# Unraveling the link: SARS-CoV-2 infections and seizures in pediatric patients (Review)

GIOVANNI CACCIAGUERRA[1], ANDREA MARINO[2], LUIGI LA VIA[3], OTTAVIA AVOLA[1], CLAUDIA PARANO[4], GIUSEPPE NUNNARI[2], SERENA SPAMPINATO[2], RENATA PAVONE[4], RAFFAELE FALSAPERLA[5] and PIERO PAVONE[4,5]

[1]Postgraduate Training Programme in Pediatrics, Department of Clinical and Experimental Medicine, University of Catania, I-95125 Catania, Italy; [2]Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Catania, I-95122 Catania, Italy; [3]Department of Anesthesia and Intensive Care, University Hospital Policlinico-San Marco, I-24046 Catania, Italy; [4]Department of Clinical and Experimental Medicine, Section of Pediatrics and Child Neuropsychiatry, University of Catania, I-95125 Catania, Italy; [5]Institute for Biomedical Research and Innovation, Italian National Research Council, I-95123 Catania, Italy

Received December 31, 2024; Accepted September 2, 2025

DOI: 10.3892/wasj.2025.398

**Abstract.** Coronavirus disease 2019 (COVID-19) caused by the highly infectious severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a relatively recent emerging public welfare issue due to the rapid pandemic diffusion of the infection and to the new data acquisitions on the acute and chronic consequences related to the disorder. The first clinical manifestations identified were the involvement of the respiratory tract, with mild fever, rhinorrhea, cough and shortness of breath; these are the most frequently reported symptoms. Adults who are older, of the male sex, have cardiovascular issues, are obese, and have high blood pressure or diabetes are more likely to have a poor outcome following infection. This is true for both healthy children and adults who are otherwise healthy. In individuals with COVID-19, neurological involvement varies, presenting with mild, or severe clinical complications; seizures are known to be the most common neurological manifestation. Neurological manifestations in childhood are less common and usually less severe than those observed in adults and may present with variable features involving the central, as well as the peripheral nervous system. The present literature review discusses the link between COVID-19 infection and infection-related seizures in children, as well as the effects of COVID-19 infection in children affected by epilepsy. Seizures in COVID-19 may raise from direct infectious, inflammatory or vascular causal effects on central nervous system structures. Indirect effects due to previous systemic disruptions or complications provoked by COVID-19 infection are other suggestive causes. The effects of COVID-19 infection on children affected by epilepsy and COVID-19 as possible causal ground for subsequent epilepsy are also discussed herein. The vaccination, early diagnosis and the correct treatment of children affected by COVID-19 are relevant factors for preventing the more aggressive course of the disorder and for preventing cerebral involvement, which may be the cause of subsequent severe clinical complications.

## Contents



*Correspondence to:* Dr Giovanni Cacciaguerra, Postgraduate Training Programme in Pediatrics, Department of Clinical and Experimental Medicine, University of Catania, I-95125 Catania, Italy
E-mail: gio.cacciaguerra@gmail.com

*Key words:* seizures, severe acute respiratory syndrome coronavirus-2, children with COVID-19, SARS-CoV-2-related complications, pediatric SARS-CoV-2, child epilepsy

## 1. Introduction

Coronavirus disease 2019 (COVID-19) caused by the highly infectious caused by the highly infectious severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan, China in December 2019 with a rapid pandemic diffusion worldwide (1). Of note, six coronavirus species are recognized to cause human diseases and among these, four viruses 229E, OC43, NL63 and HKUI are the most frequent and known cause of common cold symptoms in immune-competent individuals. The other two coronavirus strains, SARS-CoV and Middle East respiratory syndrome-coronavirus (MERS-CoV)

emerged in humans at the beginning of the 21st century, likely originating in bats (1-3). Both these infections have a zoonotic origin and may present a more severe course (2). Coronaviruses belong to the *Coronoviridae* family that comprise viruses which are characteristically identified by a ribonucleic acid core surrounded by a protein-spiked envelope and by their structural resemblance to a crown (4). SARS-CoV-2 infection had a rapid diffusion in humans, resulting in a global pandemic spread (5). The period of incubation of the infection lasts ~5 days. The most common presenting symptoms are fever, cough, malaise and fatigue (6). In adults, neurological complications of COVID-19 are frequently reported and mainly include headache and dizziness. Some authors reported the incidence of neurological manifestations to be as high as 36.4% (7), including acute cerebrovascular diseases, impaired consciousness and skeletal muscle injury. Other authors (8) have also reported encephalopathy and delirium as possible manifestations. Among these complications, the most frequently reported are cerebrovascular accidents, Guillain-Barrè syndrome, acute transverse myelitis, acute encephalitis, hyposmia and seizures (8). Anand *et al* (9) first published a case series of 7 patients who were epileptic. A following systematic review revealed that epilepsy occurred in 0.7% of critical ill adult patients with COVID-19 (10).

Neurological manifestations in individuals affected by COVID-19 have also been reported in children; however, there is common evidence to indicate that the infection is less frequent and less severe compared to that in adult patients. In fact, it has been reported that only 5.6% of children affected by COVID-19 exhibit severe clinical symptoms (11). Among these affected children, only 7% had an associated diagnosis of neurologic complications, the most frequent being febrile seizures (3.9%), non-febrile seizures (2.3%) and encephalopathy (2.2%) (12-14). Compared to adults, children appear to have a milder clinical course, not only as regards respiratory symptoms, but also in the incidence and severity of neurological complications, possibly due to differences in immune response maturity, ACE2 receptor expression and neurodevelopmental status.

