SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pediatrics

The Involvement of Neurologic Symptoms among Children with COVID-19

Ziad Nazem Zatar[1*], Hani Zoheir Deep Elkanash[1]

[1]Specialist Pediatrician, Primary Health Care Corporation (PHCC), Qatar

DOI: 10.36347/sasjm.2022.v08i08.005 | **Received:** 16.07.2022 | **Accepted:** 11.08.2022 | **Published:** 13.08.2022

***Corresponding author:** Ziad Nazem Zatar
Specialist Pediatrician, Primary Health Care Corporation (PHCC), Qatar

Abstract **Review Article**

There are different symptoms associated with COVID-19 infections. Respiratory symptoms were described firstly. Neurological symptoms among adults were further reported. It was thought that COVID-19 is less likely to affect children, and as a result, neurological symptoms among children were not receiving great attention. With increasing the prevalence of COVID-19 among the whole populations, neurological manifestations among children became important. Neurological manifestations among children are varied and including as examples encephalitis, meningitis, ischemic, and hemorrhagic strokes. The present study reviewed the most recent updates of literature regarding the involvement of neurological symptoms among children with COVID-19. Taken together, neurological symptoms associated with COVID-19 are involved in children and adults following similar patterns.

Keywords: COVID-19, neurological symptoms, children, adults, encephalitis, meningitis.

INTRODUCTION

COVID-19

In the past year, a worldwide pandemic has been brought on by the novel coronavirus disease 2019 (COVID-19), which is brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Khatoon *et al*., 2022). COVID-19 has spread uncontrollably around the world and shows no sign of stopping. This virus has infected 178 million people worldwide and killed 38 million (Khatoon *et al*., 2022). Most SARS-CoV-2 cases were asymptomatic (80%) or displayed mild flu-like symptoms, including shortness of breath, fever, sore throat, cough, myalgia, loss of taste and smell, and fatigue. SARS-CoV-2 is a 26-32 kb single-stranded RNA virus. The virus is spherical or oval with an average 100 nm diameter and covered by a crown-like spike (S) protein that binds to cellular ACE-2 receptors (Wrapp *et al*., 2020). SARS-CoV-2 enters the brain via direct and indirect pathways, like SARS-CoV and MERS-CoV (Netland *et al*., 2008; Li *et al*., 2016). It can enter the CNS by infecting blood-brain-barrier endothelial cells and blood-CSF epithelial cells. Other routes to the CNS are retrograde axonal transport, synapse-connected route after entering respiratory network peripheral nerve terminals (Bohmwald *et al*., 2018), sympathetic ENS afferent neurons, and blood circulation (Baig *et al*., 2020; Khatoon *et al*., 2020).

Neurological manifestations of COVID-19

Numerous neurological manifestations have also been linked to COVID-19 patients, in addition to severe respiratory distress. Because of these cases, SARS-CoV-2 can be regarded as an opportunistic brain pathogen. The olfactory bulb, retrograde axonal transport from peripheral nerve endings, or hematogenous or lymphatic routes are all ways that SARS-CoV-2 can enter the brain. Noteworthy neurological symptoms caused by COVID-19 infection include encephalopathy, impaired consciousness, confusion, agitation, seizure, ataxia, headache, anosmia, ageusia, neuropathies, and neurodegenerative diseases (Khatoon *et al*., 2022).

Neurological complications in COVID-19 patients are increasing globally. Yea *et al*., (2021) reported 31 headache-only patients, so we excluded them and studied 180 children with SARS-CoV-2-related neurological symptoms. Using our data and the literature review, we created a chart of the most common neurological symptoms in COVID-19 children. 2 months to 17 years. 95 patients (53.4%) were women. Half of neurologic patients with MIS-C were children (n = 90, 50.6%) (LaRovere *et al*., 2021).

Neurological manifestations like encephalitis, meningitis, ischemic, and hemorrhagic strokes are reported frequently in Coronavirus patients 2019

(COVID-19). Viral infection is a major cause of acute ischemic stroke in children. We describe a child with SARS-CoV-2 infection who developed massive right cerebral artery ischemia and a malignant cerebral infarction. The patient had a life-saving decompressive hemicraniectomy and recovered well, except for hemiplegia. During rehabilitation, the patient developed a long-Covid-related lower extremity peripheral nerve neuropathy (Scala *et al*., 2022).

