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Neuro-COVID-19 With or Without the Multisystem Inflammatory Syndrome (MIS-C): A Single-Center Study

COVID-19: Neurologic Manifestations in Children

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Abstract
This study evaluates the range of neurological manifestation in children with COVID-19 (neuro-COVID-19) both with and without the multisystem inflammatory syndrome (MIS-C) and the persistence of symptoms after hospital discharge. The study was conducted as a prospective study of children and adolescents under 18 years of age who were admitted to a children's hospital for infectious diseases from January 2021 to January 2022. The children had no previous neurological or psychiatric disorders. Out of the 3021 patients evaluated, 232 were confirmed to have COVID-19 and 21 of these patients (9%) showed neurological manifestations associated with the virus. Of these 21 patients, 14 developed MIS-C, and 7 had neurological manifestations unrelated to MIS-C. There was no statistical difference regarding the neurological manifestations during hospitalization and outcomes between patients with neuro-COVID-19 who had or did not have MIS-C, except for seizures that occurred more frequently in patients with neuro-COVID-19 without MIS-C (p-value = 0.0263). One patient died, and 5 patients still had neurological or psychiatric manifestations at discharge, which persisted for up to 7 months. The study highlights that SARS-CoV-2 infection can affect the central and peripheral nervous system, particularly in children and adolescents with MIS-C, and that it is crucial to be vigilant for long-term adverse outcomes, as the neurological and psychiatric effects of COVID-19 in children are emerging during an important stage of brain development.

Keywords COVID-19 · Children · Neuro-COVID-19 · COVID-19-associated multisystem inflammatory syndrome · SARS-CoV-2 · MIS-C

Introduction

Brazil has been severely affected by the COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Oliveira et al. 2021). Studies in different countries reported lower severity and mortality from SARS-CoV-2 infection in children and adolescents than in adults and elders (Ray et al. 2021; Feldstein et al. 2020; WHO 2020). Nevertheless, a nationwide database reported a case fatality rate of 7.6% among 11,613 hospitalized children and adolescents with confirmed COVID-19. These subjects' death variables were age, indigenous ethnicity, poor geopolitical region, and pre-existing medical conditions (Oliveira et al. 2021).

There is also growing evidence that SARS-CoV-2 infection is associated with direct and indirect neurological symptoms and central nervous system (CNS) complications, called neuro-COVID-19 (Stafstrom 2022; Shoraka et al. 2021). Clinical manifestations of neuro-COVID-19 include headaches, seizures, meningitis, encephalitis, encephalopathy, and peripheral nervous system (PNS)

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manifestations, such as Guillain-Barré syndrome, myelitis, and neuralgia (Stafstrom 2022; Shoraka et al. 2021; Abdel-Mannan et al. 2020; Moriguchi et al. 2020; Huang et al. 2020; Abu-Rumeileh et al. 2021; Toscano et al. 2020). Although neuro-COVID-19 has been associated with long-term sequelae in adults, little information is known regarding long-term adverse developmental in pediatric patients (Stafstrom 2022; Panda et al. 2021; Lindan et al. 2021; LaRovere et al. 2021). In addition, reports of neurological complications in children and adolescents have also been associated with multisystem inflammatory syndrome in children (MIS-C) (LaRovere et al. 2021).

Children and adolescents infected with SARS-CoV-2 are at increased risk for COVID-19-associated multisystem inflammatory syndrome in children (MIS-C), also known as a pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 (PIMS-TS) (Ray et al. 2021). MIS-C occurs due to a dysregulation of the innate and adaptive immune responses in the face of an intense inflammatory response (Feldstein et al. 2020). MIS-C is characterized by at least 3 days of fever; altered inflammatory tests; damage of at least two organs and tissues; evidence of COVID-19; and no other apparent causes of inflammation, according to the criteria of the World Health Organization (2020).

This study aimed to evaluate the spectrum and prevalence of neurological manifestations associated or not with MIS-C in hospitalized children infected by SARS-CoV-2 and the persistence of symptoms after hospital discharge.