The present review aimed to provide a summary of the association between SARS-CoV-2 infection and seizures as possible direct causal factors through infectious, inflammatory or vascular noxious effects on the cerebral nervous system (CNS) or as indirect events linked to the systemic complications caused by COVID-19. SARS-CoV-2 infection on epileptic children and the risk of a possible cerebral damage as basic pathway for subsequent epileptic disorder is also discussed.

## 2. Literature search methods

The authors searched clinical trials, primary research and reviews from online bibliographic databases (MEDLINE, Embase, PubMed, Cochrane Central, Web of Sciences and Scopus) selected from 2019 to October 2022. The key search terms derived from the medical subject heading terms were pertaining to 'COVID-19', 'SARS-CoV-2' and 'Neurologic manifestations', and 'neurological complication' and 'Epilepsy' and 'Seizures', and 'Febrile seizures'. The authors included case reports, retrospective studies, prospective studies, systematic reviews and meta-analyses, clinical guidelines and narrative reviews on 'COVID-19 and Epilepsy', COVID-19 and Seizures', and 'COVID-19 and Neurologic complications'. The literature research was restricted to studies published in the English language. Relevant studies were manually examined and included in the current reference list. After removing duplicate records, the main research results were included. The authors reviewed all the articles and discussed each article. A formal quality assessment of the included studies was not performed due to the narrative nature of the review and the heterogeneity of the selected studies. This constitutes a limitation of the present study.

## 3. Pathogenesis of neurological complications

In individuals affected by COVID-19, several hypotheses have been proposed to elucidate the neurological effects; however, numerous questions remain unanswered. As detailed in the study by Palabiyik *et al* (15), neurological implications associated with COVID-19 could stem from four probable pathways: i) Systemic inflammatory reactions instigated by the viral infection, either during its acute phase or in cases involving multisystem inflammatory syndrome (MIS-C); ii) vascular and prothrombotic influences of the viral infection; iii) an immune-driven parainfectious or post-infectious autoimmune reaction arising from the viral presence; iv) a direct neurotropic or neuroinvasive action of the virus via the olfactory route. SARS-CoV-2 is acknowledged for its neurotropic capability, akin to other respiratory pathogens, such as influenza, respiratory syncytial virus, human herpesvirus-6 and -7, echovirus and coxsackievirus (16). The respiratory system is initially targeted by COVID-19, subsequently progressing through three distinct stages: In the first stage, the virus adheres to epithelial cells within the respiratory tract, initiating primary replication; in this phase, most infected individuals can manage the virus, resulting in mild clinical presentations. In the second stage, the infection may extend into the lower airways, affecting alveolar epithelial cells, leading to pulmonary viral replication, inflammation, and pneumonia. The third stage is marked by rapid viral replication in the lungs, inducing cellular death (apoptosis) and vascular leakage, accompanied by the release of proinflammatory proteins (4,17,18).

It has been suggested that SARS-CoV-2 binding to pulmonary epithelial cells can initiate a systemic inflammatory response syndrome, increasing the levels of interleukin (IL)-2, IL-6, IL-7, IL-10, IL-12 and IL-15, alongside factors such as Granulocyte-macrophage colony-stimulating factor, interferon gamma-induced protein-19, macrophage chemoattractant protein-1 and TNF-α, producing an intense pro-inflammatory state similar to that observed in acute respiratory distress syndrome (ARDS) and MIS-C, among other neurological and systemic complications (4,17-22). As regards neurological effects, SARS-CoV-2 infections are considered to elevate cytokine production, referred to as a 'cytokine storm', which is deemed to cause increased permeability and the partial breakdown of the blood-brain barrier (BBB), allowing peripheral cytokines to infiltrate the CNS. This can, in turn, exacerbate or provoke neuroinflammation and impair neuronal function (23-25). CNS manifestations observed in patients with COVID-19 may also be attributed to 'endotheliopathy', either due to the direct invasion of endothelial cells in the BBB

vasculature or as a result of an immune-mediated cascade causing swelling or inflammation of these cells, ultimately leading to neurological involvement (16). Almqvist *et al* (26) noted that common neurological symptoms of COVID-19 include fatigue, headaches and disturbances in smell/taste, urging clinicians to monitor at least five major categories of neurological complications associated with COVID-19: i) Cerebrovascular conditions, such as ischemic stroke and macro/micro-hemorrhages; ii) encephalopathies; iii) para-/post-infectious immune-mediated complications, such as Guillain-Barré syndrome and acute disseminated encephalomyelitis; iv) (meningo-)encephalitis, potentially accompanied by seizures; and v) neuropsychiatric issues, including psychosis and mood disorders. They suggested that some of these complications may lead to lasting disabilities. They also suggested that genetic susceptibility factors may contribute to the development of neurological complications following SARS-CoV-2 infection, although further studies are required to clarify this role (26).

## 4. Seizures, epilepsy and COVID-19 infection

SARS-CoV-2 infection, as a potential direct or indirect contributor to seizures and epilepsy, is a subject infrequently explored in the literature, and the role of COVID-19 in worsening seizures among epileptic individuals is insufficiently addressed. The most widely accepted theories regarding SARS-CoV-2-associated seizures include the direct viral invasion of neurons, immune-mediated harm, or a combination of both mechanisms (23,27). The documented likelihood of unprovoked seizures among population-based cohorts of survivors of CNS infections from developed nations ranges between 6.8 and 8.3%, with significantly higher rates in underprivileged regions. Seizures related to COVID-19 may emerge as a consequence of encephalopathy or due to severe infection-related complications, and as noted by Al-Ramadan *et al* (28), they may sometimes be the initial indication of COVID-19. Vollono *et al* (29) documented the case of a 78-year-old female patient with COVID-19, hypertension, and well-controlled post-encephalitic epilepsy who, following a 2-year seizure-free interval, exhibited a focal seizure as her first sign of epilepsy.

