Analysis of Neurological Clinical Manifestations and Diagnostic Workups in Pediatric COVID-19: A Systematic Review

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Abstract

Background While numerous studies report neurological manifestations of COVID-19, there are fewer reviews in the pediatric population, focusing solely on the manifestations.

Aim This systematic review aims to describe the clinical manifestations and laboratory findings of pediatric patients with neurological manifestations of COVID-19.

Methods We searched Pubmed, Science Direct, Medline, Scielo, Medrxiv, Research Square, SSRN, and Biorxiv with the appropriate keywords. Inclusion criteria include new-onset neurological manifestations with a time correlation to the confirmed COVID-19 with a further diagnostic work-up. We use The Joanna Briggs Institute's (JBI) essential evaluation checklist and Newcastle Ottawa Quality Assessment Scale (NOS) to evaluate the quality of the studies. The protocol for this systematic review has been registered in The international Prospective Register of Systematic Review (PROSPERO) database (CRD42021228671).

Results 31 articles were ultimately chosen with 42 patients (26 male) included in this systematic review. The neurological diagnosis was mostly of the CNS classification (38/42) with a predomination of brain disorders (22/38). Most patients had lymphopenia, elevated C-reactive protein, procalcitonin, ferritin, creatinine kinase, blood urea nitrogen, D-dimer, and erythrocyte sedimentation rate. In the CNS group, CSF monocytes (55%; 11–80%), CSF polymorphonuclear (PMN) cells (15%; 0–96%), CSF red blood cells (282 cells/mm³; 2–4000 cells/mm³), and opening pressure (34.5 cm/H₂O; 25–100 cm/H₂O) were elevated.

Conclusions Our systematic review found that neurological manifestations in COVID-19 occurred more often in males, with a majority being CNS disorders. A majority had a favorable outcome. More studies are needed in order to elucidate the viral mechanisms of SARS-CoV-2 in CSF.

Introduction

Over a year has passed since COVID-19 is declared a pandemic, and there are no signs of it slowing down (1, 2). Numerous strategies have been employed from social distancing, adequate personal protective equipment, closing down schools and other public services, and ramping up vaccine administrations (3–6). However, these measures have mixed results, with some countries are more successful than the others (7).

SARS-CoV-2 has undergone extensive research, and its impact ranges from asymptomatic to even death, with almost every aspect of physical and mental health affected (2, 8, 9). Neurological manifestation in pediatric and adult populations is a known complication of COVID-19, and numerous studies are backing this finding (10–12).

However, most of the neurological studies in COVID-19 are based on the adult population and mainly report neurological symptoms or complications (13–17). Similarly, when reviews are done in the pediatric population, these studies also focus heavily on the pathogenesis or clinical manifestations in the neurological department (18–20). Analysis of lumbar puncture, a functional diagnostic study that may help differentiate the etiology of infections in the nervous system, is also heavily done in the adult populations (21–23).

Besides theories of pathogenesis and clinical manifestations or complications in neurological pediatric COVID-19 cases, there is still a lack of other clinical findings such as brain imaging, laboratory values, or cerebrospinal fluid (CSF) analysis, which may characterize pediatric patients with neurological manifestations in the setting of COVID-19 infection. While there are numerous case series, cohort studies, or even multi-center studies on this topic, the data are too heterogeneous, with different studies having different objectives of the studies (24–26).

Therefore, this systematic review aims to describe the clinical manifestations and outcomes, laboratory findings (such as routine blood work and inflammatory markers), radiology findings (such as brain computed tomography scan or brain magnetic resonance imaging), and specific neurological tests (such as electroencephalography and CSF analysis).

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement (27). The protocol for this systematic review has been registered in The international Prospective Register of Systematic Review (PROSPERO) database (CRD42021228671).

The authors included case reports, case series, cross-sectional studies, and cohort studies that studied neurological impacts and their neurological diagnosis about pediatric COVID-19. Inclusion criteria included new-onset neurological manifestations with a time correlation to the diagnosis of confirmed COVID-19. The other inclusion criteria also ensured that the neurological manifestations must be investigated either by one of the following tests: laboratory testings, brain imaging, electroencephalogram (EEG), and lumbar puncture and CSF analysis. Exclusion criteria comprised co-infection by other pathogens confirmed by microbiological testings, neurological comorbidities before presentation, certain study types such as editorials and reviews, and multisystem inflammatory syndrome in children (MIS-C).

The literature search was limited from 2020 onwards with no restrictions on language. In order to ensure literature selection, references from reviews and all studies included in this systematic review were scanned and included if they fulfilled the inclusion criteria.

