Insight from a noticeable difference between two families infected with COVID-19

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Shugang Cao
The Affiliated Hefei Hospital of Anhui Medical University
ORCiD: https://orcid.org/0000-0003-2304-9993

Yuancheng Li
School of Public Health, Nanjing Medical University

Hong Yue
The Affiliated Hefei Hospital of Anhui Medical University

Chenchen Li
The Affiliated Hefei Hospital of Anhui Medical University

Mingwu Xia
The Affiliated Hefei Hospital of Anhui Medical University

Fang Liu
The Affiliated Hefei Hospital of Anhui Medical University

Juncang Wu
The Affiliated Hefei Hospital of Anhui Medical University
wujuncang126@126.com Corresponding Author

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Abstract
The outbreak of COVID-19 shows a high potent of person-to-person transmission and thus contributes to a large spread of infection sweeping the world. The family cluster of infection has been paid much more attention. We reported two different families infected by SARS-CoV-2 in the context of family clustering, one of which is a typical family cluster of infection with the transmission chain being an asymptomatic patient in the incubation period. However, the outcome of another family was exactly the opposite, in which the index patient was the only individual infected and complicated with fatal ischemic stroke. These two families highlight that more attention should be paid to the distinctions underlying the family cluster of infections and the possibility of COVID-19-related stroke.

Introduction
The outbreak of COVID-19 is a highly infectious disease and thus contributes to a large spread of infection sweeping the world (1). Accumulated reports confirmed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2) could efficiently transmitted from person to person via close contact, shedding shadow upon the public health if not effectively controlled (2,3). Also, asymptomatic cases leading to a family cluster of infection emphasizes the importance of early detection of asymptomatic carrier (2–4). More attention has been paid to the family cluster of infection, which provide an opportunity to further study the different transmission ways of SARS-CoV–2. Here, we report two different families infected by COVID–19 in the context of family clustering, one of which is a typical family cluster of infection with the transmission chain being an asymptomatic patient in the incubation period. However, the outcome of another family was exactly the opposite with only 1 patient infected with COVID–19, in which the index patient was complicated with and died of severe stroke.

Case Presentation
In family 1, patient 1 drove home from another city in Anhui Province, China on January 27. The close contact in the family was patient 2 (his father). Patient 1 developed fever and cough on January 28, and received symptomatic treatment at a local clinic. As the symptoms did not improve, he went to the local hospital on January 31. However, on February 5, patient 3 (his sister), 4 (brother-in-law) and 5 (nephew) came to visit patient 2, who was asymptomatic at that time (Figure 1A). On February 9,
patient 1 was confirmed as COVID-19 via nucleic acid tests for SARS-CoV-2 and transferred to our hospital the next day. On February 13, the other 4 contacts were also tested positive for SARS-CoV-2. Patient 2 was admitted to the local hospital on February 15, while the other 3 patients were admitted to our hospital on February 16. During the hospitalization, they all had fever, cough and expectoration, and chest CT showed multiple ground-glass shadows (Figure 2). They were cured and discharged from hospital one after another after February 28, and there has been no recurrence to date.

In family 2, the index patient, a 56-year-old taxi driver, was staying at home since January 22. The close contact history could not be traced. Four close contacts lived with him, except his daughter (Figure 1B). On January 23, he developed dry cough but didn’t care. The next day, his daughter came to have a family dinner. On February 2, the cough became worse with expectoration, and he took some medicine himself. Three days later, he had chest tightness, asthma, and headache, but no fever, and received symptomatic treatment in a community hospital. On February 6, he developed numbness and weakness of left upper and lower limbs. The next day, he was presented to our stroke center due to increased left hemiplegia, but he had no stroke risk factors. Brain CT indicated multiple cerebral infarction and chest CT showed multiple shadows in both lungs (Figure 2). He was diagnosed with confirmed COVID-19 pneumonia based on positive SARS-CoV-2 throat swab test. The laboratory examination results showed decreased lymphocyte counts and lymphocyte percentage, and increased D-dimer, serum amyloid A and a high level of sensitive C-reactive protein (Supplemental Table 1). On February 8, he developed severe headache, vomiting and high blood pressure. Brain CT examination suggested the high density sign of right middle cerebral artery and massive cerebral infarction. The next day, he fell into a coma with a Glasgow coma scale (GCS) score of 7. After that, the patient’s condition continued to deteriorate and died of brain hernia on February 10. Fortunately, the other five close contacts were tested negative for SARS-CoV-2, and are still asymptomatic to date.

