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**The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients**

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**Abstract**

Following the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), another highly pathogenic coronavirus named SARS-CoV-2 (previously known as 2019-nCoV)

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emerged in December 2019 in Wuhan, China, and rapidly spreads around the world. This virus shares highly homological sequence with SARS-CoV, and causes acute, highly lethal pneumonia (COVID-19) with clinical symptoms similar to those reported for SARS-CoV and MERS-CoV. The most characteristic symptom of COVID-19 patients is respiratory distress, and most of the patients admitted to the intensive care could not breathe spontaneously. Additionally, some COVID-19 patients also showed neurologic signs such as headache, nausea and vomiting. Increasing evidence shows that coronaviruses are not always confined to the respiratory tract and that they may also invade the central nervous system inducing neurological diseases. The infection of SARS-CoV has been reported in the brains from both patients and experimental animals, where the brainstem was heavily infected. Furthermore, some coronaviruses have been demonstrated able to spread via a synapse-connected route to the medullary cardiorespiratory center from the mechano- and chemoreceptors in the lung and lower respiratory airways. In light of the high similarity between SARS-CoV and SARS-CoV2, it is quite likely that the potential invasion of SARS-CoV2 is partially responsible for the acute respiratory failure of COVID-19 patients. Awareness of this will have important guiding significance for the prevention and treatment of the SARS-CoV-2-induced respiratory failure. (229 words)

### **Keywords**

Coronavirus; Cell susceptibility; Dissemination; Nervous system

Coronaviruses (CoVs), which are large enveloped non-segmented positive-sense RNA viruses, generally cause enteric and respiratory diseases in animals and humans<sup>1</sup>. Most human CoVs, such as hCoV-229E, OC43, NL63, and HKU1, cause mild respiratory diseases, but the worldwide spread of two previously unrecognized coronaviruses, the severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), has called global attention to the lethal potential of human CoVs<sup>2</sup>. While MERS-CoV is still not eliminated from the world, another highly pathogenic CoV, currently named SARS-CoV-2 (previously known as 2019-nCoV), emerged in December 2019 in Wuhan, China. This novel CoV has caused a national outbreak of severe pneumonia (COVID-19) in China, and rapidly spreads around the world.

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Genomic analysis shows that SARS-CoV-2 is in the same Betacoronavirus clade as MERS-CoV and SARS-CoV, and shares highly homological sequence with SARS-CoV<sup>3</sup>. The public evidence shows that COVID-19 shares similar pathogenesis with the pneumonia induced by SARS-CoV or MERS-CoV<sup>4</sup>. Moreover, the entry of SARS-CoV-2 into human host cells has been identified to use the same receptor as SARS-CoV<sup>5,6</sup>.

Most CoVs share a similar viral structure and infection pathway<sup>7,8</sup>, and therefore the infection mechanisms previously found for other CoVs may also be applicable for SARS-CoV-2. A growing body of evidence shows that neurotropism is one common feature of CoVs<sup>1,9-12</sup>. Therefore, it is urgent to make clear whether SARS-CoV-2 can gain access to the central nervous system (CNS) and induce neuronal injury leading to the acute respiratory distress.

### **The clinical features of SARS-CoV-2 infection**

SARS-CoV-2 causes acute, highly lethal pneumonia with clinical symptoms similar to those reported for SARS-CoV and MERS-CoV<sup>2,13</sup>. Imaging examination revealed that most patients with fever, dry cough, and dyspnoea showed bilateral ground-glass opacities on chest CT scans<sup>14</sup>. However, different from SARS-CoV, SARS-CoV-2-infected patients rarely showed prominent upper respiratory tract signs and symptoms, indicating that the target cells of SARS-CoV-2 may be located in the lower airway<sup>2</sup>.