Neurological manifestations in adult patients affected by SARS-CoV-2, such as encephalitis, meningitis, ischemic, and hemorrhagic strokes, are reported with increasing frequency in the scientific literature (Koralnik and Tyler, 2020; Zhou *et al*., 2021). SARS-CoV-2 causes hypercoagulability through a cytokine storm that binds to ACE2 (Ranucci *et al*., 2020). Few papers reported focal arteriopathies and ischemia in SARS-COV-2-affected children (Appavu *et al*., 2021; Tiwari *et al*., 2021). In these studies, patients had obvious symptoms. We describe a child with only serological evidence of SARS-CoV-2 infection who developed massive right cerebral artery ischemia and a malignant cerebral infarction. During rehabilitation, the patient developed a long-Covid-related lower extremity peripheral nerve neuropathy (Scala *et al.*, 2021)

Lindan *et al*., (2021) found seven cases of thromboembolic or vasculitic stroke in children. Neurologic involvement was found in 4.8% of hospitalized children and adolescents with COVID-19 and/or MIS-C. Most patients with neurologic findings (80%, n = 12) were previously healthy, and most neurological manifestations (n = 15) resolved at hospital discharge. Three patients had mild-to-moderate neurologic disabilities at discharge.

Neurological symptoms in adults and children range from fatigue, headache, and anosmia to encephalopathy, seizures, and stroke (Zubair *et al*., 2019). Neurologic symptoms varied by age; young patients had seizures and status epilepticus, while older patients had headaches, taste and smell loss, and fatigue. Four patients with seizures (three with para-infectious febrile SE and one with Status Epilepticus (SE) were young children. MRI showed punctate diffusion restriction in the posterior limb of the internal capsule in a 3-month-old girl who had her first seizure postinfectious. No cause besides COVID-19 was identified. All patients were seizure-free during 3-to-6-month monotherapy follow-up.

Because there are currently no viable treatment options for the Coronavirus Disease 2019 (COVID-19), which is caused by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), the world has suffered enormous losses as a result of this illness. As a result of the fact that it can cause severe respiratory disease, neurological complications, and other associated problems, it is now considered to be a serious threat to humans. In children, COVID-19 most commonly causes symptoms that are mild and easily recoverable; however, it can cause symptoms that are serious and severe, as well as complications that can lead to death. In children, the SARS-CoV-2 virus has the potential to cause a variety of neurological complications, the most important of which include dyspnea, myalgia, stroke, and encephalopathy. These issues have a strong connection to cytokine storm and proinflammatory responses, both of which have the potential to change the physiology of the blood-brain barrier and make it easier for the virus to cross into the brain. In spite of the fact that the virus entered the brain and caused an infection there directly, these neurological complications can also be the result of indirect causes, such as severe immune responses (Khan *et al*., 2022).

COVID-19, which was caused by SARS-CoV-2, has been responsible for the deaths of a significant number of people all over the world. It is an enveloped, positive-sense, single-stranded RNA virus with a size of about 30 kilobytes (kb), and it has a sense of direction. Even though it has been reported that COVID-19 is more dangerous to adults than it is to children, the severity of the virus has also been widely reported in children (Lin *et al*., 2021). It is interesting to note that the progression of COVID-19 is the same in all individuals regardless of the severity of disease or age of the individual who is infected. The beginning of the disease is marked by the entry of the virus into the cells of the host, which is followed by the manifestation of symptoms. COVID-19 is now thought to affect multiple organ systems, especially the brain, by causing neurological complications in approximately 36 percent of the total COVID-19 patients. Although the primary symptoms of COVID-19 (pneumonia, cough, and fatigue) are associated with the pulmonary system, it is now believed that COVID-19 affects multiple organ systems. The fact that neurological complications were also reported to be caused by severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) indicates that all human coronaviruses are responsible for causing neurologic complications. On the other hand, the neurological complications brought on by COVID-19 are more widespread than those brought on by SARS and MERS. There is a lack of understanding regarding the mechanism by which COVID-19 causes these neurological complications. It is possible that the virus infected the brain directly, as it has been reported that SARS-CoV-2 can invade the brain and may also infect the peripheral and central nervous systems (Stafstrom and Jantzie, 2020). This is one of the possible explanations.