Discussion
We report here two families infected with COVID-19, with two totally different outcomes even both in the context of family clusters. The family cluster of COVID-19 infection refers to many family
members infected, even all of them, which has been reported in several literatures (2–4). Known data demonstrated that SARS-CoV-2 holded strong infectious capacity and noticeably, the last three days of the incubation period was the highest risk of transmission (5). Family 1 demonstrated a typical family cluster of COVID-19 infection. The patient 1 is symptomatic but undiagnosed at initial. The transmission chain might be through patient 2 (infected by patient 1) in the incubation period. Then, the other three patients were infected by patient 2, although they were not in contact with patient 1, endorsing that asymptomatic cases in the incubation period may also lead to a family cluster of infection.

However, the index patient was the merely individual infected in family 2, though they closely contacted in family life. Considering that the patient was a healthy middle-aged male without underlying diseases, did not develop fever, and had mild pulmonary symptoms from onset to admission, we believed that the viral load exposed to the patient was not high or the virus might show low transmission ability. According to previous studies on the family cluster of COVID-19 infection, it is not difficult to find that the proportion of family members infected and the infection symptoms were quite variable, which might be associated with the viral load of COVID-19 patients contacted, the virus virulence, the immune state and physical condition of close contacts, and so on. (2–4)

Additionally, the patient in family 2 developed into fatal stroke even without previous stroke risk factors. Because we did not know the previous conditions of cerebrovascular diseases and failed to perform a lumbar puncture for the etiological dection of cerebrospinal fluid (CSF) due to the rapid deterioration of his condition, we could not confirm that whether SARS-CoV-2 contributed to the development of stroke in the patient. However, no stroke high-risk factors and rapidly deteriorating cerebral infarction occurring after mild COVID-19 indirectly indicated that acute ischemic stroke might be associated with COVID-19. At least the inflammatory state after the onset of COVID-19 might be an inducement of stroke. Recent viral infections were reported to be associated with stroke, of which virus-induced inflammatory response is thought to be the predominant mechanism linking ischemic stroke with virus infection (6,7). The most commonly studied viruses related to increased
risk of stroke include Epstein-Barr virus, herpes simplex virus (HSV)-1 and HSV-2, and cytomegalovirus. The stroke risk was highest during the first 3 days after the diagnosis of respiratory tract infection and gradually decreased in subsequent weeks (8). Inflammatory cascades promote atherosclerosis, plaque rupture, and thrombosis, thereby leading to ischemic stroke (7,9). High-sensitive C-reactive protein might be an independent predictor of ischemic stroke, as in this patient with increased high-sensitive C-reactive protein as well as another important inflammatory marker serum amyloid A. According to a recent study, SARS-CoV-2 can bind to angiotensin-converting enzyme 2 (ACE2) and trigger functional changes in ACE2/Angiotensin II Type 2 Receptor (AT2R), thereby resulting in an imbalance in the steady-state cytokine regulatory axis and a cytokine storm (10). ACE2 exists in nervous system and skeletal muscle. The expression and distribution of ACE2 suggest that SARS-CoV-2 can cause neurological symptoms through direct or indirect mechanisms. During the epidemic period of severe acute respiratory syndrome (SARS), there were also a few SARS patients with cerebral infarction (11,12). Umapathi et al (12) once described 5 severe SARS patients developed large artery ischaemic stroke, and thought that stroke occurring in the context of SARS infection was affected by many factors, including virus-induced inflammation of the vessel wall and hypercoagulability associated with virus infection. The D-dimer level of this patient also continued to increase, suggesting that there might also be virus-induced hypercoagulability. COVID-19 might be complicated with stroke and even had stroke as the first manifestation, especially in patients with asymptomatic or mild infection. If not found promptly and accepted into stroke unit conventionally, it would bring unpredictable consequences. However, the underlying mechanism regarding stroke attack in COVID-19 patients is still lack of in-depth study.

Given the importance of early detection of asymptomatic carrier and the possibility of COVID-19-related stroke, more and more attention should be paid to the the family cluster of COVID-19 infection, and we believe our experience warrants an increased vigilance against stroke and other thrombotic complications among COVID-19 patients in future outbreaks, especially in patients with mild symptoms or asymptomatic infection.

Declarations
**Acknowledgments:** None.

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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Figures
The epidemiological and clinical characteristic of two families infected by COVID-19. A: The transmission chain from a COVID-19 patient to one family member, then his three relatives infected by the asymptomatic family member. B: The situation of a COVID-19 patient suffering from central nervous system symptoms without other close contacts infected.
Figure 2

The dynamic evolution of pulmonary shadows on Chest CT of four patients in family 1 is shown on lines 1 to 4, indicating that the lesions have gone through the process of consolidation and regression. Chest CT of the index patient in family 2 showed multiple ground-grass shadows in the extrapulmonary zone of both lungs, and brain CT showed the high density sign of M1 segment of the right middle cerebral artery (black arrows) and massive cerebral infarction on the last line.

Supplementary Files

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