



Clinical time course of COVID-19, its neurological manifestation and some thoughts on its management

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ABSTRACT

Coronavirus disease-2019 (COVID-19) has become a global pandemic. COVID-19 runs its course in two phases, the initial incubation phase and later clinical symptomatic phase. Patients in the initial incubation phase often have insidious clinical symptoms, but they are still highly contagious. At the later clinical symptomatic phase, the immune system is fully activated and the disease may enter the severe infection stage in this phase. Although many patients are known for their respiratory symptoms, they had neurological symptoms in their first 1–2 days of clinical symptomatic phase, and ischaemic stroke occurred 2 weeks after the onset of the clinical symptomatic phase. The key is to prevent a patient from progressing to this severe infection from mild infection. We are sharing our experience on prevention and management of COVID-19.

COVID-19 has become a global pandemic.¹ Its clinical course and temporal profile has not been well described. Since the outbreak, the disease is known for its respiratory symptoms including fever and coughing.² It is also widely known for its higher mortality than common influenza and elderly has more severity.³ However, we have found that many patients had neurological symptoms in their early stages,⁴ and ischaemic stroke often happened around 2 weeks after the onset of infection.⁵ Our findings have important clinical significance. If these neurological symptoms are present, test for COVID-19 may be warranted.⁶

In our previous publication in *JAMA Neurology*, we retrospectively reviewed 214 patients with confirmed diagnosis of COVID-19. Among them, 88 (41%) were severe cases and 126 (59%) were mild. Severe cases were older and often had comorbid conditions such as hypertension (36%). Neurological symptoms were reported in 78 (36%) cases, which involved central nervous system (CNS), peripheral nervous system (PNS) and skeletal muscles. The common neurological complaints include headache, dizziness, confusion, mild cognitive impairment, loss of smelling, altered taste, blurred vision,

muscle pain, nerve pain and ataxia. The most common reported symptoms in CNS manifestations were dizziness (17%) and headache (13%). And the most common PNS symptoms were taste impairment (6%) and smell impairment (5%). In severe patients, 5 (6%) had strokes, 13 (15%) had cognitive impairment and 17 (19%) had musculo-skeletal damage.⁴ Recently, loss of smell was confirmed in a study in the USA. A survey 1480 patients with influenza-like symptoms and concerns regarding potential COVID-19 found 102 patients tested positive for the virus and 1378 tested negative. They concluded that the loss of smell or taste was 10 times more likely from COVID-19 infection than other causes of infection.⁷ While the study will print next week in the *NEJM*, Washington post reported a story of “Healthy people in their 30s and 40s, barely sick with COVID-19, are dying from strokes”. The paper mentioned that about a dozen of young strokes from three major hospitals in New York and Boston will report this series next week.⁸ A French report showed that patients with COVID-19 had encephalopathy, agitation, confusion and brain abnormality on MRI.⁹

Patients with COVID-19 often have insidious clinical symptoms, without fever or coughing, even though their lungs may have rather severe damages. Their shortness of breath may not be obvious if they have no or minimal physical activities. Their respiratory symptoms may be brought on by simply walking a few more steps or climbing stairs. In these patients, their nucleic acid examination can be negative. Nucleic acid test can have a false-negative result and with limited sensitivity. Hence, a CT of lungs and/or antibody test must be done. However, at this stage, these patients are still highly contagious. At the later stage of infection when the immune system is totally activated, systemic angiopathy, thrombosis, stroke and even



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acute haemorrhagic necrotising encephalopathy¹⁰ may take place.

We have found that COVID-19 runs its course in two phases, the initial incubation phase and later clinical symptomatic phase. The initial incubation phase is about 3–5 days, during which the virus is attempting to seed at the most peripheral and inferior parts of the lungs. Since it is a RNA virus, it may take several days to replicate to a significant amount and cause organ damages.¹¹ One laboratory sign of early infection without fever and cough during this phase is the development of lymphopenia. Once clinical symptoms are onset, the patients may begin with neurological symptoms first. When neurological symptoms occur, complete blood count and lymphocyte count should be checked routinely. Mucosa is rich in angiotensin-converting enzyme 2 (ACE 2) receptors, and the virus enters the host via eyes, nose and mouth.¹² Some healthcare providers were infected because they did not wear eye shield or goggles, medical gloves and only had surgical masks at the early stages of epidemic.¹³