Growing evidence suggests that COVID-19 affects both the central nervous system (CNS) and the peripheral nervous system (PNS), causing respective complications due to either direct infectiousness or

immune-mediated disease in response to COVID-19 infection. These complications can be caused by either COVID-19 infection itself or immune response to COVID-19 infection. In addition, histopathological changes such as CNS infarction due to cerebral thromboembolism and the presence of viral RNA in the CNS further indicate the impact that SARS-COV-2 has had on alterations in the CNS (Meinhardt *et al.,* 2020). Patients who have COVID-19 have a higher risk of developing severe neurological complications, such as encephalopathies, myelitis, rhabdomyolysis, Guillain-Barré syndrome, cognitive syndrome, affective disorder, and cerebrovascular complications such as strokes, intracerebral hemorrhages, and CNS vasculitis) 4. Patients who have COVID-19 have a higher risk of developing severe neurological complications, such as taste and smell dysfunction, nausea, and headache However, the manifestation of these neurological complications can vary greatly depending on the underlying comorbidities and the patient's age (Lin *et al*., 2020).

SARS-CoV-2 must have the cellular receptor angiotensin-converting enzyme 2 (ACE2) and the serine protease TMPRSS2 in order to enter human host cells. This is necessary for the priming of the spike (S) protein. After initial infection, the virus is able to replicate and spread throughout the airway after the IFN type 1 antiviral pathway has been inhibited. In most cases, the virus will spread from the lung, but it is also capable of migrating to other tissues that express ACE2 (Rello *et al*., 2020). It is common knowledge that alveolar pneumocytes contain a high concentration of the enzyme ACE2, which makes it possible for SARS-CoV-2 to enter these cells and infect them. Furthermore, there is evidence to suggest that ACE2 is also expressed on neuronal and glial cells in the human CNS (Khan *et al*., 2020), which leads one to believe that SARS-CoV-2 is able to enter these cells. Despite the fact that the presence of SARS-CoV-2 RNA in CNS regions has been proven to exist (Meinhardt *et al.*, 2020), the path that viruses take to reach these regions and the mechanisms that lie beneath the surface have not been fully investigated. Preliminary evidence suggests that neuro-invasion of SARS-CoV-2 can occur via regional nervous structures at the neural-mucosal interface (Tsivgoulis *et al*., 2020). This leads one to believe that the possible transport of the virus along the olfactory tract of the central nervous system may be the cause of neurological complications. However, Meinhardt *et al*., (2020). found that there is no direct connection between viral RNA in the central nervous system and the olfactory mucosa. This suggests that the virus entry into the central nervous system may involve other pathways or mechanisms, such as CNS endothelia, axonal transport, and leukocytes (Tsivgoulis *et al*., 2020).

Children who have COVID-19 have an increased risk of developing respiratory and neurological complications. Children are not immune to the widespread effects of the currently ongoing COVID-19 pandemic, which is affecting people of all ages. It is now clear that fever and cough are two of the most common clinical manifestations of the COVID-19 virus in children. These symptoms typically manifest themselves in an abnormal manner in comparison to adults. In children, the disease can range from being asymptomatic to causing severe illness and even putting their lives at risk. Despite this, severe illness is not common in children because children are less likely to have underlying diseases such as hypertension, diabetes, or cardiovascular problems. In addition, factors such as differential expression of ACE2, co-morbidities, and predisposition to pro-inflammatory states are all conditions that have the potential to influence viral entry, replication, inflammation, hypoxia, and tissue injury. It is further helped by the increased effectiveness of the innate immune response, which normally weakens with increasing age (Williams *et al*., 2020).

CNS symptoms

Headache, dizziness

Headaches and dizziness are common neurological symptoms of COVID-19 (Guan *et al.,* 2020; Mao *et al*., 2020). Mao *et al*., (2020) reported dizziness and headache in 16.8% and 13.1% of patients. 13.6 percent of 1099 Chinese patients reported headaches in a population-based study (Guan *et al.,* 2020). Headaches are not a specific symptom of any viral infection, but they are commonly reported in COVID-19 patients, ranging from 3% to 15% in some studies (Roy *et al.,* 2020). Headaches can be a sign of viral meningitis or encephalitis and cerebrovascular disease (Wang *et al*., 2020).

