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Review Article

A SARS-COV-2 Entry Pathway Shift for the Omicron Variant Might Explain a Less Severe Disease

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Abstract

The Omicron variant led to exponential increases in cases and a sharp rise in hospital admissions. The wave increased faster than previous waves, completely displacing the Delta variant within weeks, creating worldwide worries about the final pandemic control. Omicron is the fifth variant to be named as a variant of concern (VOC) by the World Health Organisation (WHO) and the third (after Alpha and Delta) to achieve global dominance. Although Omicron is fast-moving, several initial reports suggest a less severe disease. Some authors have emphasized that the symptoms associated with Omicron have differed from these "traditional" symptoms and are closer to the common cold. It is also curious that one major COVID-19 symptom rare-the loss of taste and smell. Dr. Machado has suggested that one of the main causes to explain ARDS refractory to treatments is the direct invasion of SARS-CoV-2 to the brainstem from the olfactory nerves through transsynaptic pathways. SARS-CoV-2 infection of the brainstem can deeply damage the respiratory center, triggering functional deviations that affect involuntary respiration leading to ARDS refractory to treatments, which is the main cause of death in Covid-19 patients. A shift in the Omicron SARS-CoV-2 entry pathway from cell surface fusion, triggered by TMPRSS2, to cathepsin-dependent fusion within the endosome, may impact transmission, cellular tropism, and pathogenesis. Therefore, we can hypothesize that this entrance modification may impact transmission from the olfactory nerve to the brainstem through transsynaptic pathways. Hence, a decrement of the virus's direct invasion to the brainstem would diminish respiratory center dysfunction, with less possibility of an ARDS complication and the need for mechanical ventilation in ICUs.

Keywords: *Covid-19; SARS-CoV-2; Omicron Variant; Acute Respiratory Distress Syndrome (ARDS); Entry Route*

Introduction

The Omicron variant has led to an exponential increase in cases and a sharp rise in hospital admissions. The wave's amplitude has increased faster than previous waves, completely displacing the Delta variant within weeks, creating worldwide new worries about the final pandemic control [1,2].

Omicron is the fifth variant to be named as a variant of concern (VOC) by the World Health Organization (WHO) and the third (after Alpha and Delta) to achieve global dominance [3]. The Omicron variant was first documented in the City of Tshwane, Gauteng Province,

South Africa, on 9 November 2021 [1] and in quarantined travelers in Hong Kong [4]. It has split into three divergent sublineages (BA.1, BA.2, and BA.3), of which BA.1 has spread rapidly around the world [1,3,5-7].

Although Omicron is fast-moving, several initial reports suggest a less severe disease. Researchers in South Africa, where the variant is spreading quickly, say it may cause less serious Covid cases than other forms of the virus [1,8,9]. Early indications in young people are that Omicron is 40 - 70% less severe than Delta. Omicron SARS-CoV-2 infects and multiplies 70 times faster than the Delta variant and original SARS-CoV-2 in the human bronchus, which may explain why Omicron may transmit faster between humans than previous variants [6,10]. Moreover, Omicron variant's infection in the lung is significantly lower than the original SARS-CoV-2, mainly affecting the upper respiratory tract, which may be an indicator of lower disease severity [10-13].

Some authors have emphasized that the symptoms associated with Omicron have been found to differ from these "traditional" symptoms and are closer to the common cold [14]. It is also curious that one major COVID-19 symptom is rare-the loss of taste and smell [15]. Some research suggests that 48% of people with the original mutation of the novel coronavirus lost smell, and 41% had a loss of taste. However, among a small group of Omicron patients, that number jumped down to 23% for loss of taste and 12% for loss of smell. Then, several authors have warned that many people may not realize they have Covid-19 and will instead mistake it for a common cold because they do not have cough, fever, or loss of taste or smell [16]. A virus that sits in the higher respiratory tract is associated with increased transmissibility, but the less severe disease, with similitudes from what scientists know about various flu strains. Although comparing the flu to SARS-CoV-2 is an imperfect extrapolation [10].

The most deadly symptom of Covid-19 patients is acute respiratory distress syndrome (ARDS), leading to severe disease and the need for mechanical ventilatory support in ICUs [17-20]. Wang., *et al*. initially reported that 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 [21].

Dr. Machado has suggested that one of the main causes explaining ARDS refractiveness to treatments is the direct invasion of SARS-CoV-2 to the brainstem. SARS-CoV-2 infection of the brainstem can deeply damage the respiratory center, triggering functional deviations that affect involuntary respiration leading to ARDS refractory to treatments, which is the main cause of death in Covid-19 patients [22].

The anatomical organization of the human olfactory system makes it an attractive site for pathogens to gain entry into the host. The olfactory system is directly connected to the central nervous system (CNS) via the olfactory bulb, and therefore numerous neurotropic agents, including parasites, bacteria, and viruses, can reach the CNS via transport along the olfactory nerve [18,23-29].

The olfactory nerve is the main route for SARS-CoV-2 to invade CNS. SARS-CoV-2 enters the nasal and mouth tissues through the angiotensin-converting enzyme 2 (ACE2) receptor [30], due to high ACE2 and TMPRSS2 in olfactory epithelium cells, both of which are required for viral binding and accumulation. Entering the nose and mouth through this protein may cause temporary damage to smell and taste nerves. However, this damage appears to Improve within one to two weeks after the onset of the disease [31-33]. Stem cells probably have a role in smell and taste recovery [34].

Hence, SARS-CoV-2 infection spreads from the olfactory epithelium to the olfactory bulb and then to the olfactory nerve, applying endocytosis and exocytosis for trans-synaptic transfers, can reach different areas of the brain [18,27,29]. MRI findings have shown virus spread to cortical regions connected through neural pathways to the olfactory system [19,35,36].

