doi: 10.48095/cccsnn2024213

Prevalence of neurological complications in children hospitalized with SARS-CoV-2 infection or MIS-C in children – single center observational study

Prevalence neurologických komplikací u dětí hospitalizovaných s infekcí SARS-CoV-2 nebo MIS-C – monocentrická observační studie

Abstract

Introduction: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused the enduring global COVID-19 pandemic, which has already begun in late 2019. The virus affects various organs, including the nervous system. This study investigates neurological complications in children with COVID-19 or multisystem inflammatory syndrome in children (MIS-C) in the South Moravia region (Czech republic), where a high COVID-19 rate among children (35.790/100.000) allows for a comprehensive analysis. Methods: Data from the University Hospital Brno (from March 2020 to February 2022) were analyzed to study two groups of hospitalized children diagnosed with COVID-19 or MIS-C: one experiencing neurological complications, and the other without neurological symptoms. The analysis included demographics, admission reasons, infection severity and progression, objective neurological findings, hospitalization details, MIS-C presence and therapies used. Descriptive statistics and statistical testing were employed to assess how individual factors influenced neurological complication rates within these groups. Results: Among 420 hospitalized children with COVID-19 or MIS-C, 26 (6.2%) had neurological complications. Preexisting neurological deficits increased the likelihood of worse outcomes (P = 0.0224). Significant differences in hospitalization length (P = 0.0012), infection severity (P = 0.0052), and outcome (P < 0.0001) occurred between groups. Conclusion: Continuous monitoring and further research on neurological complications in children with COVID-19 or MIS-C are crucial for better understanding of the course of the disease and minimize complications after infection.

Key words

SARS-CoV-2 infection – MIS-C – children – neurological complications – epidemiology

Klíčová slova

infekce SARS-CoV-2 – MIS-C – děti – neurologické komplikace – epidemiologie

The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

- P. Mužlayová¹, P. Danhofer¹, K. Španělová¹, S. Kolář¹, O. Horák¹, J. Klučka^{2,3}, P. Štourač^{2,3},
- J. Šenkyřík⁴, M. Malá⁵, L. Homola^{5,6}
- ¹ Department of Pediatric Neurology, Faculty of Medicine of Masaryk University, University Hospital Brno, Czech Republic
- ² Department of Pediatric Anesthesiology and Intensive Care Medicine, Faculty of Medicine of Masaryk University, University Hospital Brno, Czech Republic
- ³ Department of Simulation Medicine, Faculty of Medicine, Masaryk University Brno, Czech Republic
- ⁴ Department of Pediatric Radiology, Faculty of Medicine of Masaryk University, University Hospital Brno, Czech Republic
- ⁵ Department of Pediatric Infectious Diseases, Faculty of Medicine of Masaryk University, University Hospital Brno, Czech Republic
- ⁶ European Reference Network on Rare Respiratory Diseases Centre, University Hospital Brno, Czech Republic



Lukáš Homola, MD

Department of Pediatric Infectious Diseases Faculty of Medicine of Masaryk University University Hospital Brno Černopolní 9 Brno 613 00 Czech Republic e-mail: homola.lukas@fnbrno.cz