Methods

This study was approved by the Research Ethics Committee of Hospital Infantil João Paulo II (HIJPII) (Belo Horizonte – MG, Brazil) under number 132/2009 and by the Universidade Federal de Minas Gerais: CAE number: 09273012.9.0000.5149. For all study subjects, legal guardians signed the consent form for research.

We carried out a prospective study in Hospital Infantil João Paulo II, a reference children's hospital, to care for infectious diseases in Minas Gerais state, Southeast Brazil, throughout 2021. Children and adolescents aged 18 or under were included in the study if they had (i) laboratory-confirmed SARS-CoV-2 infection and new-onset neurological, or (ii) complication of previous neurological disease, or (iii) psychiatric disorders during or after COVID-19. Patients were excluded if diagnosed with another viral or bacterial co-infection or if the legal guardians did not sign the consent form for research. None of the children and adolescents in this study had received the COVID-19 vaccine.

All children and adolescents admitted to the hospital with flu-like symptoms, or severe acute respiratory syndrome, were investigated for SARS-CoV-2 infection by real-time polymerase chain reaction (CDC Protocol respiratory virus or NCOV 500 T SINTESE BIO 10006713 IDT—Integrate) or nasopharyngeal swab antigen test (qualitative immunoassay, ACRO BIOTECH, INC). Patients with signs of MIS-C, or neurological manifestations, but without flu-like symptoms, were investigated by serological examination using the chemiluminescence immunoassay method with sensibility of 84.7 (CI 95% 79.2–96) and specificity of 97% (CI 95% 95–99.5) (kit SARS-CoV-2 IgG and IgM Abbott). Only patients with neurological symptoms and laboratory-confirmed SARS-CoV-2 infection were included in the analysis. We used the World Health Organization criteria adopted by the Brazilian Ministry of Health to define clinical cases of MIS-C associated with COVID-19 (WHO 2020).

All neurological symptoms or manifestations were evaluated by pediatric neurologists and classified as headache, meningitis, encephalitis/encephalopathy, simple febrile seizures, complex seizures, cerebrovascular event, or peripheral neuropathies (Guillain-Barré syndrome, paresis, myelitis).

Patients, who presented neurological manifestations secondary to acute infection or post-infection by SARS-CoV-2 and did not meet the criteria for MIS-C, were gathered in the neuro-COVID-19 without MIS-C group. Patients with neurological symptoms associated with the multisystem inflammatory syndrome were defined as the neuro-COVID-19/MIS-C group.

Cerebrospinal fluid (CSF) was collected from patients suspected of having a central nervous system acute infection or Guillain-Barré syndrome by lumbar puncture. Real-time polymerase chain reaction (RT-PCR) was used to investigate viral RNA or DNA of SARS-CoV-2, dengue virus (DENV), Zika virus (ZIKV), chikungunya virus (CHIKV), herpes 1, 2, and 3 virus, Epstein-Barr virus (EBV), and West Nile virus (WNV), according to research protocol. To rule out other infections, patients with meningitis were also investigated by RT-PCR, routine isolation, and culture for *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*.

Children who had severe acute respiratory syndrome were evaluated by RT-PCR for other respiratory viruses such as respiratory syncytial virus, adenovirus, influenza A and B, parainfluenza, metapneumovirus, and bocavirus, according to hospital laboratory routine. Children and adolescents were also evaluated for D-dimer, troponin, C-reactive protein, and blood count according to medical assistance evaluation (Table 1).

All patients followed up with neurologists and child psychiatrists until clinical improvement. Some patients continue in clinical follow-up until the publication of this study.

The statistical analysis was made using notification data and test results for SARS-CoV-2 to estimate the prevalence of cases admitted to the hospital between January 2021 and January 2022. Descriptive analyses were performed using Student's *t*-tests or Mann–Whitney *U* tests to compare quantitative variables and the chi-square test for categorical variables. The tests investigated any significant differences between groups in the COVID-19-related

Table 1 Clinical features, investigations, treatment, and outcomes of patients with COVID-19 and neurological manifestations