In their study, Román *et al* (30) emphasized that amidst various COVID-19-related complications, isolated cases of seizures, encephalopathy, meningitis, encephalitis and myelitis have been observed. Mithani *et al* (31) detailed the cases of three critically ill adult patients with COVID-19 undergoing EEG monitoring who experienced new-onset seizures and encephalopathy up to 3.5 weeks following symptom onset. CNS infections, as highlighted by Vezzani *et al* (27), are among the leading risk factors for developing epilepsy. In pediatric studies, COVID-19-related seizures or epilepsy are seldom mentioned. It is well-established that children and adolescents appear less susceptible to SARS-CoV-2, and the disease trajectory in this population is generally milder than that in adults. The mechanisms underlying seizure onset in children appear to differ from those in adults, with a greater role attributed to systemic inflammatory responses and multisystem inflammatory syndrome rather than direct viral invasion.

Common causes of seizure-inducing disorders, epilepsy and severe neurological complications are rarely reported in children. This rarity may be attributed to the recent emergence of the infection and the longer time required to observe systemic and neurological disorders stemming from COVID-19 that could later manifest as epilepsy or other conditions. Some researchers have suggested that children with pre-existing severe health conditions are more prone to experiencing severe complications. The study by Tiruneh (32) stated that the clinical symptoms of COVID-19 in children are non-specific and difficult to define. The majority of affected children present mild symptoms without fever or pneumonia, with favorable outcomes. According to the author, only a small proportion of infected children experience severe complications. Underlying health issues, such as chronic pulmonary or cardiovascular conditions, immunosuppression and obesity, may increase the severity of the course of the disease (32). Other factors contributing to clinical severity include seizures, kidney or liver disease, endocrine disorders and being <1 year of age (32).

In a previous systemic review and meta-analysis involving 3,707 patients, only 1% of children were found to have definitive neurological complications, most of which were linked to pre-existing severe conditions. Among these cases, 25 children experienced encephalopathy, 12 had seizures and 17 exhibited meningeal involvement, all exhibiting signs indicative of MIS-C or Kawasaki-like syndrome (33). MIS-C represents a severe complication of SARS-CoV-2 in children, also referred to as Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). Common MIS-C symptoms include fever, gastrointestinal issues, rash and conjunctivitis; however, in severe cases, cardiac symptoms may necessitate intensive care (34).

Neurological features and laboratory analyses of patients with MIS-C suggest a post-infectious immune response, similar to COVID-19-related autoimmune meningoencephalitis reported in adults (35). Yilmaz Ciftdogan *et al* (36), in a review of 614 children with COVID-19 and MIS-C, noted that 17 (2.8%) had seizures. The clinical presentation of MIS-C shares a number of features with incomplete Kawasaki disease and toxic shock syndrome, requiring careful differential diagnosis. However, as Hogan *et al* (37) stated in a large cohort study, seizures and epilepsy are rarely reported in mild COVID-19 cases, although they may appear in more severe instances at later stages in the progression of the disease.

In a prospective observational cohort study of 651 children and young individuals <19 years of age admitted to 138 hospitals in the UK, Wales, and Scotland, Swann *et al* (38) identified three distinct clinical phenotypes: The most common was a respiratory illness cluster involving upper and lower respiratory symptoms; the second was a systemic muco-cutaneous-enteric illness cluster; and the third was a rarer neurologic cluster characterized by seizures and confusion. These findings align with the general observation that seizures and epilepsy associated with COVID-19 are uncommon.

Among adult patients with COVID-19, various seizure types have been reported, including new-onset focal seizures, serial seizures and status epilepticus (39). In the majority of cases, these seizures are multifactorial in origin, with affected individuals often having prior vascular issues or

Table I. Seizures in children with SARS-CoV-2 infection identified in the literature.

| Author(s) | Period of recruitment | No. of children | Seizures (%) | (Refs.) |
|---|---|---|---|---|
| Ray *et al* | April, 2020-February, 2021 | 51/1,334 | 7 SE (13.7%) | (40) |
| Riva *et al* | April, 2020-March, 2021 | 237 | 5 (6.3%) | (41) |
| Garazzino *et al* | April, 2020 | 168 | 5 (2.5%) | (42) |
| Kurd *et al* | March-December, 2020 | 175 | 11 (6%) | (43) |
| Cloete *et al* | October-December, 2021 | 139 | 14 (20%) | (44) |
| Lin *et al* | March-June, 2020 | 82 | 4 (11%) | (45) |
| Ludvigsson | - | - | 3 | (46) |
| Cadet *et al* | - | 8,854 | 44 (0.5%); 30 FSS (68%); 14 FSC (31.8%) | (47) |

SE, status epilepticus; FS, febrile seizure; FSS, simple febrile seizures; FSC, complex febrile seizures; NG, neurological group; PIMS-TS, pediatric inflammatory multisystem syndrome-temporally associated.

other comorbidities such as diabetes, obesity, kidney disease, multiorgan failure and metabolic imbalances (39). In children, the mechanisms leading to new-onset seizures related to COVID-19 remain poorly understood and are likely diverse. These seizures may result from viral encephalitis directly affecting the CNS, metabolic or respiratory dysfunction, or complications associated with COVID-19. Children with underlying health problems, immunosuppression, or poor general health are more prone to developing neurological complications, including seizures. MIS-C, one of the most severe COVID-19-related complications, frequently presents with seizures (36).