Accepted for review: 11. 10. 2023 Accepted for print: 28. 5. 2024

Souhrn

Úvod: Koronavirus typu 2, jako původce těžkého akutního respiračního syndromu (SARS-CoV-2) zapříčinil celosvětovou pandemii onemocnění COVID-19, která vypukla již koncem roku 2019. Virus postihuje různé orgány, vč. nervového systému. Tato studie zkoumá neurologické komplikace u dětí s COVID-19 nebo multisystem inflammatory syndrome in children (MIS-C) v Jihomoravském kraji (ČR), kde vysoká četnost infekce COVID-19 u dětí (35 790/100 000) umožňuje komplexní analýzu. *Metodika*: Data Fakultní nemocnice Brno (březen 2020 až únor 2022) byla analyzována pro dvě skupiny hospitalizovaných dětí s diagnózou COVID-19 nebo MIS-C: jednu s neurologickými komplikacemi a druhou bez neurologických komplikací. Analýza zahrnovala demografické údaje, důvod přijetí, tíži infekce a její vývoj, objektivní neurologický nález, detaily hospitalizace, přítomnost MIS-C a specifikaci terapeutických postupů. K posouzení jednotlivých faktorů ovlivňujících výskyt neurologických komplikací v rámci těchto skupin byly použity metody deskriptivní statistiky a statistické testy. *Výsledky*: Ze 420 hospitalizovaných dětí s COVID-19 nebo MIS-C mělo 26 (6,2 %) neurologické komplikace. Dřívější neurologický deficit zvyšoval pravděpodobnost horšího výsledného stavu (p = 0,0224). Mezi skupinami se objevily významné rozdíly v délce hospitalizace (p = 0,0012), závažnosti průběhu infekce (p = 0,0052) a výsledném stavu (p < 0,0001). *Závěr*: Pro lepší pochopení průběhu onemocnění a minimalizaci komplikací po infekci je zásadní průběžné sledování a další výzkum neurologických projevů u dětí s COVID-19 nebo MIS-C.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic causing COVID-19 disease broke out in late 2019 in China and is now in its 4th year. It still appears to be very dynamic, with new variants of the virus emerging and vaccinations becoming available, leading to changes in the clinical presentation and complications of the disease. While the SARS-CoV-2 virus primarily targets the pulmonary system, it is now evident that COVID-19 is a multisystem disease with manifestations and sequelae affecting multiple organ systems [1]. Severe cases can present with pneumonia, acute respiratory distress syndrome, acute cardiac dysfunction, and multiorgan failure [2]. Although the disease course in children is typically mild, there have been reported complications, including multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. MIS-C is characterized by fever, gastrointestinal discomfort mimicking sudden abdominal death, and neurological symptoms alongside multiorgan failure [3]. Several case reports have confirmed the ability of SARS-CoV-2 to invade the central nervous system, leading to neurological symptoms. Research on SARS-CoV-2 has implicated the angiotensin-converting enzyme-2 receptor as a mediator of coronary disease associated with neuronal damage and has shown that the virus can infect the cerebrovascular endothelium and brain tissue, primarily in the medial temporal lobe, resulting in apoptosis and necrosis. Neurological symptoms of infection can range from anosmia or ageusia to severe disability due to thrombosis or hemorrhage in the central nervous system [4–6].

The urgency of the pandemic, with its profound health, social, psychological, and eco-

nomic implications, has led to numerous publications aimed at understanding the pathophysiology of the disease from various perspectives. Several studies have specifically focused on the neurological complications of COVID-19 in children [1,7-11]. In this study, our focus is on investigating the incidence of neurological complications in children hospitalized with COVID-19 or MIS-C. We present an overview of the pediatric population in the South Moravian region of the Czech Republic, which has a population of just over one million (approximately 10% of the Czech population) and around 247,000 children aged 0-18 years. The 2-year cumulative incidence of COVID-19 in this region was 35,790 cases per 100,000 children between March 2020 and February 2022, meaning that one out of every three children in the South Moravian region had a confirmed SARS-CoV-2 infection during this period. We believe that the high prevalence of COVID-19 in the region provides a relatively objective representation of the neurological complications in children with COVID-19.

Methods

Data analysis for this study was conducted over a 2-year period following the onset of the pandemic. The study population consisted of individuals aged 0–19 years who were hospitalized due to COVID-19 and admitted to the University Hospital Brno between March 2020 and February 2022. Cases were identified through the hospital database using International Classification of Diseases (ICD-10) codes at discharge (specifically code U071). In addition to the ICD-10 codes, we included cases from two other data sources: a follow-up database of MIS-C patients and the Department of Pediatric Neurology database at the University Hospi-

tal Brno, which records patients with neurological complications. To verify the relationship between hospitalization and COVID-19, we checked the SARS-CoV-2 test results (PCR, antigen, and serology) in the medical records of each case.

Exclusion criteria were applied to cases that were determined to be unrelated to COVID-19 or were re-hospitalizations of the same individual. Repeated admissions were observed in immunocompromised subjects with prolonged positivity of SARS-CoV-2 who came for cancer treatment cycles; in such cases, only the first hospitalization was included in the analysis, and subsequent re-admissions were excluded. Cases of uninfected individuals in quarantine were also omitted from the analysis, as they could not be identified.