	Neuro-COVID-19 without MIS-C ($n = 7$)	Neuro-COVID-19/ MIS-C ($n = 14$)	p-value
	Number of patients (%)	Number of patients (%)	
Age	4.4 (1 mo–10.5 yr)	5.9 (4 mo–12.2 yr)	0.3887
Sex			
Male	6 (85.7%)	10 (71.4%)	
Female	1 (14.3%)	4 (28.6%)	0.6244
Clinical features			
Rash	0 (0%)	8 (57.1%)	**0.0179**[a]
Myocarditis or coronary dilatation	0 (0%)	6 (42.8%)	0.0609
Shock or hypotension	1 (14.3%)	8 (57.1%)	0.1588
Respiratory symptoms	5 (71.4%)	6 (42.8%)	0.3615
Headache	3 (71.4%)	9 (64.3%)	0.3972
Meningitis	3 (42.8%)	2 (14.3%)	0.2800
Encephalitis	3 (42.8%)	5 (35.7%)	1
Seizures	3 (42.8%)	0 (0%)	**0.0263**[a]
Ataxia	2 (28.7%)	1 (7.1%)	0.2474
Peripheral nervous system involvement	3 (42.8%)	2 (14.3%)	0.2800
Behavioral changes	1 (14.3%)	0 (0%)	0.3333
Investigations			
SARS-CoV-2 PCR positive	6 (85.7%)	6 (42.8%)	0.1588
SARS-CoV-2 IgG positive	2 (28.6%)	9 (64.3%)	0.1827
Elevated acute-phase reactants*	0 (0%)	13 (92.8%)	**0.0003**[a]
C-reactive protein, mg/dl	22.7 (0.9–261)	233 (72–595)	**0.0118**[b]
Blood white cell count (cells/mm^3)	8280 (4470–10,280)	15,895 (5080–47,000)	**0.0149**[b]
CSF white cell count (cells/mm^3)	51.8 (1–250)	38.2 (1–175)	0.8033
Treatment			
Intensive care unit admission	4 (57.1%)	7 (50%)	1
Inotropic support	1 (14.3%)	4 (28.6%)	0.6244
Immunomodulation**	1 (14.3%)	11 (78.6%)	**0.0158**[a]
Outcome			
Disability***	2 (28.6%)	2 (14.3%)	0.5743
Death	1 (14.3%)	0 (0%)	0.3333

*Combined acute-phase reactants were defined as lactate dehydrogenase, ferritin, and D-dimers

**Immunoglobulin and/or corticosteroid

***Disability: defined as an altered neurological examination performed by a neurologist at hospital discharge

[a]Student's t-tests

[b]Mann–Whitney U tests

symptoms, laboratory exams, and neurological symptoms. Statistical analyses were done with R software, and p-values less than 0.05 were considered significant.

Results

Between January 2021 and January 2022, 3021 children and adolescents with clinical suspicion of COVID-19 were admitted to the hospital and eligible to participate in the study.

Samples from the 3021 patients were collected and screened for SARS-CoV-2 infection. A total of 232 patients had laboratory confirmation of SARS-CoV-2 infection. COVID-19 diagnosis was performed by RT-PCR from nasopharyngeal swabs in 114/232 patients (49.1%), by antigen test in 97/232 (41.8%), and by serological test in 21/232 (9.1%) patients.

Regarding the 232 patients with confirmed SARS-CoV-2 infection, the mean age of the patients was 4 years

and 6 months (ranging from 1 month to 18 years), but 163 (70.2%) were younger than 6 years. A total of 128 patients (55%) were male, and 151 (65.1%) had no known comorbidity (Centers for Disease Control and Prevention 2022). The clinical presentations of COVID-19 observed were severe acute respiratory syndrome in 171 (73.7%), a flu-like syndrome in 33 (14.3%), and COVID-19-associated MIS-C in 28 patients (12%). Neurological manifestations were identified in 21 patients (9%), of which 14 presented neuro-COVID-19/MIS-C and 7 presented neuro-COVID-19 without MIS-C (Table 1). The pediatric neurologists diagnosed and evaluated all children during the hospital stay. There was 1 death, and at hospital discharge, 4 (19%) still had some neurological manifestations such as paresis, ataxia, or diplopia (Table 1). Only one 7-year-old child presented psychiatric manifestations with auditory hallucinations and behavioral changes, such as aggression, during acute SARS-CoV-2 infection. In this cohort, the patients who developed neurological and psychiatric manifestations associated with SARS-CoV-2 infection had no previous neurological or psychiatric disorders.