Based upon the first-hand evidence from Wuhan local hospitals<sup>2,14-15</sup>, the common symptoms of COVID-19 were fever (83% ~ 99%) and dry cough (59.4% ~ 82%) at the onset of illness. However, the most characteristic symptom of patients is respiratory distress (~55%). Among the patients with dyspnoea, more than half needed intensive care. About 46% ~ 65% of the patients in the intensive care worsened in a short period of time and died due to respiratory failure. Among the 36 cases in the intensive care reported by Wang et al.<sup>15</sup>, 11.1% received high-flow oxygen therapy, 41.7% received noninvasive ventilation, and 47.2% received invasive ventilation. These data suggest that most (about 89%) of the patients in need of intensive care could not breathe spontaneously.

It is now known that CoVs are not always confined to the respiratory tract and that they may also invade the CNS inducing neurological diseases. Such neuroinvasive propensity of CoVs has been documented almost for all the betacoronaviruses, including SARS-CoV<sup>1</sup>, MERS-CoV<sup>11</sup>, HCoV-229E<sup>16</sup>, HCoV-OC43<sup>12</sup>, mouse hepatitis virus (MHV)<sup>17</sup>, and porcine hemagglutinating encephalomyelitis coronavirus (HEV)<sup>9-10, 18-19</sup>.

In light of the high similarity between SARS-CoV and SARS-CoV2, it is quite likely that the potential neuroinvasion of SARS-CoV-2 plays an important role in the acute respiratory failure of COVID-19 patients. According to the complaints of a survivor, the medical graduate student (24 years old) from Wuhan University, she must stay awake and breathe consciously and actively during the intensive care. She said that if she fell asleep, she might die because she had lost her natural breath.

### **The neuroinvasive potential of SARS-CoV-2**

It is believed that the tissue distributions of host receptors are generally consistent with the tropisms of viruses<sup>20-22</sup>. The entry of SARS-CoV into human host cells is mediated mainly by a cellular receptor angiotensin-converting enzyme 2 (ACE2), which is expressed in human airway epithelia, lung parenchyma, vascular endothelia, kidney cells, and small intestine cells<sup>23-25</sup>. Different from SARS-CoV, MERS-CoV enters human host cells mainly via dipeptidyl peptidase 4 (DPP4), which is present in the lower respiratory tract, kidney, small intestine, liver, and the cells of the immune system<sup>26-27</sup>.

However, the presence of ACE2 or DPP4 solely is not sufficient to make host cells susceptible to infection. For example, some ACE2-expressing endothelial cells and human intestinal cell lines failed to be infected by SARS-CoV<sup>28-29</sup>, while some cells without a detectable expression level of ACE2 such as hepatocytes could also be infected by SARS-CoV<sup>20</sup>. Likewise, the infection of SARS-CoV or MERS-CoV was also reported in the CNS, where the expression level of ACE2<sup>30</sup> or DPP4<sup>31</sup> is very low under normal conditions.

Early in 2002 and 2003, studies on the samples from SARS patients have demonstrated the presence of SARS-CoV particles in the brain, where they were

located almost exclusively in the neurons<sup>32-34</sup>. Experimental studies using transgenic mice further revealed that either SARS-CoV<sup>30</sup> or MERS-COV<sup>11</sup>, when given intranasally, could enter the brain, possibly via the olfactory nerves, and thereafter rapidly spread to some specific brain areas including thalamus and brainstem. It is noteworthy that in the mice infected with low inoculum doses of MERS-CoV virus particles were detected only in the brain, but not in the lung, which indicates that the infection in the CNS was more important for the high mortality observed in the infected mice<sup>11</sup>. Among the involved brain areas, the brainstem has been demonstrated to be heavily infected by SARS-CoV<sup>30,35</sup> or MERS-CoV<sup>11</sup>.

The exact route by which SARS-CoV or MERS-COV enters the CNS is still not reported. However, hematogenous or lymphatic route seems impossible, especially in the early stage of infection, since almost no virus particle was detected in the non-neuronal cells in the infected brain areas<sup>32-34</sup>. On the other hand, increasing evidence shows that CoVs may first invade peripheral nerve terminals, and then gain access to the CNS via a synapse-connected route<sup>9-10, 19, 36</sup>. The trans-synaptic transfer has been well documented for other coronaviruses, such as HEV67<sup>9-10, 18-19</sup> and avian bronchitis virus<sup>36-37</sup>.

