

# **Heterogeneity of Neurological Manifestations of SARS-CoV-2 Infection in Hospitalized Patients Across Periods of Different Viral Variant Dominance**

## **Background:**

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus Disease 2019 (COVID-19), was first identified in China in December 2019. Its uncontrolled, rapid, and global spread led to a dramatic pandemic. Repeated viral mutations resulted in the emergence of new variants: Alpha, Beta, Gamma, Delta, and the currently dominant Omicron variant, along with its clinically relevant subvariants. Beyond the typical respiratory symptoms of SARS-CoV-2 infection, neurological symptoms and complications have been reported since the pandemic's outset. Neurological manifestations during COVID-19 can result from both the direct action of the virus on the nervous system and indirect effects of the infection, such as coagulopathy, hypoxia, or systemic inflammation. SARS-CoV-2 is a neurotropic and neuroinvasive virus, possessing neurotransmissible and neuropathogenic properties. Furthermore, the virus has been shown to induce immune processes, potentially leading indirectly to the development of autoimmune diseases, including anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Neurological symptoms, involving both the central and peripheral nervous systems, as well as muscles, occur in approximately one-third of COVID-19 patients and significantly impact the disease course and prognosis. Multiple studies have shown that specific SARS-CoV-2 variants and subvariants differ in their transmissibility, general clinical presentation, disease severity, mortality rates, immunomodulatory mechanisms, and spectrum of neurological manifestations.

## **Objectives:**

1. To describe the life-threatening neurological complications in a hospitalized COVID-19 patient during the dominance of pre-Delta variants in Poland.
2. To demonstrate the association between anti-NMDAR encephalitis and SARS-CoV-2 infection.
3. To assess the frequency and differences in neurological symptoms and complications during three consecutive waves of the SARS-CoV-2 pandemic in hospitalized Polish patients. To evaluate the impact of neurological manifestations on the severity of the infection.
4. To determine the spectrum of neurological manifestations of the Omicron variant in hospitalized Polish patients, considering the differences between individual subvariants.

## **Material and Methods:**

This was a retrospective, single-center analysis of medical data of adult patients at the Specialist Regional Hospital J. Gromkowskiego in Wrocław, Poland. A case study analysis of a COVID-19 patient hospitalized in March 2020 was conducted. An analysis was performed on 600 and 426 patients, respectively, diagnosed with COVID-19 and hospitalized during three pandemic waves: pre-Delta (1 March 2020 – 30 June 2021), Delta (1 July 2021 – 31 December 2021), and Omicron (1 January 2022 – 30 June 2022), as well as during the dominance periods of Omicron subvariants (1 January 2022 – 31 December 2023). The statistical analysis included patient characteristics, differences in neurological manifestations of SARS-CoV-2 infection depending on the dominant viral variant/subvariant in the population and the impact of neurological symptoms on the disease course. A systematic review of an internet database was conducted using PRISMA 2020 (preferred reporting items for systematic reviews and meta-analyses 2020) guidelines to identify scientific articles published during the pandemic regarding the association between anti-NMDAR encephalitis and COVID-19.

## **Results:**

In the detailed case report, the patient developed multiple severe neurological complications during COVID-19, including critical illness polyneuropathy, ischemic stroke of the right occipital lobe, and thrombosis of the left transverse and sigmoid sinuses. Among the 649 articles reviewed, spanning various pandemic periods, only 16 cases were identified with confirmed SARS-CoV-2 infection and concurrent encephalitis diagnosed by clinical presentation and ancillary tests, including the presence of IgG antibodies against the NMDA receptor. All patients received typical, recommended first-line treatment, and five received second-line immunotherapy. Complete remission of encephalitis symptoms or significant improvement was observed in nine patients. The severity of SARS-CoV-2 infection was not found to influence the course of anti-NMDAR encephalitis.

Among hospitalized patients, neurological manifestations of SARS-CoV-2 infection occurred in approximately half of the patients (49% and 55.4%), with the most common: headaches, dizziness, consciousness disorders, myalgia, or ischemic stroke. During the dominance of the Omicron variant, disturbances of smell and taste were the least common compared to previous pandemic waves ( $p=0.032$  and  $p=0.007$ , respectively), whereas cerebrovascular diseases and ischemic stroke were predominant during the pre-Delta period ( $p=0.011$  and  $p=0.008$ , respectively). With the emergence of successive Omicron subvariants, the frequency of neurological manifestations of COVID-19 increased, particularly: altered consciousness, transient ischemic attack, and encephalopathy. The presence of a headache during COVID-19 was associated with a better prognosis and a lower risk of death ( $p=0.02$ ), whereas the co-occurrence of altered consciousness

or ischemic stroke statistically significantly worsened the disease course and increased patient mortality. The severity of the disease upon admission and inflammatory markers in laboratory tests were lowest during the Omicron variant dominance; furthermore, with each subsequent Omicron subvariant, the number of Intensive Care Unit admissions and deaths decreased ( $p=0.007$  and  $p<0.001$ , respectively).

### **Conclusions:**

Various symptoms and life-threatening neurological complications are frequently observed during the course of COVID-19. SARS-CoV-2 is a possible, albeit low-risk, cause of anti-NMDAR encephalitis; however, the appearance of characteristic clinical symptoms of encephalitis after COVID-19 necessitates rapid diagnosis, as early initiation of treatment significantly improves the prognosis. Among hospitalized patients during the dominance of the Omicron variant, disturbances of smell and taste occur less frequently, while cerebrovascular diseases were more common during the pre-Delta period. The frequency of neurological manifestations increases with subsequent Omicron subvariants. Co-occurring headache is a favorable prognostic sign, whereas the onset of altered consciousness or stroke during COVID-19 worsens the disease course and increases mortality. The overall prognosis of COVID-19 improves with each successive SARS-CoV-2 variant and subsequent Omicron subvariants.