Cerebrospinal fluid was harvested from 12 patients. Ten patients were male between 1 month and 10 years (mean: 3.9 years; median: 2.6 years). SARS-CoV-2 infection was diagnosed in eight patients detecting the presence of SARS-CoV-2 antigen or RNA indicating acute infection. Four patients had laboratory tests showing the previous infection by detecting SARS-CoV-2 IgG (Table 2).

A total of 14 patients diagnosed with MIS-C were classified as neuro-COVID-19/MIS-C. The neurological symptoms or manifestations presented by 9 patients were headaches, 5 had encephalitis/encephalopathy, 2 had meningitis, 2 had peripheral neuropathy, and 1 patient presented with ataxia, diplopia, and muscle weakness (Table 1). Four of the 6 CSF samples collected from these patients showed alterations in cellularity, ranging from 8 to 175 cells/mm^3, with a predominance of lymphomononuclear cells (80–100%). Two patients in this group also showed a significant increase in CSF protein (210–270 mg/dL) (Table 2).

Regarding the 7 patients with neuro-COVID-19 without MIS-C symptoms, 3 patients presented headache, 3 encephalitis/encephalopathy, 3 meningitis, 3 seizures, 2 ataxia, 1 Guillain-Barré syndrome, 1 meningitis, seizures, and cerebrovascular event, and 1 patient presented a psychiatric disorder. Six patients had neurological symptoms during the acute phase of SARS-CoV-2 infection. Two of the 6 CSF collected from these patients showed cellularity alterations (55–250 cells/mm^3), and 3 had increased protein levels (117–580 mg/dL). Viral investigations in CSF performed by RT-PCR of PCR for SARS-CoV-2, DENV, ZIKV, CHIKV, herpes 1, 2, and 3 viruses, EBV, and WNV were negative (Table 2).

Four patients (19%) at hospital discharge still had some neurological manifestations such as muscle weakness, ataxia, and diplopia. Only one child presented with muscle weakness and diplopia for 7 months; the other 3 patients improved between 1 and 2 months. The child who presented changes in behavior continues to use risperidone and is being followed up with a psychiatrist.

When we compared patients with neuro-COVID-19 without MIS-C ($n=7$) and neuro-COVID-19 with MIS-C ($n=14$), we found no statistical difference between the neurological manifestations presented during hospitalization and outcomes at hospital discharge between the 2 groups, except for seizures that occurred more frequently in the group without MIS-C ($p=0.0263$). However, as expected in the neuro-COVID-19 with MIS-C group, there was a significant statistical difference regarding inflammatory response markers such as D-dimer, ferritin, and lactate dehydrogenase ($p<0.0003$), C- reactive protein ($p=0.0118$), and treatment with immunoglobulin and corticosteroid ($p=0.0158$).

Discussion

This study evaluated the neurological manifestations of SARS-CoV-2 infection in pediatric patients with neuro-COVID-19 without or with MIS-C. We observed 9% of neurological manifestations among all pediatric patients confirmed for COVID-19. The main neurological manifestations observed were headache, meningitis, and encephalitis/encephalopathy.

Previous studies in the UK and the USA observed 3.8% and 22% of the prevalence of neurological manifestations in pediatric patients with COVID-19 (Feldstein et al. 2020; LaRovere et al. 2021). A systematic review with meta-analysis that evaluated 3707 children and adolescents with SARS-CoV-2 infection in 25 studies reported 15.6% of nonspecific neurological manifestations such as headache, myalgia, and fatigue and 1% of neurological complications such as encephalopathy, seizures, and meningeal signs (Panda et al. 2021). However, a study conducted in Poland, and limited to children with MISC-C using data from national registers found a higher prevalence of neurological symptoms, including lethargy (59.4%), headache (46.1%), irritability (41.7%), photophobia (11%), and meningeal signs (10.4%) (Ludwikowska et al. 2021).