HEV 67N is the first coronavirus found to invade the porcine brain, and it shares >91% homology with HCoV-OC43<sup>38-39</sup>. HEV first oronasally infects the nasal mucosa, tonsil, lung, and small intestine in suckling piglets, and then is delivered retrogradely via peripheral nerves to the medullary neurons in charge of peristaltic function of the digestive tract, resulting in the so-called vomiting diseases<sup>18-19</sup>. The transfer of HEV67N between neurons has been demonstrated by our previous ultrastructural studies to use the clathrin-coating-mediated endo-/exocytotic pathway<sup>10</sup>.

Similarly, the trans-synaptic transfer has been reported for avian bronchitis virus<sup>36-37</sup>. Intranasal inoculation in mice with avian influenza virus was reported to cause neural infection besides bronchitis or pneumonia<sup>36</sup>. Of interest, viral antigens have been detected in the brainstem, where the infected regions included the nucleus of the solitary tract and nucleus ambiguus. The nucleus of the solitary tract receives sensory information from the mechano- and chemoreceptors in the lung and respiratory tracts<sup>40-42</sup>, while the efferent fibers from the nucleus ambiguus and the nucleus of the

solitary tract provide innervation to airway smooth muscle, glands, and blood vessels. Such neuroanatomic interconnections indicate that the death of infected animals or patients may be due to the dysfunction of the cardiorespiratory center in the brainstem <sup>11, 30, 36</sup>.

Taken together, the neuroinvasive propensity has been demonstrated as a common feature of CoVs. In light of the high similarity between SARS-CoV and SARS-CoV2, it is quite likely that SARS-CoV-2 also possesses a similar potential. Based on an epidemiological survey on COVID-19, the median time from the first symptom to dyspnea was 5.0 days, to hospital admission was 7.0 days, and to the intensive care was 8.0 days <sup>15</sup>. Therefore, the latency period is enough for the virus to enter and destroy the medullary neurons. As a matter of fact, it has been reported that some patients infected with SARS-CoV-2 did show neurologic signs such as headache (about 8%), nausea and vomiting (1%).

### **The implications of the potential neuroinvasion of SARS-CoV-2**

As an emerging virus, no effective treatment has been developed for the disease resulting from SARS-CoV-2. Therefore, awareness of the possible entry of SARS-CoV-2 into the CNS will have important guiding significance for the prevention and treatment.

If the neuroinvasion of SARS-CoV-2 does take a part in the development of respiratory failure in COVID-19 patients, the precaution with masks will absolutely be the most effective measure to protect against the possible entry of the virus into the CNS. It may also be expected that the symptoms of the patients infected via facial-oral or conjunctival route will be lighter than those infected intranasally. The possible neuroinvasion of SARS-CoV-2 may also partially explain why some patients developed respiratory failure, while others not. It is very possible that most of the persons in Wuhan, who were the first exposed to this previously unknown virus, did not have any protective measure, so that the critical patients is much more in Wuhan than in other cities in China.

Considering the potential neuroinvasion of SARS-CoV-2, antiviral therapy should be carried out as early as possible to block its entry into the CNS. Airway

inhalation of antiviral agents will be the first choice at the early stage of infection, which will inhibit the replication SARS-CoV-2 in the respiratory tracts and lung and prevent from its subsequent neuroinvasion. It is also urgent to find effective antiviral drugs that can cross the blood-brain barrier. Moreover, corticosteroids, which are used frequently for severe patients, may have no treatment effect, but rather accelerate the replication of the virus within the neurons.

Since SARS-CoV2 may conceal itself in the neurons from the immune recognition, complete clearance of the virus may not be guaranteed even the patients have recovered from the acute infection. In support of this, there is evidence that SARS-CoV-2 is still detectable in some patients during the convalescent period<sup>43</sup>. Therefore, given the probable neuroinvasion the risk of SARS-CoV-2 infection may be currently underestimated.

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