We analyzed basic demographic data, including patient sex and age at the time of COVID-19 diagnosis. We also focused on the reason for hospitalization due to COVID-19, the course of COVID-19 infection - ranging from asymptomatic with comorbidities requiring hospitalization to symptoms without the need for oxygen therapy, the need for oxygen therapy, or the need for artificial lung ventilation (ALV) in cases of respiratory failure, and the presence of MIS-C syndrome. We evaluated the duration of hospitalization in both the standard ward and intensive care unit (ICU), as well as patient outcomes. Another aspect of our evaluation involved assessing the therapies administered, such as immunotherapy (including corticosteroids, intravenous immunoglobulin [IVIG], plasmapheresis, and remdesivir), and determining if oxygen administration or extracorporeal membrane oxygenation (ECMO) was necessary. We also evaluated the results of paraclinical and laboratory tests, as well as neurological findings.

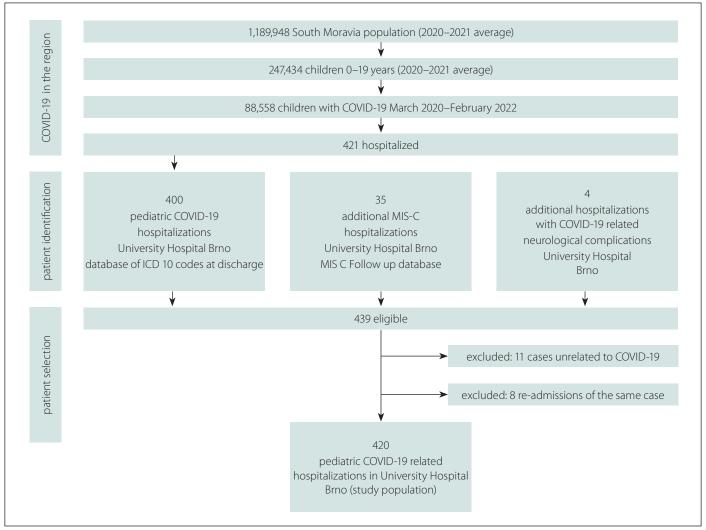


Fig. 1. Sample population algorithm: number of patients with COVID-19 (age 0–19 years) requiring hospitalization in the period 2/2020–2/2022 in the South Moravia region of the Czech Republic.

Obr. 1. Algoritmus výběru populace: počet pacientů s COVID-19 (věk 0–19 let) vyžadujících hospitalizaci v období 2/2020–2/2022 v Jihomoravském kraji v ČR.

Statistics

Statistical analysis was conducted using GraphPad Prism 9 (Boston, MA, USA). Descriptive statistics and statistical testing were utilized to determine cohort demographics and identify statistically significant differences between groups with or without neurological complications. Logistic and linear regressions were employed to examine the effects of individual parameters.

Results Population

According to the Czech Statistical Office, the South Moravian region has a total population of 1,189,948 individuals, including 247,434 children aged 0–19 years (average for 2020–2021). The Czech Institute of Health Information and Statistics recorded 88,558 SARS-CoV-2 in-

fections in children from the region between March 2020 and February 2022, resulting in a 2-year cumulative incidence rate of 35,790 cases per 100,000 children. Among these infections, 422 cases required hospitalization (170 per 100,000), with 95% of hospitalizations occurring at the University Hospital Brno, totaling 421 patients.

Out of the 421 pediatric COVID-19-related hospitalizations at the University Hospital Brno in the region, 400 cases were identified using the ICD-10 code U071 in the hospital's database. An additional 35 MIS-C subjects were not recognized by the code but were found in the MIS-C follow-up database. Furthermore, four patients with COVID-19-related neurological complications were identified in the medical records of the Department of Pediatric Neurology.

We excluded 11 cases that were determined to be unrelated to COVID-19 (no mention of SARS-CoV-2 in their medical records) and eight cases that were re-admissions. As a result, our selection consisted of 420 COVID-19-related hospitalizations. The identification and selection of patients are summarized in Fig. 1.

Demographic data and basic characteristics of the cohort

The study included 420 children aged 0–19 years who were hospitalized at the University Hospital Brno with confirmed SARS-CoV-2 infection between March 2020 and February 2022. The mean patient age was 7.39 years (range 0–19; standard deviation [SD] 6.21). The cohort consisted of 241 males (57.4%) and 179 females (42.6%).