The differences between the prevalence of neurological manifestations of COVID-19 detected in children and adolescents may be due to the different neurological manifestations considered in the studies and whether there is an association with MIS-C. There may be significant differences in neurovirulence SARS-CoV-2 variants circulating during the periods.

Six patients of each group neuro-COVID-19 without MIS-C or neuro-COVID-19/MIS-C had CSF collected

Table 2 Laboratory results, SARS-CoV-2 tests, and neurological and MISC symptoms of patients from whom cerebrospinal fluid was collected

Tests (units) demographic / patient	1	2	3	4	5	6	7	8	9	10	11	12	Reference range
Age (y,m)	3y,2 m	1y,11 m	1 m	6y	7y	10y	2y	1y	4y	5 m	8y,3 m	3ys	-
Sex	M	M	M	M	M	M	M	F	M	M	M	F	-
Neurological symptoms	E	Guillain-Barré	E	E	Paresis behavior changes	Seizures, thrombosis	Cerebellitis	Meningitis	E	E	Meningitis	E	-
MISC symptoms	No	No	No	No	No	No	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	-
Treatment	-	IGH*, gabapentin	Cefepime	Aciclovir, phenytoin	Risperidone	Ceftriaxone, noradrenalin	IGH prednisolone, aspirin	IGH, prednisolone, aspirin	IGH, predni solone, aspirin	IGH, aspi rin	IGH predni solone, aspirin, ceftria xone	IGH predni solone, aspirin, ceftria xone	-
Days of hospitalization	2	10	12	6	9	4	12	16	6	4	14	13	-
SARS-CoV-2 IgG/IgM	-	-	-	**IgG: 1234 IgM: 0.36**	-	-	-	-	**IgG: 3074 IgM: 0.71**	**IgG: 1119 IgM: 0.12**	**IgG: 2036 IgM: 0.28**	**IgG 3245 IgM: 0.76**	IgG > 50.0 IGM > 1.00
SARS-CoV-2 Antigen	-	-	-	-	**P**	**P**	-	-	N	N	N		N
Real-time RT SARS-CoV-2	**D**	**D**	**D**	U	**-**	**-**	**D**	**D**	**D**	U	U	U	U
Real-time RT *Haemophilus/ Neisseria/ Pneumococus*	U	-	U	U		U	-	U		-	U		U
Other negative diagnostic tests	-	DENV, CHIKV, ZIKV, Polio, HTLV, EBV, CMV	Influenza and VRS test rapid	Adenovirus, metapneumo-virus, parainfluenza 1–3, influenza A and B, VRS, rinovirus			-	CMV, EBV, toxoplasmosis	Adenovirus, metapneumo-virus, parainfluenza 1–3, influenza A and B, VRS, rinovirus		-	Ns1 DENV	N
LCR leukocytes (cells /mm3) (% LMN)	1 (98%)	3 (90%)	1 (80%)	**55 (88%)**	**1**	**250**	**12 (100%)**	**175 (90%)**	1 (90%)	**32 87%**	**8 (80%)**	1 (100%)	< 5
LCR glucose (mg/dL)	51	55	63	40	50	53	47	**25**	48	46	60	57	> 40
LCR protein (mg/dL)	< 10	**117**	41	**152**	9	**580**	< 10	**210**	14	43	**277**	< 10	< 40
Hemoglobin (g/fdL)	13	12.4	**7.1**	11.9	11.7	**10.2**	**10.1**	**8.3**	**11.2**	**9.3**	11.0	11.4	11.5 – 13.5
Leukocytes (cells /mm3)	8700	10,280	8900	**4470**	6010	7860	**22,236**	**23,590**	8430	11,110	14,600	**30,530**	5000–14,500
Neutrophil/ lymphocyte ratio	1.72	0.8	0.98	2.88	1.34	**18.8**	3.45	2.7	**7.2**	0.65	**10.6**	**11.25**	< 5

Table 2 (continued)