## 5. Seizures and COVID-19 in children/adolescents

Following a search of the literature, in children, eight clinical reports of SARS-CoV-2-related seizures were identified (Table I). In the UK, during the period from April 2, 2020, to February 1, 2021, 52 cases out of 1,334 children and adolescents were hospitalized with COVID-19, indicating an estimated prevalence of 3.8 (95% CI 2.9-4.9) cases per 100 pediatric patients. These children had a median age of 9 years (range, 10-17 years); 22 (42%) were girls, and 30 (58%) were boys (40). Children exhibiting neurological symptoms were categorized into two groups: 27 (52%) in the COVID-19 neurology group and 25 (48%) in the PIMS-TS neurology group. In the first group, diagnoses included status epilepticus in 7 children, encephalitis in 5 children, Guillain-Barré syndrome in 5 children, acute demyelinating syndrome in 3 children, chorea in 2 children, psychosis in 2 children, isolated encephalopathy in 2 children and transient ischemic attack in 1 child. The PIMS-TS group predominantly displayed features, such as encephalopathy in 22 children, the involvement of the peripheral nervous system in 10 children, behavioral changes in 9 children and hallucinations during presentation in 6 children. Of the PIMS-TS group, 20 out of 25 children were admitted to intensive care units, compared to 6 out of 27 children in the neurology group. No seizures were explicitly reported within the PIMS-TS group (40). In another study, between April 2020 and March 2021, a cohort of 237 children with a median age of 3.2 years, who tested positive for SARS-CoV-2 via molecular swabs, was recruited from an Italian tertiary pediatric center (41). Neurological symptoms were noted in 32 (13.5%) children, while 205 (86.5%) children exhibited no neurological involvement. Among those without neurological symptoms, respiratory issues (59.5%) and gastrointestinal complaints (25.3%) were most common. In the group with neurological impairments, the following symptoms were observed: Headache (65.6%), altered consciousness (18.8%), anosmia/ageusia (12.5%), seizures (6.3%) and vertigo (6.3%), with combined symptoms in 7 (21.9%). In this cohort, 5 (2.1%) children had a prior history of epilepsy, which included symptomatic epilepsy (1 arachnoid cyst and 1 astrocytoma), genetic generalized epilepsy, developmental epileptic encephalopathy and epilepsy linked to fragile X syndrome. All these seizures were well-managed. However, new-onset seizures occurred in a 5-year-old girl with a history of ischemic stroke and jejunal atresia who was admitted to the emergency department with a focal-onset motor seizure. Her EEG revealed left frontotemporal epileptiform abnormalities (41). In their study, Garazzino *et al* (42) described, in April 2020, 168 children, the majority of whom were hospitalized, with an average age of 5 years, along with 5 neonates. The most prevalent symptoms were fever (82.1%), cough (48.8%), rhinitis (26.8%) and gastrointestinal issues (18.4%). Among these children, 5 (2.5%) children experienced seizures: 2 were febrile and 3 were non-febrile. Among children with non-febrile seizures, 3 children had a known history of epilepsy. Of the 2 children with febrile seizures, 1 child had a prior history of febrile seizures, and the other was experiencing their first episode (42). In another study, out of a group of 175 children (age range, 0-18 years) admitted to the emergency department with acute SARS-CoV-2 infection, 11 children were hospitalized due to seizures (43). Among these, 9 children presented with tonic-clonic seizures, 1 child had a focal tonic seizure, and 1 child, a 5-month-old infant, exhibited bilateral symmetrical tonic-clonic seizures. Five children had convulsive status epilepticus; none had a prior history of status epilepticus, and only 1 child had no prior history of seizures. Of these, 7 children had a pre-existing neurological condition, 5 children

had epileptic seizures, 1 child had a single unprovoked seizure three years prior and 1 child had intellectual disability (43). In another study, from October to December 2021, 6,287 children and adolescents were admitted to 42 hospitals in the Tshwane District, South Africa, with COVID-19, 99% of whom were affected by the Omicron variant. Detailed clinical data were available for 139 out of 183 (76%) hospitalized children. Reported symptoms included fever (47%), coughing (40%), vomiting (24%), difficulty breathing (23%), diarrhea (20%) and convulsions (20%). The majority of children (92%) were treated in standard care wards, with 31 (25%) requiring oxygen therapy. A total of 7 children (6%) were ventilated, and 4 children, all with severe comorbidities, succumbed (44). Data from the New York-Presbyterian Morgan Stanley Children's Hospital, involving 82 children aged 5 days to 18 years hospitalized between March and June, 2020, revealed that 35 (43%) children developed neurological symptoms, including headache in 12 (12.4%) children, fatigue or malaise in 9 (25%) children, an altered mental state in 8 (23%) children, weakness in 5 (14%) children and seizures in 4 (11%) children (45). Ludvigsson (46) reported on 3 children who were positive for COVID-19 with seizures: A 3-month-old with prolonged convulsions, a 21-month-old with 15-20 min of continuous seizures, and a 14-year-old who experienced a 30-60-min seizure followed by an unusual aggressive episode. Cadet *et al* (47) retrospectively analyzed a series of febrile seizures in children with COVID-19. Among 8,854 children aged 0-5 years across 34 healthcare facilities, 44 (0.5%) children experienced febrile seizures, of which 30 (68.2%) children were classified as simple and 14 (31.8%) children as complex. None of these children had a prior history of epilepsy or seizures. In total, 3 children (6.8%) exhibited status epilepticus. In that study, no deaths were reported among children diagnosed with epilepsy (47). Additionally, other post-infectious inflammatory complications, such as recurrent otitis media, have been reported in pediatric patients following COVID-19, supporting the hypothesis of a broader inflammatory impact of the infection even beyond the neurological system.