	All patients	Patients with neurological symptomatology	Patients without neurological symptomatology	Statistical signifikance (P)
number of patients	420	6.2% (26/420)	93.8% (394/420)	
age mean, min–max, SD (years)	7.39 (0–19.4; SD 6.21)	8.42 (0–19; SD 5.46)	7.35 (0–19; SD 6.28)	0.4872
males	57.4% (241/420)	69.2% (18/26)	56.6% (223/394)	0.2265
females	42.6% (179/420)	30.8% (8/26)	43.4% (171/394)	0.2265

Body mass index (BMI) values were obtained for 153 patients, with a mean value of 18.55 (range 6–44; SD 5.69). The demographics of the study population are summarized in Tab. 1.

Out of the 420 patients, COVID-19 was symptomatic with the need for hospital admission in 191 cases (45.5%). MIS-C was diagnosed in 49 cases (11.7%), and hospitalization was indicated as part of patient isolation and for mild or asymptomatic cases in 180 cases (42.9%).

When assessing the severity of the disease, 20% of children (84/420) were asymptomatic. Mild disease without the need for oxygen therapy was observed in 71.0% of cases (298/420). Moderate disease requiring oxygen therapy was present in only 6.2% of patients (26/420), while severe/critical cases requiring life support and ventilation (ALV) accounted for 2.9% (12/420).

The total average length of hospital stay was 6.91 days (range 1–100; SD 7.95). In the standard ward, the mean length of hospital stay was 4.77 days (range 1–28; SD 4.13), while in the ICU ward, it was 7.29 days (range 1–60; SD 7.23). Among the 420 patients, 362 (86.2%) fully recovered from the disease, 46 (11.0%) had a short residual deficit lasting up to three months, and 12 (2.9%) experienced long-term sequelae. No deaths related to COVID-19 were recorded.

We conducted a detailed evaluation of patients who presented with neurological symptoms alongside COVID-19. Notably, anosmia and ageusia, which were relatively common, were not assessed or included. Neurological symptoms occurred in 26 out of 420 patients (6.2%). In this group, the mean age was 8.42 years (range 0–19; SD 5.46), and there were 18 males and 8 females. BMI was assessed in 14 of these 26 children, with an average value of 18.21 (range 14–24; SD 3.14).

Among the patients with neurological symptoms, 14 (53.9%) required ICU care, while 12 (46.6%) were admitted to a standard ward. In the group without neurological involvement, 139 out of 394 patients (35.9%) were admitted to the ICU, and 255 out of 394 patients (64.7%) were admitted to the standard ward. Among the patients with neurological symptoms, 73.1% (19/26) had mild COVID-19, 3.9% (1/26) had a moderate course, and 23.1% (6/26) experienced a severe course. In the group without neurological symptoms, 6.4% (25/394) had a moderate course, and 1.5% (6/394) had a severe course.

The average length of hospitalization for patients with neurological symptoms was 19.15 days (range 2-100; SD 23.15), compared to 6.11 days (range 1-29; SD 4.76) for those without neurological symptoms. In the standard ward, the average length of hospitalization for patients with neurological symptoms was 8.71 days (range 1-24; SD 7.19), while it was 4.51 days (range 1-28; SD 3.73) for those without neurological symptoms. In the ICU, the average length of hospitalization for patients with neurological symptoms was 13.17 days (range 1-60; SD 14.38), compared to 6.34 days (range 1-29; SD 4.70) for those without neurological symptoms. The results and comparison of the groups with and without neurological manifestations are summarized in Tab. 2.

Among the 26 patients with neurological symptoms, 65.4% (17/26) experienced complete recovery within one month. Two patients (7.7%) had residual symptoms lasting up to three months, and seven patients (26.9%) had long-term consequences. In the group of 394 patients without neurological symptoms, 87.6% (345/394) experienced complete recovery within one month, 11.2% (44/394) had residual symptoms lasting up to three months, and 1.3% (5/394) had long-

term consequences. No deaths related to COVID-19 occurred in either group.

A detailed overview of all patients with neurological complications is provided in Tab. 3.

