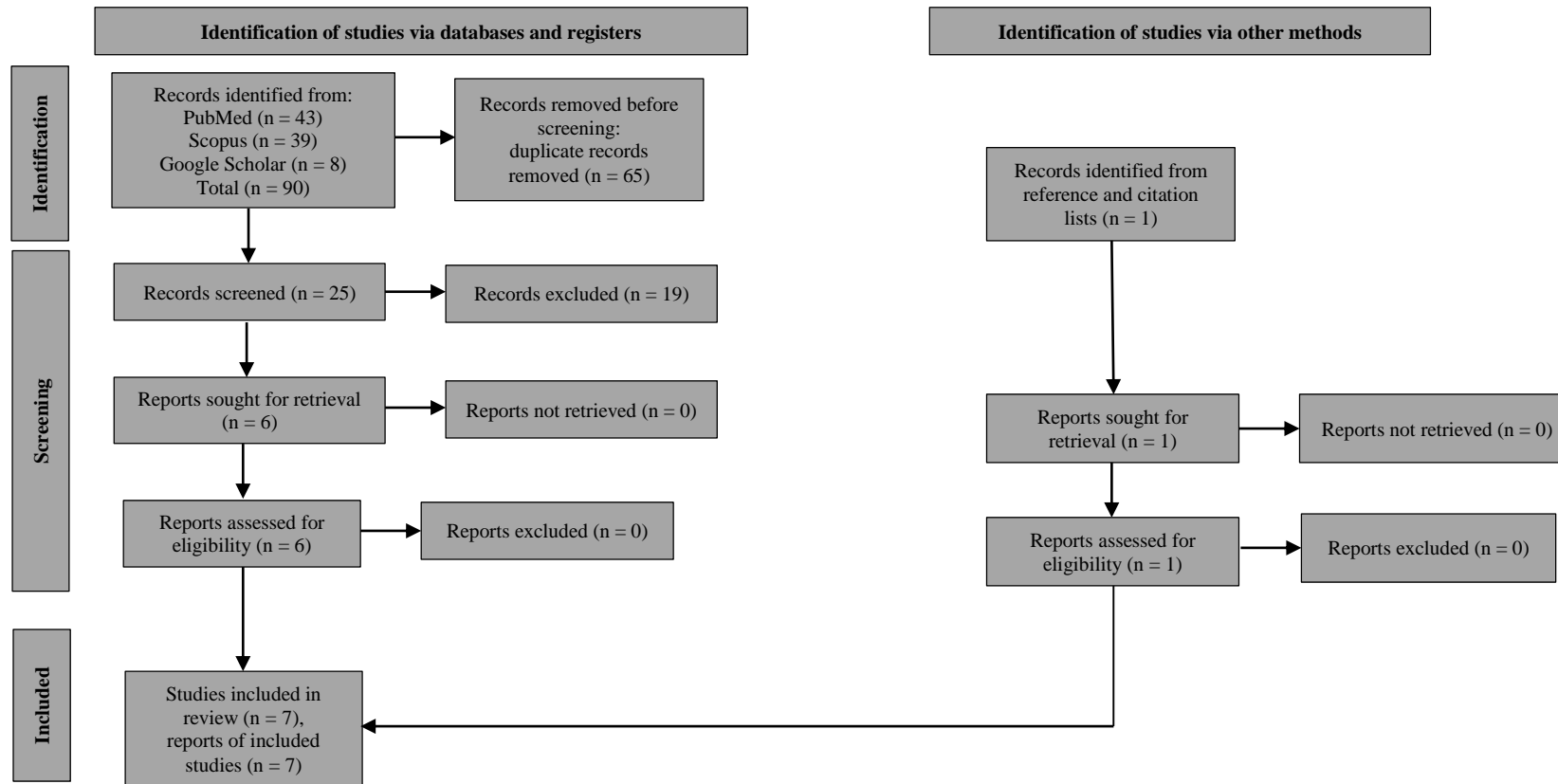
Figure 1. Systematic scoping review flowchart