Anosmia/hypogeusia

Up to 40% of COVID-19 infected adults have post-viral anosmia (Giacomelli *et al*., 2020). Hypogeusia/ageusia is reported in the US, Italy, China, UK, France, and Korea (Roy *et al*., 2020). 33.9 percent of infected patients have taste or olfactory disturbances, and 18.3 percent have both (Giacomelli *et al*., 2020). In 83% of infected patients, anosmia was the first symptom. In most cases, olfactory disturbances occurred despite no nasal inflammation or coryzal symptoms (Heidari *et al*., 2020). SARS-CoV-2 may target the odor-processing mechanism (Khatoon *et al*., 2022).

Neurological manifestations of COVID-19 among children

Schlarb *et al*., (2020) studied 5–10-year-olds and their parents, they found that 67% of kids slept less during COVID-19. A 16-year-old with extreme and persistent health concerns responded quickly to low antidepressant and antipsychotic doses (Colizzi *et al*., 2020).

In pediatric patients, respiratory disease and multisystem inflammatory syndrome in children (MIS-C) are the main concerns, but SARS-CoV-2 may target the nervous system (Ellul *et al*., 2020; Zubair *et al*., 2020).

312 COVID-19-infected children were hospitalized. Median age was 10.8 (range: 1 month–17.5 years). Fifteen (4.8%) consecutive SARS-CoV-2 cases had acute neurological symptoms. The median age of these patients at admission was 5 years. 6 (40%) women to 9 (60%) men (60 percent). Three patients had diseases: asthma, factor V Leiden mutation, and sensorineural hearing loss (Gürlevik *et al*., 2022).

In infants, the COVID-19 virus has the potential to cause life-threatening illness; as a result, it requires serious consideration. Studies have shown that fever is the most common symptom of COVID-19 in children. In addition to fever, other symptoms that have been reported in children include rhinorrhea, cough, gastrointestinal symptoms, headache, encephalopathy, mild shortness of breath, and myalgia. It is interesting to note that ground-glass opacities and mild bronchial thickening can be visible in some cases even when there are no symptoms present. On the other hand, there have been some reports that suggest children who are infected with SARS-CoV-2 might not present any clinical or radiological symptoms (Tsivgoulis *et al*., 2020). According to a report that was published not too long ago, the clinical manifestations of COVID-19 in children included a high temperature in 64 percent of cases, a cough in 35 percent of cases, and rhinorrhea in 16 percent of cases. However, 15 percent of cases were asymptomatic. In total, 54 percent of the cases presented ground-like opacities in radiological investigations, and the most common findings from laboratory tests were an elevated D-dimer level (52 percent of the cases), a low lymphocyte count (40 percent of the cases), and C-reactive protein level (40 percent of the cases) (33 percent). 15 percent of these patients, the majority of whom required intensive care, developed a multisystem inflammatory syndrome that manifested with significantly elevated inflammatory biomarkers, gastrointestinal symptoms, shock, and left ventricular systolic dysfunction. In total, this affected 15 percent of the patients. Despite this, children are at risk for developing severe symptoms. Consequently, proper management and prevention of transmission requires early detection of COVID-19 as well as timely diagnosis of the multisystem inflammatory syndrome (Yasuhara *et al*., 2020).

Headaches, encephalopathy, and altered mental status are some of the neurological complications that have been associated with COVID-19 in children. This is in addition to the multisystem inflammatory syndrome and the respiratory symptoms that have been observed. In addition, children who were diagnosed with multisystem inflammatory syndrome had severe neurological abnormalities, such as encephalitis, seizure, coma, demyelinating disorders, dysgeusia or ageusia, aseptic meningitis, stroke dysarthria, dysphagia, cerebellar ataxia, axial hypotonia, drowsiness, or moaning, and peripheral neuropathy. These symptoms were all present in the children. MRI or CT changes involving the splenium of the corpus callosum were seen in COVID-19 infected children who presented with fever, shock, and rash. These changes may increase the risk of Kawasaki disease or a disease similar to it, as well as inflammatory encephalopathies (Lin *et al*., 2021). On the other hand, additional research is necessary to confirm the actual neurological conditions that are brought on by the conditions.