Statistics

There was a statistically significant difference in the relative frequency of moderate and severe disease severity between the groups with and without neurological symptoms. The group with neurological symptoms more often had a moderate or severe course (P = 0.0052). There was also a statistically significant difference in the length of hospitalization between the group with neurological impairment and the group without neurological symptoms (P = 0.0012). Furthermore, a statistically significant difference was observed in the length of hospitalization in the standard ward (P = 0.00226) and in the ICU ward (P = 0.0198)between the group with neurological impairment and the group without neurological symptoms. The group of patients with neurological symptoms showed a statistically significant difference in long-term outcome compared to the group without neurological symptoms, with long-term residual effects being more frequent in the former (P < 0.0001). A correlation was found between the severity of impaired consciousness and outcome (P = 0.0062). The quantitative impairment of consciousness predicted a prolonged length of hospitalization (P = 0.01). Children with preexisting neurological diseases such as epileptic and developmental encephalopathy, epilepsy, and cerebral palsy had worse COVID-19 disease outcomes (P = 0.0224). The deterioration of outcomes encompassed not only neurological deficits but also respiratory and cardiovascular failure, as well as an extended period of recovery.

In this group of children, certain individuals exhibited the emergence of pre-

	All patients	Patients with neurological symptomatology	Patients without neurological symptomatology	Statistical signifikance (P)	
Primary diagnosis					
patients with acute COVID-19 infection	45.5% (191/420)	39.5% (10/26)	45.9% (181/394)		
patient with MIS-C	11.7% (49/420)	15.4% (4/26)	11.4% (45/394)	0.7052	
patients in isolation	42.9% (180/420)	46.2% (12/26)	42.4% (168/394)		
Admission					
ICU	36.4% (153/420)	53.8% (14/26)	35.3% (139/394)	0.616	
standard unit	63.6% (267/420)	46.2% (12/26)	64.7% (255/394)	0.010	
everity					
asymptomatic	20.0% (84/420)	26.9% (7/26)	19.5% (77/394)		
mild (without oxygen therapy)	71.0% (298/420)	46.2% (12/26)	72.6% (286/394)		
moderate (with oxygen therapy)	6.2% (26/420)	3.9% (1/26)	6.4% (25/394)	0.0052	
severe (with artificial lung ventilation and life support)	2.9% (12/420)	23.1% (6/26)	1.5% (6/394)		
lospital stay					
lenght of hospitalization; mean, min–max, SD (days)	6.9 (1–100; SD 7.95)	9.2 (2–100; SD 23.15)	6.1 (1–29; SD 4.76)	0.0012	
standard unit stay; mean, min–max, SD (days)	4.8 (1–28; SD 4.13)	8.7 (1–24; SD 7.20)	4.5 (1–28; SD 3.73)	0.0226	
ICU stay; mean, min-max, SD (days)	7.3 (0-60; SD 7.26)	13.2 (0-60; SD 14.38)	6.3 (1–29; SD 4.70)	0.0198	
Outcome					
complete remission	86.2% (362/420)	65.4% (17/26)	87.6% (345/394)		
brief residual symptoms (up to 3 months)	11.0% (46/420)	7.7% (2/26)	11.2% (44/394)	< 0.0001	
long-term residual symptoms (more than 3 months)	2.9% (12/420)	26.9% (7/26)	1.3% (5/394)	< 0.0001	
death	0% (0/420)	0% (0/26)	0% (0/394)		

viously unobserved neurological complications, such as cranial nerve lesions. However, a significant majority experienced a deterioration of their preexisting symptoms, leading to an exacerbation of epileptic seizures.

Statistical significance was not found in the other evaluated parameters. The results are presented in Tab. 2.

Discussion

SARS-CoV-2, the causative agent of COVID-19, has been shown to affect both the central and peripheral nervous systems in pediatric and adult populations. Neurological involvement can present with specific or non-specific symptoms, including olfactory/gustatory dysfunction, headache, myalgias, confusion/encephalopathy, cerebro-

vascular events, seizures, and other diverse presentations [12]. The underlying mechanisms responsible for the neurological manifestations of COVID-19 remain uncertain, as most studies indicate that SARS-CoV-2 brain invasion occurs in only a limited number of fatal COVID-19 cases. It is known that SARS--CoV-2 enters the host using its spike glycoprotein, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor expressed in the lungs, heart, kidneys, and endothelial cells. The presence of ACE2 in the brain and nerves puts them at risk of being infected by SARS-CoV-2, leading to neurological damage. The utilization of ACE2 as an entry receptor by SARS-CoV-2 could result in its depletion and the accumulation of Angiotensin II, raising blood pressure through vasoconstriction and fluid retention. Elevated Angiotensin II levels could also trigger inflammation and increase the risk of blood clots [8,13].