Tests (units) demographic / patient	1	2	3	4	5	6	7	8	9	10	11	12	Reference range
Platelets (cells/ $mm^3 \times 10^3$)	411	480	365	**103**	275	**131**	**86**	**702**	**78**	226	229	**89**	150–400
C-reactive protein (mg/L)	0.9	27.7	19.7	25.7	13.1	**261**	**371**	**216.5**	**149.2**	**192**	**346.3**	**595**	< 12
D-dimer (mcg/mL)	-	0.92	-	-	-	-	**5.91**	**3.77**	**51.09**	1.03	**4.22**	**5.24**	≤0.5
Troponin (ng/mL)	-	< 1.5	-	-	-	-	**49.14**	< 1.5	**53.4**	9.86	**627.2**	**1498**	< 11

IGH immunoglubulin, *E* encephalitis/encephalopathy, *D* detectable, *U* undetectable, *M* male, *F* female, *P* positive, *N* negative, -, not done

Bold numbers or results represent alterations related to reference range

by lumbar puncture, but we did not detect SARS-CoV-2 genomic RNA by RT-PCR in any CSF; however, 58% showed changes in cellularity or CSF protein (Table 2). Failure to detect the SARS-CoV-2 in the CSF patient samples supports an immune mechanism rather than direct CNS viral invasion in patients with neuro-COVID-19 (Stafstrom 2022; Shoraka et al. 2021; Abdel-Mannan et al. 2020; Moriguchi et al. 2020; Huang et al. 2020; Abu-Rumeileh et al. 2021; Toscano et al. 2020; Panda et al. 2021; Lindan et al. 2021; LaRovere et al. 2021; Centers for Disease Control and Prevention 2022).

A review study of the neurological manifestations in children with SARS-CoV-2 infection also reported a low rate of viral detection in CSF, which may be due to either low viral invasion or poor sensitivity of the test (Valderas et al. 2022).

The intense inflammatory response and immune dysregulation triggered by SARS-CoV-2 infection are pathophysiological mechanisms that can cause the neurological manifestations seen in patients with COVID-19 (Stafstrom 2022; Shoraka et al. 2021; Valderas et al. 2022). Metabolic hypoxemia and acidosis triggered by severe acute respiratory syndrome can cause symptoms of mental confusion, delirium, encephalopathy, hypotonia, and ataxia (Fotuhi et al. 2020; Valderas et al. 2022). The immune dysregulation described in children with MIS-C leads to a cytokine storm, with a significant increase in the interleukins (IL-1, IL-6, IL-10) and tumor necrosis factor (TNF-a), increasing the permeability of the blood–brain barrier, attracting leukocytes, and causing inflammation in the CNS with symptoms of encephalitis and meningitis (Stafstrom 2022; Moriguchi et al. 2020; Boldrini et al. 2021; Valderas et al. 2022).

Within the neuro-COVID-19 without MIS-C group, a 1-year and 11-month-old child was diagnosed with Guillain-Barré syndrome associated with acute COVID-19, with the presentation of muscle weakness, hyporeflexia, and meningeal signs (Table 2). It has been shown that SARS-CoV-2 can dysregulate the immune response and trigger acute disseminated encephalomyelitis, autoimmune encephalitis, Guillain-Barré syndrome, and other neurological complications (Stafstrom 2022; Shoraka et al. 2021; Abdel-Mannan et al. 2020; Moriguchi et al. 2020; Huang et al. 2020; Abu-Rumeileh et al. 2021; Toscano et al. 2020; Panda et al. 2021; Lindan et al. 2021; LaRovere et al. 2021). Molecular mimicry between SARS-CoV-2 and neural antigens is another possible mechanism of post-infection neurological complications, commonly described with other microorganisms triggering Guillain-Barré syndrome (Shoraka et al. 2021). However, there is a lack of studies evaluating the presence of antiganglioside antibodies in patients with COVID-19 (Shoraka et al. 2021; Abu-Rumeileh et al. 2021; Toscano et al. 2020).

One fatal case described here was represented by one patient also classified within the neuro-COVID-19 without MIS-C group. This patient presented flu-like symptoms and

seizures, and brain tomography indicated a cerebrovascular event (Table 2). It has been demonstrated that endothelial cells of brain vessels also have receptors for SARS-CoV-2. Once infected, these cells release neutrophils and macrophages and increase thromboembolic factors causing microthrombosis, minor ischemia, and tissue damage related to COVID-19 pathogenesis (Fotuhi et al. 2020; Boldrini et al. 2021; Valderas et al. 2022).