After the initial phase of incubation, a patient may become better if the replication of virus is contained and symptoms will improve. However, if not controlled, the disease enters the second phase or severe infection stage. When the replication of virus in the lungs reaching a critical level and lung damage becomes more serious, fever, coughing and shortness of breath will ensue. During this phase, lung CT shows the typical glassy appearance or acute respiratory distress syndrome-like changes.² The patient is now in trouble. Ventilator support may be needed. Due to cytokine-mediated autoimmune storm, multi-organ failure may follow. Opportunistic infection, such as staphylococcus and pneumococcus pneumonia, may begin followed by bacteremia. The key is to prevent a patient from progressing to this severe infection from a mild infection. The rate of severe cases is around 20%. Many treatments in the severe infection stage have minimal benefits.

During this progression, D-dimer might have been a marker indicative of the seriousness of the infection. High level D-dimer was closely related to the severe stage of infection.⁴ D-Dimer elevation may be a turning point. Microangiopathy (autopsy proven) and thrombosis causing pulmonary embolism or myocardial infarction will occur and are responsible for sudden death.^{14 15}

In severe patients, retaining CO₂ is a challenging problem. Due to extensive damage to the lungs, gas exchange becomes difficult. Frequent checking of arterial blood gas is needed to monitor PCO₂ levels. Only using pulse oximeter to monitor PO₂ may be misleading.

Currently, the treatment and vaccine for COVID-19 is under development. Those principles have been so effective to manage patients in our clinical practice:

1. Be vigilant of neurological symptoms with low lymphocyte count and if they occur, consider CT of chest and test for COVID-19.
2. If symptoms detected and nucleic acid is positive, start prescribing Arbidol or hydrochloroquine as treatment

daily and quarantine in a hospital ward. Management of neurological symptoms continued.

3. Mild patients cannot go home but be quarantined somewhere else. About 20% of them will turn into severe cases.
4. More than a week later if fever and lung infections happen, broad-spectrum antibiotics should be started when either sputum or blood cultures are positive, with or without elevated C reactive protein level.
5. When D-dimer is elevated, systemic anticoagulation is indicated. Antiplatelet therapy will fail.
6. Monitor arterial blood gas often and be aware of hypercapnia from the retention of PCO₂. Ventilator support when PO₂ is low and PCO₂ is high.
7. Consider intravenous immunoglobulin at the later phase.

In our practice, we have encountered those who had negative nucleic acid tests and later with confirmed diagnosis. Such phenomenon could be due to inadequate sampling, insensitivity of the test and sampling during the incubation period. Therefore, high index of suspicion and paying attention to clinical presentation can be very important. Repeat nucleic acid test and/or obtain serology on antibodies of virus are warranted if a patient is suspected of COVID-19.

The Neurology Department at Wuhan Union Hospital of Huazhong University of Science and Technology Tongji Medical College has a faculty of 45 neurologists. They began treating COVID-19 on 23 January, 32 neurologists became frontline physicians staffing the fever clinic and intensive care units (ICUs). They co-managed 6 ICUs with a total of 300 beds designated for COVID-19 pneumonia since the end of January. At the peak of the epidemic, the fever clinic saw 850 patients a day. In order to accommodate those with severe symptoms and were critical, the hospital system quickly designated and equipped 2000 beds, including 810 ICU beds for severe cases with dyspnoea and SpO₂ <93%. During this course, very few doctors and nurses were infected, and they have all recovered. The infection of healthcare providers was mainly due to the insufficient protective equipment at the early stages of epidemic. After the protective measures were sufficient, no further cross-infection in healthcare providers reported.

On 16 January, one nosocomial transmission case was an acute stroke patient who received intravenous tPA. This patient developed fever after 36 hours of admission to ICU and showed lymphopenia. His nucleic acid testing of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was positive. A neurologist who treated him was found to be infected. He wore personal protective equipment (PPE) but without eye shields at the time. Fortunately, he recovered three weeks later.

Some advices from our colleagues in Wuhan. Safety and protection of the healthcare providers are the priority since they are at the highest risk from treating patients with COVID-19 or those asymptomatic carriers every day. Take COVID-19 very seriously. Wear PPE in high-risk

environment including N95 mask, eye shields and gloves. Neurologists are likely going to be needed in every hospital to be in the front line treating COVID-19 since there will be a healthcare provider shortage everywhere. They will also be consulted on those with neurological symptoms that can be early signs of COVID-19 infection.

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