It is generally believed that COVID-19 infection in children follows an asymptomatic or mild course. However, there is a lack of literature on the neurological manifestations of COVID-19 in this population, with existing publications primarily consisting of case reports or series. Studies involving larger cohorts have mostly focused on adult patients [8,10,14].

Our study is unique because the South Moravian region of the Czech Republic has a high prevalence of COVID-19, with a cumulative incidence of 35,790/100,000 children between March 2020 and February 2022, pro-

Tab. 3. Patients with neurological complications hospitalized with SARS-CoV-2 infection or MIS-C overview	Tab. 3. Patients with neurolog	ical complications hos	pitalized with SARS-CoV-2	2 infection or MIS-C overviev
---	--------------------------------	------------------------	---------------------------	-------------------------------

Patient No.	Neurological complication	Sex	Age (years)	•	Days at Standard ward	Days at ICU	Preexisting neurological disease	Out- come*	CT/MRI brain findings	Treatment
1	ASS	М	18	36	18	18	Ν	3	normal	anticoagulation therapy, corticosteroids, oxygen therapy
2	ASS	Μ	15	3	2	1	Υ	1	NA	symptomatic treatment
3	altered state of consciousness	F	13	5	5	0	Ν	1	NA	symptomatic treatment
4	cranial nerve lesion	F	12	3	3	0	N	1	NA	ATB, anticoagulation therapy
5	dystonia	F	12	3	2	1	N	1	NA	symptomatic treatment
6	first attack of migraine with aura	М	12	5	5	0	N	1	NA	symptomatic treatment
7	cranial nerve lesion	М	10	12	12	0	N	1	NA	ATB
8	diplopia in demyelinating disease of the brain	М	10	15	15	0	Υ	1	abnormal	corticosteroids
9	diplopia	Μ	9	2	2	0	Ν	2	NA	symptomatic treatment
10	first attack of migraine with aura	F	9	3	3	0	N	1	NA	symptomatic treatment
11	ASS	F	7	5	1	4	Ν	3	NA	symptomatic treatment
12	ASS	M	7	4	0	4	N	1	NA	symptomatic treatment
13	ASS	М	4	4	0	4	N	1	normal	symptomatic treatment
14	ASS	F	1	11	11	0	Ν	1	abnormal	symptomatic treatment
15	acute decompensation of seizures (<i>SCN1A</i> asociated encephalopathy)	М	0	100	0	100	Υ	4	abnormal	ATB, corticosteroids, oxygen therapy, ALV
16	dystonia	F	0	8	8	0	N	1	abnormal	symptomatic treatment
17	vasculitis of the brainstem	М	0	39	0	39	Υ	3	abnormal	ATB, anticoagulation therapy, corticosteroids, ALV
18	myoclonic jerks	M	0	3	3	0	Ν	1	NA	symptomatic treatment
19	acute decompensation of seizures (NPRL3 asociated encephalopathy)	F	0	14	0	14	Y	2	NA	ATB, corticosteroids
20	extrapontine central myelinolysis with extrapy- ramidal symptoms	М	14	36	20	16	N	3	abnormal	ATB, anticoagulation therapy, corticosteroids, ALV
21	cranial nerve lesion	М	12	16	3	13	Ν	1	normal	ATB, anticoagulation therapy, corticosteroids
22	altered state of consciousness	М	12	11	2	9	N	1	NA	ATB, anticoagulation therapy, corticosteroids
23	AMAN	М	6	49	19	30	N	3	normal	ATB, anticoagulation therapy, corticosteroids, IVIG, plasmapheresis
24	AMAN	М	4	41	24	17	N	3	normal	ATB, anticoagulation therapy, corticosteroids, IVIG, plasmapheresis
25	meningitis with subdural hemorrhage	М	11	15	15	0	N	1	NA	corticosteroids
26	CVT with hemorrhage	М	4	57	9	48	N	3	abnormal	ATB, anticoagulation therapy, corticosteroids, IVIG, REGEN-COV, ALV