Table 1. Brief description of the included reports

Authors	Type of article	Age (year)	Sex	Other medical conditions	Drugs and substance history	Emotional stressor	Physical stressor	Duration of amnesia	Amnestic gap	Physical examination and associated symptoms	Brain imaging finding	Other abnormal workups	COVID-19 infection
Ramanathan and Wachsman[21]	CR	48	F	Hypertension	NR	NR	NR	24 hours	Yes	Elevated BP	Brain MRI: small acute bilateral medial temporal infarcts	Normal	Yes
Ramanathan and Wachsman[21]	CR	71	F	Hypertension	NR	NR	NR	8 hours	Yes	Elevated BP	Brain MRI: acute small right medial temporal infarct	D-dimer was slightly on the higher side (315)	Yes
Hussein[22]	CR	53	M	Asthma, mild obesity, obstructive sleep apnea	Beta-agonists, steroid inhalers, occasional alcohol usage	NR	NR	17 hours	Yes	Elevated BP, disorientation to time and space but not to the people around, low-grade fever	Normal	Serum Na: 134 mEq/l, serum Ca: 7.9 mg/dl, serum glucose: 179 mg/dl, abnormal CXR	Yes
Nishizawa et al.[23]	CR	57	M	Dyslipidemia, type 2 DM	NR	Yes (fear of infection)	NR	NR	Yes	Normal	Brain MRI: a single punctate focus of restricted diffusion within the bilateral hippocampal regions, along with a corresponding focus of low signal intensity on the apparent diffusion coefficient map, these findings had reversed in a 2-week follow-up.	Normal	NR
Yang et al.[24]	CR	53	F	Migraine	Zolmitriptan	Yes (worry about losing the job in COVID-19 pandemic)	Head and neck massage	24 hours	Yes	Headache, vomit	Normal	Normal	NR
Ravaglia et al.[25]	CR	58	F	Mild overweight	No	Yes (procedure stress)	Swab test	2 hours	Yes	Anxiety	Brain MRI: hippocampal punctate area of DWI restriction	Normal	No
Werner et al.[18]	Letter to editor	86	F	Takotsubo	NR	NR	NR	NR	NR	Chest pain	NR	NR	NR (probably no)

NR: Not reported; CR: Case report; DM: Diabetes mellitus; COVID-19: Coronavirus disease-2019; BP: Blood pressure; MRI: Magnetic resonance imaging; DWI: Diffusion-weighted imaging; CXR: Chest X-ray

The presence of a withstanding brain imaging abnormality in cases with TGA has been a hot topic for debates among the scientific community, with the reported incidence falling within a range of zero to several, some even reversible.[13,17,28,29] We also realized through investigations of our included studies' cases that although two had no abnormalities in their obtained brain imaging results, the other four were quite the opposite (with both bilateral and unilateral findings reported), bar one case with no imaging data obtained. Moreover, one of the latter also demonstrated clearance of the lesion in two weeks.

Furthermore, as recent data indicate, there is a greater prevalence of underlying vascular-related risk factors in those with TGA along with abnormalities on their DWI-MRI compared to those without;[30] this might point to our hypothesis that thrombotic vascular events caused by COVID-19 might play a much more prominent role compared to the stress from the adversities during and from the pandemic.[26]

However, it needs to be mentioned that in two of the seven cases, only emotional stress could be found to have an effect. In addition, the COVID-19 pandemic has imposed an unprecedented burden on global mental health, and most studies indicate a high prevalence of adverse psychological symptoms.[31] However, to this date, the direct effect of virus or an encephalitic autoimmune pathology behind this phenomenon is also yet to be adequately investigated.[32]

Ultimately, to clarify the existing differences and similarities between TGA before and after the COVID-19 pandemic, a side-by-side comparison of the characteristics of the two is brought below.

The age distribution of our included cases (ranging from 48 to 86, mean of approximately 61 years) is relatively consistent with that of the prior TGA cases.[13] Concerning gender distribution, consistent with the results of relatively similar studies before the pandemic (50.7%), the female predominance also existed in the COVID-induced TGA cases (71%).[29] Moreover, a search for epidemiologic studies regarding gender distribution in the COVID-era TGA has revealed that the gap between the sexes has widened even more (75%).[18] The duration of amnesia was reported in five patients, and the mean was 15 hours, with the shortest lasting about two and the longest lasting for 24 hours, which is in line with what the criteria for TGA suggest.[13,33] An amnestic gap period was present in 6 individuals and was unclear in the other.

Conclusion

Psychological and physical factors were detected to precede the TGA presentations. Although TGA may have an association with COVID-19 infection, the psychological burden imposed by the pandemic is also presumed to relate to TGA.

In the confirmed cases of TGA and COVID-19, the abnormal findings may be due to COVID-19 infection. As TGA is less frequently discussed in the context of the COVID-19 pandemic and because of limited reports on this issue, presenting future reports in more detail is recommended. Finally, in the current pandemic condition, we would suggest that physicians in the field consider the probability of COVID-19 infection in cases presenting with TGA.

Ultimately, other possible mechanisms, including hypoxia and immune system hyperactivation, may negatively impact memory. Moreover, COVID-19 therapy regimens such as remdesivir may be responsible. Therefore, further studies are required to investigate the mentioned possibilities.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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