## 6. Epilepsy and COVID-19 in children/adolescents

In the study by Yoo *et al* (48) regarding the influence of COVID-19 infection on adult patients with epilepsy, the researchers addressed two key points: i) Whether individuals with epilepsy are more likely to contract COVID-19; and ii) whether epileptic patients with COVID-19 are at an increased risk of developing severe complications compared to those without epilepsy. Among the 212,678 participants, 3,919 (1.8%) had a history of epilepsy. Following a detailed statistical analysis, the authors of that study concluded that epilepsy was not associated with increased vulnerability to COVID-19 infection, nor was there elevated mortality linked to the infection. However, that study underscored a higher likelihood of severe complications from COVID-19 in patients with epilepsy (48). There are limited studies available exploring why epileptic children may have a greater predisposition to COVID-19. Parihar *et al* (49) suggested that epileptic children who administered immunosuppressive treatments, including steroids, adrenocorticotropic hormone and other medications for underlying conditions, may exhibit an increased susceptibility to COVID-19. Furthermore, psychological stress commonly observed in individuals with COVID-19 may lower immune defenses in epileptic children, potentially increasing the risk of infection (50). Currently, there is no direct evidence to indicate that COVID-19 itself increases seizure frequency in children with pre-existing epilepsy. However, in certain epileptic syndromes or children with febrile seizures, fever, a common early symptom of COVID-19, may act as a significant trigger for initiating or worsening seizures. This is particularly true in cases such as severe myoclonic epilepsy of infancy (Dravet syndrome), characterized by seizures beginning at 6-8 months of age, typically associated with fever at either high or low temperatures. Clinical features include severe myoclonic seizures, multiple seizure types, prolonged episodes of status epilepticus, often prompted by fever (51). Additionally, poor sleep reported in children with COVID-19 may precipitate seizures in generalized epilepsy syndromes, such as juvenile myoclonic epilepsy (49). The potential of COVID-19 to exacerbate epileptic seizures is highlighted in the study by Brisca *et al* (52), which detailed 2 children with pre-existing epilepsy who, following prolonged seizure-free intervals, experienced seizure recurrence during COVID-19. One case involved a 5-year-old girl with a history of perinatal ischemic stroke complicated by focal epilepsy, well-controlled with levetiracetam. Following 4 years being seizure-free, she developed focal motor status epilepticus, resolved with intravenous midazolam. The second case involved an 11-year-old girl with fragile X syndrome and recurrent status epilepticus linked to febrile episodes. Following 6 years of being seizure-free on levetiracetam, she experienced prolonged focal seizures triggered by a febrile episode lasting 2 days. Both girls tested positive for COVID-19 through polymerase chain reaction testing. Children with chronic comorbidities are at an increased risk of developing severe COVID-19 outcomes. In their study, Farrar *et al* (53) examined 544 children, 330 (60.7%) hospitalized for COVID-19-related illnesses, while the remaining were admitted for unrelated care (n=201, 36.9%) or for social or infection control reasons (n=13, 2.4%). Among the COVID-19-related hospitalizations, 70.3% (n=232) were classified as non-severe cases, while 29.7% (n=98) were severe. In the group of children with existing morbid conditions, 142 (43.0%) were hospitalized, including 79 (23.9%) with non-complex conditions and 63 (19.1%) with complex conditions. Neurological and neurodevelopmental disorders were the most prevalent among comorbidities, affecting 46 children (13.9%), including epilepsy (n=20), chronic encephalopathies (19, with 8 cases of cerebral palsy), and chromosomal/genetic disorders (n=9, including trisomy 21). That study concluded that severe outcomes occurred across all age groups, regardless of comorbidities, although neurological and pulmonary disorders and dependency on medical technology were associated with higher risks of severe COVID-19 complications (53).

The reasons why children with epilepsy experience more severe COVID-19 outcomes remain unclear. As noted by Berg and Jobst (54), children who are at higher risk of developing neuro-COVID conditions often have pre-existing neurological issues, with epilepsy being the most common. In neuro-COVID cases, epilepsy was present in 16% of patients compared to 3% in non-neuro-COVID cases. One explanation

for the more severe disease course in epileptic patients may involve interactions between seizure medications and other factors, including the presence of additional neurological and non-neurological complications. Pre-existing epilepsy is often considered a clinical risk factor during COVID-19 infection. As previously reported by LaRovere *et al* (14), children who were most vulnerable to neuro-COVID during hospitalization were those with pre-existing neurological conditions, particularly epilepsy. This highlights the importance of early identification and close clinical monitoring in children with epilepsy affected by COVID-19, particularly for the prevention of severe disease courses and long-term consequences.