^{*1 –} no residual deficit; 2 – short-term residual deficit (less than 1 month); 3 – long-term residual deficit (more than 1 month); 4 – exitus letalis A – abnormal; ALV – artificial lung ventilation; AMAN – acute motor axonal neuropathy; ASS – acute symptomatic seizure; ATB – antibiotics; CVT – cerebral venous thrombosis; F – female; ICU – intensive care unit; IVIG – intravenous immune globuline; M – male; MIS-C – multisystem inflammatory syndrome in children; N – no; NA – not applicable; No – normal; Y – yes

viding researchers with a unique opportunity to examine the incidence of neurological complications in hospitalized children with COVID-19 or MIS-C. According to the national database, there were 88,558 cases of COVID-19 in children from the region, and 420 of them required hospitalization at the University Hospital Brno. Upon further analysis of the clinical progression of COVID-19 in these children, the results appear favorable. Out of the 420 children, 20% were asymptomatic and 70% experienced a mild course of the disease. Only 3% of patients had a severe course requiring ALV. Among the 420 patients, a total of 26 (6.2%) experienced neurological symptoms such as acute motor axonal neuropathy, newly onset extrapyramidal symptoms, cranial nerve lesion, spontaneous subdural hematoma, or severe cerebral venous thrombosis with secondary hematoma.

Among these patients, 21 had undergone neurological monitoring for a previous diagnosis before the development of COVID-19 symptoms. One patient with the sequence variant *SCN1A* and clinical Dravet syndrome deteriorated significantly, requiring ICU care. Another patient with multiple internal comorbidities died three months after a COVID-19 infection, although these were no longer direct sequelae of the infection. Statistically, patients with pre-existing neurological diseases had worse COVID-19 disease outcomes, considering the initial neurological defect.

A crucial finding of the study is that COVID-19 patients with neurological symptoms had longer hospital stays (19 vs. 6 days) and spent more time in the ICU (13 vs. 6 days). In comparison to the neurologically naive group, 27% of patients had long-term neurological consequences, whereas the number was only 1% in the group without neurological symptoms. Fortunately, these numbers are low, and no patients died as a direct result of COVID-19.

Comparing our findings with the results of an extensive cross-sectional study conducted in the USA involving 52 children's hospitals [15], we observed a striking similarity between the two. Out of a total of 15,137 children admitted to those hospitals due to COVID-19, 1,060 (7.0%) had a co-existing diagnosis of a neurological complication. The prevalent neurological issues were febrile seizures, nonfebrile seizures, and encephalopathy. A prospective national cohort study in the UK yielded comparable outcomes [16].

These findings suggest that pediatric patients with neurological symptoms impose

a greater socio-economic burden on society, emphasizing the need for continued monitoring of children with COVID-19 or MIS-C and highlighting the importance of further research to better understand the mechanisms underlying the neurological complications of COVID-19 in children. The study serves as a reminder of the wide-ranging impact of COVID-19 and the ongoing efforts needed to control the spread of the virus and develop effective treatments for those affected.

Conclusion

SARS-CoV-2 can affect the central and peripheral nervous systems, leading to various neurological symptoms. The underlying mechanisms are uncertain, but the virus may infect the brain and nerves through the ACE2 receptor. Limited studies have focused on neurological complications in children with COVID-19. Our study found that 6.2% of children hospitalized with COVID-19 experienced neurological symptoms, and these children had longer hospital stays, a higher likelihood of needing intensive care, and poorer outcomes. Although COVID-19 is generally considered mild in children, this study highlights the importance of continued monitoring and research into the neurological complications of COVID-19 in children.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University Hospital Brno (number: 15-160322/EK, date: March 3, 2022). Patient consent was waived due to the retrospective and anonymous nature of the analysis.

Conflict of interest

None of the authors have any conflicts of interest to disclose. The authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those quidelines.