CONCLUSIONS

Neurological manifestations associated with COVID-19 among children are likely to those reported among adults. Due to the considerations that children are less likely to be affected by COVID-19, their neurological manifestations are not well reported, particularly at the early stages of the pandemic. However, neurological manifestations of the COVID-19 among children should be investigated and treated as a part of the COVID-19 management.

REFERENCES

- Giacomelli, A., Pezzati, L., Conti, F., Bernacchia, D., Siano, M., Oreni, L., ... & Galli, M. (2020). Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. *Clinical infectious diseases*, *71*(15), 889-890.
- Schlarb, A. A., Schulte, H., Selbmann, A., & Och, I. (2020). Online cognitive behavioral group therapy (iCBT-I) for insomnia for school children and their parents. *Somnologie*, *24*(4), 259-266.
- Baig, A. M., Khaleeq, A., Ali, U., & Syeda, H. (2020). Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS chemical neuroscience*, *11*(7), 995-998.
- Zubair, A. S., McAlpine, L. S., Gardin, T., Farhadian, S., Kuruvilla, D. E., & Spudich, S. (2020). Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA neurology*, *77*(8), 1018-1027. 10.1001/jamaneurol.2020.2065.
- Appavu, B., Deng, D., Dowling, M. M., Garg, S., Mangum, T., Boerwinkle, V., & Abruzzo, T. (2021). Arteritis and large vessel occlusive strokes in children after COVID-19 infection. *Pediatrics*, *147*(3).
- Lindan, C. E., Mankad, K., Ram, D., Kociolek, L. K., Silvera, V. M., Boddaert, N., ... & Vézina, G. (2021). Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational,

multicentre collaborative study. *The Lancet Child & Adolescent Health*, *5*(3), 167-177. 10.1016/S2352-4642(20)30362-X.

- Roy, D., Ghosh, R., Dubey, S., Dubey, M. J., Benito-Leon, J., & Ray, B. K. (2021). Neurological and neuropsychiatric impacts of COVID-19 pandemic. *Canadian Journal of Neurological Sciences*, *48*(1), 9-24.
- Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., ... & Peng, Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*, *323*(11), 1061-1069.
- Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., ... & McLellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*, *367*(6483), 1260-1263.
- Heidari, F., Karimi, E., Firouzifar, M., Khamushian, P., Ansari, R., Ardehali, M. M., & Heidari, F. (2020). Anosmia as a prominent symptom of COVID-19 infection. *Rhinology*, *58*(3), 302-303.
- Khatoon, F., Prasad, K., & Kumar, V. (2020). Neurological manifestations of COVID-19: available evidences and a new paradigm. *Journal of neurovirology*, *26*(5), 619-630.
- Khatoon, F., Prasad, K., & Kumar, V. (2022). COVID-19 associated nervous system manifestations. *Sleep medicine*, *91*, 231-236.
- Netland, J., Meyerholz, D. K., Moore, S., Cassell, M., & Perlman, S. (2008). Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *Journal of virology*, *82*(15), 7264-7275.
- Bohmwald, K., Gálvez, N. M., Ríos, M., & Kalergis, A. M. (2018). Neurologic alterations due to respiratory virus infections. *Frontiers in cellular neuroscience*, *12*, 386.
- Li, K., Wohlford-Lenane, C., Perlman, S., Zhao, J., Jewell, A. K., Reznikov, L. R., ... & McCray Jr, P. B. (2016). Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *The Journal of infectious diseases*, *213*(5), 712-722.
- LaRovere, K. L., Riggs, B. J., Poussaint, T. Y., Young, C. C., Newhams, M. M., Maamari, M., ... & Overcoming COVID-19 Investigators. (2021). Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. *JAMA neurology*, *78*(5), 536-547. 10.1001/jamaneurol.2021.0504
- Khan S, Gomes J. (2020). Neuropathogenesis of SARS-CoV-2 infection. eLife, 9, e59136. https://doi.org/10.7554/eLife.59136.
- Khan, S., Siddique, R., Hao, X., Lin, Y., Liu, Y., Wang, X., ... & Nabi, G. (2022). The COVID-19 infection in children and its association with the immune system, prenatal stress, and neurological complications. *International journal of biological sciences*, *18*(2), 707-716. https://doi.org/10.7150/ijbs.66906.
- Koralnik, I. J., & Tyler, K. L. (2020). COVID-19: a global threat to the nervous system. *Annals of neurology*, *88*(1), 1-11.
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., ... & Hu, B. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA neurology*, *77*(6), 683-690.
- Lin, J. E., Asfour, A., Sewell, T. B., Hooe, B., Pryce, P., Earley, C., ... & Geneslaw, A. S. (2021). Neurological issues in children with COVID-19. *Neuroscience letters*, *743*, 135567.
- Colizzi, M., Bortoletto, R., Silvestri, M., Mondini, F., Puttini, E., Cainelli, C., ... & Zoccante, L. (2020). Medically unexplained symptoms in the times of COVID-19 pandemic: a case-report. *Brain, behavior, & immunity-health*, *5*, 100073.
- Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., ... & Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, *19*(9), 767-783.10.1016/S1474-4422(20)30221-0.
- Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., ... & Heppner, F. L. (2021). Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nature neuroscience*, *24*(2), 168-175.
- Ranucci, M., Ballotta, A., Di Dedda, U., Baryshnikova, E., Dei Poli, M., Resta, M., ... & Menicanti, L. (2020). The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *Journal of Thrombosis and Haemostasis*, *18*(7), 1747-1751.
- Rello, J., Belliato, M., Dimopoulos, M. A., Giamarellos-Bourboulis, E. J., Jaksic, V., Martin-Loeches, I., ... & Dimopoulos, G. (2020). Update in COVID-19 in the intensive care unit from the 2020 HELLENIC Athens International symposium. *Anaesthesia Critical Care & Pain Medicine*, *39*(6), 723-730.
- Scala, M. R., Spennato, P., Cicala, D., Piccolo, V., Varone, A., & Cinalli, G. (2022). Malignant cerebral infarction associated with COVID-19 in a child. *Child's Nervous System*, *38*(2), 441-445. https://doi.org/10.1007/s00381-021-05273-x.
- Gürlevik, S. L., Günbey, C., Ozsurekci, Y., Oygar, P. D., Kesici, S., Gocmen, R., ... & Yalnızoglu, D. (2022). Neurologic manifestations in children with COVID-19 from a tertiary center in Turkey and literature review. *European Journal of Paediatric Neurology*, 37, 139-154.