## 7. New-onset epilepsy and COVID-19

Several theories have been proposed regarding the development of neurological symptoms and new-onset epilepsy associated with COVID-19 infection; however, the exact pathogenic mechanism remains uncertain. One hypothesis suggests that the virus reaches the central nervous system either directly via neural pathways or indirectly through the ACE2 receptor, resulting in brain damage that may lead to epilepsy. COVID-19 infection induces a significant elevation of proinflammatory cytokines in the nervous system. This 'cytokine storm' can disrupt the BBB, increase concentrations of glutamate and aspartate, reduce gamma amino butyric acid levels and impair ion channel functions, thereby enhancing excitability and triggering epileptic seizures (55,56). Vezzani *et al* (27) proposed that viral infections may impact brain parenchyma through two distinct mechanisms once the virus penetrates the brain: The first involves the direct viral infection of neurons, causing neuronal destruction and death, accompanied by the release of pro-inflammatory cytokines and cellular byproducts acting as danger signals. The second mechanism involves these pro-inflammatory cytokines and danger signals activating innate immunity, which eventually leads to adaptive immune responses and subsequent immunopathology or tissue damage (27). In the study by Lu *et al* (57), which included 304 participants, 108 of whom were severely affected, none had a documented history of epilepsy, acute symptomatic seizures or status epilepticus. Among children, there is no concrete evidence to indicate a connection between COVID-19 infection and the onset of epilepsy. However, given the potential for inflammatory injury to the CNS, prospective studies are warranted to monitor long-term neurological outcomes in pediatric populations. The potential for COVID-19 to create conditions conducive to epilepsy development has not been demonstrated, as the clinical progression of COVID-19 in children is typically milder compared to that observed in adults.

## 8. Treatment of seizures and epilepsy

Children experiencing seizures related to COVID-19 and those with pre-existing epilepsy affected by COVID-19 infection should receive the standard and appropriate treatment for these conditions. It is important to highlight that certain combinations of anti-epileptic medications and COVID-19 treatments (e.g., the combination of eslicarbazepine/lacosamide with atazanavir/lopinavir/ritonavir) have been reported to result in severe complications in adult patients (58-61). Vaccination against SARS-CoV-2 is strongly advised for healthy children to prevent the spread of the infection. Research has shown that COVID-19 vaccination does not increase seizure frequency in the majority of epileptic patients, and no significant interactions between antiepileptic medications and COVID-19 vaccines have been documented. In children predisposed to febrile seizures, the fever induced by the vaccine may potentially trigger seizures; however, the likelihood of this occurrence is extremely low (59). Particular attention should be paid to the management of pediatric patients with epilepsy in resource-limited settings, where access to diagnostic tools and therapeutic interventions may be reduced during pandemic peaks. Strategies to ensure continuity of care and seizure control are essential.

## 9. Conclusions and future perspectives

According to the data obtained from the literature, the incidence of seizures in children occurring during the infection is extremely low. Seizures may be caused by direct invasion or immune-mediated mechanisms or both conditions in association. More often, chronic underlying diseases, such as pulmonary disorders, cardiovascular diseases, immunosuppressive illnesses, or complications such as MIS-c, obesity and seizures per se, may be the secondary cause of the onset of seizures and in same case, may constitute the cerebral environment for the subsequent development of epilepsy. The incidence of epilepsy as a direct consequence of COVID-19 infection is not yet known (60-62). The present review aimed to fill part of the existing knowledge gaps by summarizing the available clinical reports and highlighting the importance of the early diagnosis and management of seizures in children with COVID-19 infection.

Future prospective studies are warranted to better clarify the associations between SARS-CoV-2 infection and the possible development of epilepsy during childhood. Clinicians should be aware of the need for long-term neurological monitoring, particularly in children with pre-existing comorbidities or severe disease presentations. Further studies and clinical experiences are required to address this critical issue.

## Acknowledgements

Not applicable.

## Funding

No funding was received.

## Availability of data and materials

Not applicable.

## Authors' contributions

GC, PP, RF and AM conceptualized the study. LLV was involved in the literature search. CP, GN, SS and OA were involved in the investigative aspects of the review (analyzing the data from the literature). GC and AM were involved in the writing and preparation of the original draft of the manuscript. OA, CP and RP were involved in the writing, reviewing and

editing of the manuscript. PP and RF supervised the study. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**