Contributors statement

PM – conceptualization, validation, data curation, writing-original draft preparation

PD – conceptualization, methodology, validation, writing-review and editing, project administration

KŠ, OH, JK, JŠ – investigation

SK – formal analysis

 $P\S-conceptualization, supervision\\$

MM – validation, data curation

LH – conceptualization, methodology, data curation, writing-review and editing, visualization

Data Availability Statement

The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to ethical restrictions.

Acknowledgments

The authors would like to thank Anne Johnson for grammatical assistance.

References

- **1.** Stafstrom CE. Neurological effects of COVID-19 in infants and children. Dev Med Child Neurol 2022; 64(7): 818–829. doi: 10.1111/dmcn.15185.
- **2.** Hanafi R, Roger PA, Perin B et al. COVID-19 neurologic complication with CNS vasculitis-like pattern. AJNR Am J Neuroradiol 2020; 41(8): 1384–1387. doi: 10.3174/ajnr.A6651.
- **3.** Klučka J, Kratochvíl M, Dominik P et al. COVID-19 associated Paediatric Inflammatory Multisystem Syndrome (PIMS) in children. Epidemiol Mikrobiol Imunol 2021; 70(4): 281–284.
- **4.** Aghagoli G, Gallo Marin B, Katchur NJ et al. Neurological involvement in COVID-19 and potential mechanisms: a review. Neurocrit Care 2021; 34(3): 1062–1071. doi: 10.1007/s12028-020-01049-4.
- **5.** Herzig R, Mikulík R, Tomek A et al. COVID-19 a iktus. Cesk Slov Neurol N 2021; 84/117(1): 31–37. doi: 10.48095/cccsnn202131.
- **6.** Šmahel P, Chmelař J, Šimůnek L et al. Intracerebral haemorrhage in COVID-19. Cesk Slov Neurol N 2022; 85/118(3): 213–217. doi: 10.48095/cccsnn2022213.
- 7. LaRovere KL, Riggs BJ, Poussaint TY et al. Overcoming COVID-19 investigators. neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol 2021; 78(5): 536–547. doi: 10.1001/iamaneurol.2021.0504.
- 8. Španělová K, Skříšovská T, Mužlayová P et al. Cerebrovascular complications of COVID-19 disease in children: a single-center case series. Pediatr Neurol 2022; 134: 18–24. doi: 10.1016/j.pediatrneurol.2022.06.007.
- **9.** Fink EL, Robertson CL, Wainwright MS et al. Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID) investigators. Prevalence and risk factors of neurologic manifestations in hospitalized children diagnosed with acute SARS-CoV-2 or MIS-C. Pediatr Neurol 2022; 128: 33–44. doi: 10.1016/j.pediatrneurol.2021.12.010.
- **10.** Španělová K, Mužlayová P, Horák O et al. Extrapontine central myelinolysis with extrapyramidal symptoms in a 14-year-old-boy with COVID-19 disease related PIMS-TS. Cesk Slov Neurol N 2022; 85/118(6): 503–505. doi: 10.48095/cccsnn2022503.
- **11.** Antoon JW, Hall M, Howard LM et al. COVID-19 and acute neurologic complications in children. Pediatrics 2022; 150(5): e2022058167. doi: 10.1542/peds.2022-058167
- **12.** Stafstrom CE. Neurological effects of COVID-19 in infants and children. Dev Med Child Neurol 2022; 64(7): 818–829. doi: 10.1111/dmcn.15185.
- **13.** Shehata GA, Lord KC, Grudzinski MC et al. Neurological complications of COVID-19: underlying mechanisms and management. Int J Mol Sci 2021; 22(8): 4081. doi: 10.3390/ijms22084081.
- **14.** Dvořáková T, Bušková J, Bartoš A. Neurologické příznaky asociované s onemocněním COVID-19 podle celostátního online průzkumu. Cesk Slov Neurol N 2022; 85/118(3): 220–227. doi: 10.48095/cccsnn2022220.
- **15.** Antoon JW, Hall M, Howard LM et al. COVID-19 and acute neurologic complications in children. Pediatrics 2022; 150(5): e2022058167. doi: 10.1542/peds.2022-058167.
- **16.** Ray STJ, Abdel-Mannan O, Sa 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 2021; 5(9): 631–641 doi: 10.1016/S2352-4642(21)00 193-0.