- Stafstrom, C. E., & Jantzie, L. L. (2020). COVID-19: neurological considerations in neonates and children. *Children*, *7*(9), 133.
- Tiwari, L., Shekhar, S., Bansal, A., & Kumar, S. (2021). COVID-19 associated arterial ischaemic stroke and multisystem inflammatory syndrome in children: a case report. *The Lancet Child & Adolescent Health*, *5*(1), 88-90.
- Tsivgoulis, G., Palaiodimou, L., Zand, R., Lioutas, V. A., Krogias, C., Katsanos, A. H., ... & Tsiodras, S. (2020). COVID-19 and cerebrovascular diseases: a comprehensive overview. *Therapeutic advances in neurological disorders*, *13*, 1756286420978004.
- Williams, P. C., Howard-Jones, A. R., Hsu, P., Palasanthiran, P., Gray, P. E., McMullan, B. J., ... & Bartlett, A. W. (2020). SARS-CoV-2 in children: spectrum of disease, transmission and immunopathological underpinnings. *Pathology*, *52*(7), 801-808.
- Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., ... & Zhong, N. S. (2020). Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*, *382*(18), 1708-1720.
- Yasuhara, J., Kuno, T., Takagi, H., & Sumitomo, N. (2020). Clinical characteristics of COVID-19 in children: a systematic review. *Pediatric pulmonology*, *55*(10), 2565-2575.
- Yea, C., Barton, M., Bitnun, A., Morris, S. K., El Tal, T., Ulloa-Gutierrez, R., ... & Yeh, E. (2021). Neurological Manifestations of SARS-CoV-2 in Hospitalized Children: A Multi-National Cohort Study. Available at: SSRN: https://ssrn.com/abstract=3831858 or https://doi.org/10.2139/ssrn.3831858.
- Zhou, Z., Kang, H., Li, S., & Zhao, X. (2020). Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. *Journal of neurology*, *267*(8), 2179-2184.