1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, *et al*: A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382: 727-733, 2020.
2. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, Liu W, Bi Y and Gao GF: Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol 24: 490-502, 2016.
3. Cui J, Li F and Shi ZL: Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 17: 181-192, 2019.
4. Sharma S, Sharma U, Chaudhary A, Naithani M, Naithani P, Prashar S, Sharma B, Nagar RK, Bhukya PL, Bhalerao U, *et al*: SARS-CoV-2: Insights from the immunopathogenesis and current clinical diagnosis and therapeutic strategies. J Immunological Sci 5: 1-15, 2021.
5. World Health Organization. Coronavirus disease 2019 (COVID-19): Situation report, 102. World Health Organization, 2020. Available from: https://apps.who.int/iris/handle/10665/332055.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, *et al*: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506, 2020.
7. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, *et al*: Neurologic Manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 77: 683-690, 2020.
8. Ahmad I and Rathore FA: Neurological manifestations and complications of COVID-19: A literature review. J Clin Neurosci 77: 8-12, 2020.
9. Anand P, Al-Faraj A, Sader E, Dashkoff J, Abdennadher M, Murugesan R, Cervantes-Arslanian AM and Daneshmand A: Seizure as the presenting symptom of COVID-19: A retrospective case series. Epilepsy Behav 112: 107335, 2020.
10. Cagnazzo F, Arquizan C, Derraz I, Dargazanli C, Lefevre PH, Riquelme C, Gaillard N, Mourand I, Gascou G, Bonafe A and Costalat V: Neurological manifestations of patients infected with the SARS-CoV-2: A systematic review of the literature. J Neurol 268: 2656-2665, 2021.
11. Sinha IP, Harwood R, Semple MG, Hawcutt DB, Thursfield R, Narayan O, Kenny SE, Viner R, Hewer SL and Southern KW: COVID-19 infection in children. Lancet Respir Med 8: 446-447, 2020.
12. Antoon JW, Hall M, Howard LM, Herndon A, Freundlich KL, Grijalva CG and Williams DJ: COVID-19 and acute neurologic complications in children. Pediatrics 150: e2022058167, 2022.
13. Fink EL, Robertson CL, Wainwright MS, Roa JD, Lovett ME, Stulce C, Yacoub M, Potera RM, Zivick E, Holloway A, *et al*: Prevalence and risk factors of neurologic manifestations in hospitalized children diagnosed with acute SARS-CoV-2 or MIS-C. Pediatr Neurol 128: 33-44, 2022.
14. LaRovere KL, Riggs BJ, Poussaint TY, Young CC, Newhams MM, Maamari M, Walker TC, Singh AR, Dapul H, Hobbs CV, *et al*: Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol 78: 536-547, 2021.
15. Palabiyik F, Koral K and Pruthi S: Nonvascular nervous system complications in pediatric patients with COVID-19 infection. J Pediatr Neurol 20: 319-326, 2022.
16. Govil-Dalela T and Sivaswamy L: Neurological effects of COVID-19 in children. Pediatr Clin North Am 68: 1081-1091, 2021.
17. Zimmermann P and Curtis N: Coronavirus infections in children including COVID-19: An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J 39: 355-368, 2020.
18. Jurado Hernández JL and Álvarez Orozco IF: COVID-19 in children: Respiratory involvement and some differences with the adults. Front Pediatr 9: 622240, 2021.
19. Bridwell R, Long B and Gottlieb M: Neurologic complications of COVID-19. Am J Emerg Med 38: 1549.e3-1549.e7, 2020.
20. Nakra NA, Blumberg DA, Herrera-Guerra A and Lakshminrusimha S: Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: Review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel) 7: 69, 2020.
21. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, Gillen JK, Perez MM, Soshnick SH, Conway EE Jr, *et al*: Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): A multi-institutional study from New York City. J Pediatr 224: 24-29, 2020.
22. Severo Bem Junior L, do Rego Aquino PL, Nunes Rabelo N, do Rego Aquino MA, Veiga Silva AC, Ferreira Valenca Mota RC and Rocha Cirne de Azevedo Filho H: SARS-CoV-2 and nervous system-neurological manifestations in patients with COVID-19: A systematic review. J Neurol Res 10: 113-121, 2020.
23. Tsai C, Wilson SE and Rubinos C: SARS-CoV-2 infection and seizures: The perfect storm. J Integr Neurosci 21: 115, 2022.
24. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F and Moch H: Endothelial cell infection and endotheliitis in COVID-19. Lancet 395: 1417-1418, 2020.
25. Varatharaj A and Galea I: The blood-brain barrier in systemic inflammation. Brain Behav Immun 60: 1-12, 2017.
26. Almqvist J, Granberg T, Tzortzakakis A, Klironomos S, Kollia E, Öhberg C, Martin R, Piehl F, Ouellette R and Ineichen BV: Neurological manifestations of coronavirus infections-a systematic review. Ann Clin Transl Neurol 7: 2057-2071, 2020.
27. Vezzani A, Fujinami RS, White HS, Preux PM, Blümcke I, Sander JW and Löscher W: Infections, inflammation and epilepsy. Acta Neuropathol 131: 211-234, 2016.
28. Al-Ramadan A, Rabab'h O, Shah J and Gharaibeh A: Acute and post-acute neurological complications of COVID-19. Neurol Int 13: 102-119, 2021.
29. Vollono C, Rollo E, Romozzi M, Frisullo G, Servidei S, Borghetti A and Calabresi P: Focal status epilepticus as unique clinical feature of COVID-19: A case report. Seizure 78: 109-112, 2020.
30. Román GC, Spencer PS, Reis J, Buguet A, Faris MEA, Katrak SM, Láinez M, Medina MT, Meshram C, Mizusawa H, *et al*: The neurology of COVID-19 revisited: A proposal from the environmental neurology specialty group of the world federation of neurology to implement international neurological registries. J Neurol Sci 414: 116884, 2020.
31. Mithani F, Poursheykhi M, Ma B, Smith RG, Hsu SH and Gotur D: New-onset seizures in three COVID-19 patients: A case series. J Clin Neurophysiol 38: e5-e10, 2021.
32. Tiruneh FT: Clinical profile of Covid-19 in children, review of existing literatures. Pediatric Health Med Ther 11: 385-392, 2020.
33. Panda PK, Sharawat IK, Panda P, Natarajan V, Bhakat R and Dawman L: Neurological complications of SARS-CoV-2 infection in children: A systematic review and meta-analysis. J Trop Pediatr 67: fmaa070, 2021.
34. Siebach MK, Piedimonte G and Ley SH: COVID-19 in childhood: Transmission, clinical presentation, complications and risk factors. Pediatr Pulmonol 56: 1342-1356, 2021.
35. Chen TH: Neurological involvement associated with COVID-19 infection in children. J Neurol Sci 418: 117096, 2020.
36. Yilmaz Ciftdogan D, Ekemen Keles Y, Cetin BS, Dalgic Karabulut N, Emiroglu M, Bagci Z, Buyukcam A, Erdeniz EH, Arga G, Yesil E, *et al*: COVID-19 associated multisystemic inflammatory syndrome in 614 children with and without overlap with Kawasaki disease-Turk MIS-C study group. Eur J Pediatr 181: 2031-2043, 2022.
37. Hogan RE, Grinspan Z, Axeen E, Marquis B and Day BK: COVID-19 in patients with seizures and epilepsy: Interpretation of relevant knowledge of presenting signs and symptoms. Epilepsy Curr 20: 312-315, 2020.

38. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, Seth S, Egan C, Hardwick HE, Halpin S, *et al*: Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: Prospective multicentre observational cohort study. BMJ 370: m3249, 2020.
39. Asadi-Pooya AA, Simani L, Shahisavandi M and Barzegar Z: COVID-19, de novo seizures, and epilepsy: A systematic review. Neurol Sci 42: 415-431, 2021.
40. Ray STJ, Abdel-Mannan O, Sa M, Fuller C, Wood GK, Pysden K, Yoong M, McCullagh H, Scott D, McMahon M, *et al*: Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: A prospective national cohort study. Lancet Child Adolesc Health 5: 631-641, 2021.
41. Riva A, Piccolo G, Balletti F, Binelli M, Brolatti N, Verrotti A, Amadori E, Spalice A, Giacomini T, Mancardi MM, *et al*: Acute neurological presentation in children with SARS-CoV-2 infection. Front Pediatr 10: 909849, 2022.
42. Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, Bernardi S, Giacchero R, Lo Vecchio A, Marchisio P, *et al*: Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Euro Surveill 25: 2000600, 2020.
43. Kurd M, Hashavya S, Benenson S and Gilboa T: Seizures as the main presenting manifestation of acute SARS-CoV-2 infection in children. Seizure 92: 89-93, 2021.
44. Cloete J, Kruger A, Masha M, M du Plessis NM, Mawela D, Tshukudu M, Manyane T, Komane L, Venter M, Jassat W, *et al*: Rapid rise in paediatric COVID-19 hospitalisations during the early stages of the Omicron wave, Tshwane District, South Africa. medRxiv preprint, 2021.
45. Lin JE, Asfour A, Sewell TB, Hooe B, Pryce P, Earley C, Shen MY, Kerner-Rossi M, Thakur KT, Vargas WS, *et al*: Neurological issues in children with COVID-19. Neurosci Lett 743: 135567, 2021.
46. Ludvigsson JF: Convulsions in children with COVID-19 during the Omicron wave. Acta Paediatr 111: 1023-1026, 2022.
47. Cadet K, Boegner J, Ceneviva GD, Thomas NJ and Krawiec C: Evaluation of febrile seizure diagnoses associated with COVID-19. J Child Neurol 37: 410-415, 2022.
48. Yoo J, Kim JH, Jeon J, Kim J and Song TJ: Risk of COVID-19 infection and of severe complications among people with epilepsy: A nationwide cohort study. Neurology 98: e1886-e1892, 2022.
49. Parihar J, Tripathi M and Dhamija RK: Seizures and epilepsy in times of corona virus disease 2019 pandemic. J Epilepsy Res 10: 3-7, 2020.
50. Hao X, Zhou D, Li Z, Zeng G, Hao N, Li E, Li W, Deng A, Lin M and Yan B: Severe psychological distress among patients with epilepsy during the COVID-19 outbreak in southwest China. Epilepsia 61: 1166-1173, 2020.
51. Pavone P, Corsello G, Ruggieri M, Marino S, Marino S and Falsaperla R: Benign and severe early-life seizures: A round in the first year of life. Ital J Pediatr 44: 54, 2018.
52. Brisca G, Siri L, Olcese C, Brunenghi BM, Pirlo D and Mancardi MM: Is SARS-CoV-2 infection a risk for potentiation of epileptic seizures in children with pre-existing epilepsy? Pediatr Neurol 116: 31, 2021.
53. Farrar DS, Drouin O, Hepburn CM, Baerg K, Chan K, Cyr C, Donner EJ, Embree JE, Farrell C, Forgie S, *et al*: Risk factors for severe COVID-19 in hospitalized children in Canada: A national prospective study from March 2020-May 2021. Lancet Reg Health Am 15: 100337, 2022.
54. Berg AT and Jobst B: Epilepsy and COVID-19's double-edged sword: More severe disease and delayed epilepsy care. Neurology 98: 779-780, 2022.
55. Heuser K, Berger TC, Henning O, Svalheim S, Sibeko JM, Nakken KO and Taubøll E: COVID-19 and epilepsy. Tidsskr Nor Laegeforen 141, 2021 (In English, Norwegian).
56. Nikbakht F, Mohammadkhanizadeh A and Mohammadi E: How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. Mult Scler Relat Disord 46: 102535, 2020.
57. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, Mu J, Guo J, Li W, Wang G, *et al*: New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. Epilepsia 61: e49-e53, 2020.
58. Kuroda N: Epilepsy and COVID-19: Updated evidence and narrative review. Epilepsy Behav 116: 107785, 2021.
59. Marino A, Pampaloni A, Scuderi D, Cosentino F, Moscatt V, Ceccarelli M, Gussio M, Celesia BM, Bruno R, Borraccino S, *et al*: High-flow nasal cannula oxygenation and tocilizumab administration in patients critically ill with COVID-19: A report of three cases and a literature review. World Acad Sci J 2: 23, 2020.
60. Cosentino F, Moscatt V, Marino A, Pampaloni A, Scuderi D, Ceccarelli M, Benanti F, Gussio M, Larocca L, Boscia V, *et al*: Clinical characteristics and predictors of death among hospitalized patients infected with SARS-CoV-2 in Sicily, Italy: A retrospective observational study. Biomed Rep 16: 34, 2022.
61. Marino A, Cacciaguerra G, Sangiorgio G, Maniaci A, La Via L, Cocuzza S, Stracquadanio S, Leonardi R, Spampinato S, Cacopardo B, *et al*: SARS-CoV-2-related parotitis in children: A narrative-focused review. COVID 4: 1100-1112, 2024.
62. Valencia I, Berg AT, Hirsch LJ, Lopez MR, Melmed K, Rosengard JL, Tatum WO and Jobst BC: Epilepsy and COVID 2021. Epilepsy Curr 22: 398-403, 2022.