SARS-CoV-2 spread to the brainstem in the area of the medullar respiratory control centers, might produce a discoordination of the sequence inspiration- expiration, explaining the appearance of other abnormal respiratory patterns: hyperpnea, tachypnea, hyperventilation, hypoventilation and not necessarily dyspnea [18].

Several reports have affirmed that Omicron has switched its entry route into human cells, from cell surface fusion to cathepsin-dependent fusion within the endosome. This fundamental biological shift is likely to influence Omicron spread and the types of cells it can hijack. These changes may also affect the pathogenesis and severity of disease, and researchers say they require further evaluation in population-based studies [37].

The entry of SARS-CoV-2, and related coronaviruses, can proceed via two routes (Figure 1) [38]:

1. Cell surface fusion following proteolysis by TMPRSS2
2. Fusion from the endosome after endocytosis and activation by the endosomal proteases Cathepsin B or L independent of TMPRSS2.

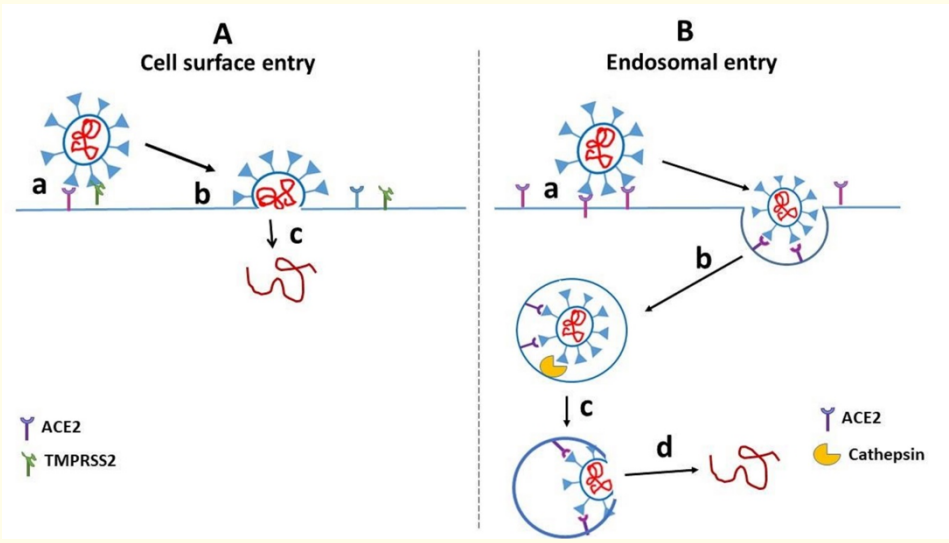

Figure 1: *1A: a) Binding of the S1 subunit of the viral S protein to the ACE2 receptor at the cell membrane surface and proteolytic activation of the spike by the plasma membrane protease TMPRSS2; b) conformational change in the S2 subunit and large-scale rearrangements of the S protein, resulting in the fusion between virus and cell membranes; c) uncoating and release of viral nucleocapsid into the cytoplasm of the host cell. Figure 1B: a) Binding of the S1 subunit of the viral S protein to the ACE2 receptor at the cell membrane surface; b) endocytosis of the viral particle; c) activation by the endosomal proteases Cathepsin B or L, which leads to fusion within the endosome; d) uncoating and release of viral nucleocapsid into the cytoplasm of the host cell.*

Cell entry of coronaviruses depends on the viral spike (S) proteins' binding to cellular receptors and S protein priming by host cell proteases. SARS-CoV-2 uses the ACE2 receptor for entry and the serine protease TMPRSS2 for S protein priming [38-43].

The ability of SARS-CoV-2 to achieve cell surface fusion is dependent on its S1/S2 polybasic cleavage site; this is absent from most closely related sarbecoviruses, which are confined to endosomal fusion. This suggests that Omicron, like Pangolin CoV, is optimized for endosomal entry. Therefore, while Delta entrance is improved for fusion at the cell surface, Omicron preferentially achieves entry through endosomal fusion. This shift in the SARS-CoV-2 entry pathway from cell surface fusion, triggered by TMPRSS2 to cathepsin-dependent fusion within the endosome, may impact transmission, cellular tropism, and pathogenesis. Moreover, this switch away from TMPRSS2-mediated activation offers a mechanistic explanation for reduced syncytia formation by Omicron infected cells. These properties can substantially change the cellular tropism and pathogenesis of the disease [37].

Concerning the neuroinvasive potential of SARS-CoV-2, the modification of Omicron's biological properties might result in less effective transmission along the olfactory nerve, resulting in less frequent impairment of smell and taste and its projection to the brainstem. There is information strongly supporting the association of neurological involvement with the lethality of SARS-CoV-2 infection, and it is now evident that severity and lethality with the Omicron variant are much lower [44].

Other causes might explain why the Omicron variant is related to less severe disease. The Omicron infection in the lung is significantly lower than the original SARS-CoV-2, mainly attacking upper respiratory structures, indicating lesser disease severity. Moreover, the increment of the vaccinated population, even after receiving the booster shot, and the accumulated herd immunity during almost two years of the pandemic might also explain a lesser-severe disease.

Conclusion

There is a shift in the SARS-CoV-2 entry pathway from cell surface fusion, triggered by TMPRSS2, to cathepsin-dependent fusion within the endosome in the Omicron variant. Therefore, we can hypothesize that this entrance modification may impact transmission from the olfactory nerve to the brainstem through transsynaptic pathways. Hence, a decrement of the virus's direct invasion to the brainstem would diminish respiratory center dysfunction, with less possibility of an ARDS complication and the need for mechanical ventilation in ICUs.

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