Our study observed no significant differences between patients with neuro-COVID-19 with or without MIS-C, except for seizures that occurred more frequently in the group with neuro-COVID-19 without MIS-C (p-value = 0.0263). A similar study that evaluated 52 children found a statistical difference between patients who presented recognized para-infectious or post-infectious neurologic disease (p-value = 0.0003), hallucinations (0.032), headache, or meningism (0.041) (Feldstein et al. 2020).

Although the inflammatory response in children in the group of neuro-COVID-19/MIS-C was more significant than in children with neuro-COVID-19 without the MIS-C group, the neurological manifestations, complications, and death were not statistically different. This corroborates multicenter study results in the UK (Feldstein et al. 2020).

However, the small number of patients evaluated here is a limitation of the study. A larger number of patients should be further evaluated to understand neurological manifestations of COVID-19, assessing the immune and inflammatory response and the presence of autoantibodies with molecular mimicry between SARS-CoV-2 and neuronal antigens.

Adults who have recovered from a severe illness or after being hospitalization for COVID-19 have reported prolonged neurologic symptoms such as headache, cognitive dysfunction, anosmia/dysgeusia, and insomnia; these symptoms are referred to as "long COVID-19" (Taquet et al. 2021; Balcom et al. 2021). If these symptoms persist between 4 and 12 weeks after the initial symptoms, they are considered to be long COVID. In children, although data is still limited, the main neurological manifestations associated with long-term COVID include changes in cognition, such as decreased attention and recent memory, headaches, numbness, dysgeusia, anosmia, dizziness, blurred vision, and tinnitus (Valderas et al. 2022).

A case–control study that evaluated the neurodevelopment at babies exposed to COVID during pregnancy at 6 months of age found no difference compared to the neurodevelopment of unexposed babies. However, there was a significant delay observed between children born during the pandemic and historical cohorts (Shuffrey et al. 2022). Thus, it is essential to conduct prospective studies evaluating the neurodevelopment of infants and children after SARS-CoV-2 infection or exposure to the stressors of the pandemic.

From January 2021 and January 22nd, 9% of children and adolescents admitted to the hospital with confirmed SARS-CoV-2 infection presented with neurological or psychiatric manifestations. One child died due to a cerebrovascular event, 4 were discharged with neurological symptoms, and 1 patient remained with psychiatric disorders. The results of the study emphasize the importance of investigating the viral cause in children with acute neurological manifestations and conducting clinical follow-up after hospital discharge of pediatric patients to assess persistent neurological and psychiatric complications.

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Data Availability All clinical data from this research can be made available upon request from the corresponding author.

Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Research Ethics Committee of Hospital Infantil João Paulo II (HIJPII) (Belo Horizonte – MG, Brazil) under number 132/2009 and by the Universidade Federal de Minas Gerais: CAE number: 09273012.9.0000.5149.

Consent to Participate For all study subjects, legal guardians signed the consent form for research.

Consent to Publish Written informed consent was obtained from the parents.

Competing Interests The authors have no relevant financial or non-financial interests to disclose.

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References

Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, Hemingway C, Hacohen Y (2020) Neurologic and radiographic findings associated with COVID-19 infection in children. JAMA Neurol 11:1440–1445. https://doi.org/10.1001/jamaneurol.2020.2687

Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M (2021) Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol 268:1133–1170. https://doi.org/10.1007/s00415-020-10124-x

Balcom EF, Nath A, Power C (2021) Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain 144:3576. https://doi.org/10.1093/brain/awab302

Boldrini M, Canoll PD, Klein RS (2021) How COVID-19 affects the brain. JAMA Psychiat 78:682–683. https://doi.org/10.1001/jamapsychiatry.2021.0500

Centers for Disease Control and Prevention (2022) Underlying medical conditions associated with high risk for severe COVID-19: information for healthcare providers. Available at:https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. (Accessed on 01 Mar 2022)

Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF et al (2020) Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 383:334–346. https://doi.org/10.1056/NEJMoa2021680

Fotuhi M, Mian A, Meysami S, Raji CA (2020) Neurobiology of COVID-19. J Alzheimers Dis 76:3–19. https://doi.org/10.3233/JAD-200581

Huang YH, Jiang D, Huang JT (2020) SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. Brain Behav Immun 87:149. https://doi.org/10.1016/j.bbi.2020.05.012

LaRovere KL, Riggs BJ, Poussaint TY, Young CC, Newhams MM, Maamari M et al (2021) Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol 78:536–547. https://doi.org/10.1001/jamaneurol.2021.0504

Lindan CE, Mankad K, Ram D, Kociolek LK, Silvera VM, Boddaert N et al (2021) Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Health 3:167–177. https://doi.org/10.1016/S2352-4642(20)30362-X

Ludwikowska KM, Okarska-Napierała M, Dudek N, Tracewski P, Kusa J, Piwoński KP et al (2021) Distinct characteristics of multisystem inflammatory syndrome in children in Poland. Sci Rep 11(1):23562.https://doi.org/10.1038/s41598-021-02669-2. PMID:34876594;PMCID:PMC8651720

Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J et al (2020) A first case of meningitis/encephalitis associated with SARS-coronavirus-2. Int J Infect Dis 94:55–58. https://doi.org/10.1016/j.ijid.2020.03.062

Oliveira EA, Colosimo EA, Silva SE, AC, Mak RH, Martelli DB, Silva LR et al (2021) Clinical characteristics and risk factors for death among hospitalized children and adolescents with COVID-19 in Brazil: an analysis of a nationwide database. Lancet Child Adolesc Health 8:559–568. https://doi.org/10.1016/S2352-4642(21)00134-6

Panda PK, Sharawat IK, Panda P, Natarajan V, Bhakat R, Dawman L (2021) Neurological complications of SARS-CoV-2 infection in children: a systematic review and meta-analysis. J Trop Pediatr 67:fmaa070. https://doi.org/10.1093/tropej/fmaa070

Ray STJ, Abdel-Mannan O, Sa M, Fuller C, Wood GK, Pysden K et al (2021) Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. Lancet Child Adolesc Health 9:631–641. https://doi.org/10.1016/S2352-4642(21)00193-0

Shoraka S, Ferreira MLB, Mohebbi SR, Ghaemi A (2021) SARS-CoV-2 infection and Guillain-Barré syndrome: a review on potential pathogenic mechanisms. Front Immunol 12:674922. https://doi.org/10.3389/fimmu.2021.674922

Shuffrey LC, Firestein MR, Kyle MH, Fields A, Alcántara C, Amso D et al (2022) Association of birth during the COVID-19 pandemic with neurodevelopmental status at 6 months in infants with and without in utero exposure to maternal SARS-CoV-2 infection. JAMA Pediatr 176(6):e215563. https://doi.org/10.1001/jamapediatrics.2021.5563. Epub 2022 Jun 6. PMID:34982107;PMCID:PMC8728661

Stafstrom CE (2022) Neurological effects of COVID-19 in infants and children. Dev Med Child Neurol 00:1–12. https://doi.org/10.1111/dmcn.15185

Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ (2021) Incidence, co-occurrence, and evolution of long-COVID features: a 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med 18:e1003773. https://doi.org/10.1371/journal.pmed.1003773

Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG et al (2020) Guillain-Barré syndrome associated with SARS-CoV-2. N Engl J Med 382:2574–2576. https://doi.org/10.1056/NEJMc2009191

Valderas C, Méndez G, Echeverría A, Suarez N, Julio K, Sandoval F (2022) COVID-19 and neurologic manifestations: a synthesis from the child neurologist's corner. World J Pediatr 18(6):373–382. https://doi.org/10.1007/s12519-022-00550-4. Epub 2022 Apr 27. PMID:35476245;PMCID:PMC9044375

WHO (2020) – Multisystem inflammatory syndrome in children and adolescents with COVID-19. Scientific Brief, 15 May 2020. Available at: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. (Accessed on 20 Feb 22)

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