The literature search started on January 14, 2021, and ended on January 15, 2021. The authors used four unique databases, such as PubMed, Science Direct, Medline, and Scielo, and four different preprint databases such as Medrxiv, Research Square, Social Science Research Network (SSRN), and Biorxiv. The keywords are listed in Table 1. Each research's data was compiled in a standardized format, including study citations, demographic characteristics of the

included participants, neurological manifestations and diagnosis, COVID-19 severity, patient's length of stay and outcomes, laboratory and imaging results, as well as CSF analysis. The corresponding author of that particular study will be sent an email if some data are missing pertaining to this systematic review.

Table 1
Sets of keywords used for this systematic review in each database

Database	Keywords
First set	COVID-19; COVID-2019; severe acute respiratory syndrome coronavirus 2; 2019-nCoV; SARS-CoV-2; 2019 novel coronavirus; 2019 nCoV
Second set	pediatric; paediatric; children; infant; adolescent; child; neonate
Third set	cerebrospinal fluid; liquor cerebrospinalis; lumbar puncture; lumbal puncture; computed tomography scan; magnetic resonance imaging; electroencephalography; EEG
Fourth set	neurological; neurology; central nervous system; CNS; brain; manifestation; symptom; presentation; feature; complication; peripheral nervous system; neuropathy; skeletal muscle; myositis; neuromuscular junction; headache; anosmia; olfactory; ageusia; cranial neuropathy; cranial nerve; seizures; encephalitis; meningitis; stroke; cerebrovascular disease; cerebral hemorrhage; intracerebral hemorrhage; cerebral infarct; cortical venous thrombosis; deep cerebral venous thrombosis; impaired consciousness; confusion; weakness; Guillain-Barre syndrome; Miller Fisher syndrome; ataxia; myopathy; myelitis; myelopathy; encephalopathy; meningoencephalitis; convulsion; neuropsychiatric

Dong et al. classified COVID-19 severity as follows: (a) asymptomatic (absence of signs and symptoms associated with COVID-19, routine clinical imaging, but positive ribonucleic acid SARS-CoV-2 test); (b) mild (presence of symptoms limited to upper respiratory tract infections, such as fever, fatigue, myalgia, cough, sore throat, runny nose or nasal congestion, or gastrointestinal symptoms); (c) moderate (presence of mild symptoms plus clinical signs and symptoms of pneumonia but no hypoxemia); (d) severe (presence of mild symptoms plus dyspnea, central cyanosis, and oxygen saturation of 92 percent); and (e) critical (presence of mild symptoms plus clinical signs and symptoms of pneumonia but no hypoxemia) (presence of acute respiratory distress syndrome, respiratory failure, encephalopathy, myocardial injury, coagulation dysfunction, and acute kidney injury) (28).

Three independent reviewers (GS, SC, JH) conducted the initial search and the quality assessment of each study. The Joanna Briggs Institute's (JBI) essential evaluation checklist for case reports was used to measure the general consistency of case series and case reports (29). In contrast, the Newcastle Ottawa Quality Assessment Scale was used to assess case management and longitudinal studies (NOS) (30). Any differences between JBI and NOS results were discussed until a conclusion could be reached. If there were still any unresolved disagreements, an expert reviewer (AJ) was consulted, and the decision was made based on his expertise and consensus. In order to be included in this systematic review, the case reports needed to fulfill the majority of JBI criteria and scored ≥ 7 in NOS score.

Age and gender, the severity of COVID-19 events, fatality, laboratory values, and variations in CSF protein and cell count markers dependent on the central nervous system (CNS) or peripheral nervous system (PNS) classification were all assessed using pooled descriptive tests.

Results

There were 2073 articles found initially, and 31 articles were ultimately chosen for this systematic review (Fig. 1). Almost all of the articles are case reports or case series except four studies (31–34). The list and specifications of each study are listed in Table 2. There are 42 patients included in this systematic review, with 26 of them being male. When EEG was done, it was primarily due to acute symptomatic seizure or concomitant encephalopathy, and all the results ($n = 11$) showed some abnormalities. There are 11 computed tomography (CT) scans (6/11 abnormal findings), 20 magnetic resonance imaging (MRI) (14/20 abnormal findings), and two magnetic resonance angiography (MRA) (2/2 abnormal findings) done for the brain or spinal cord. Imaging was done in infectious diseases such as encephalitis to rule out underlying pathologies, vascular diseases such as stroke and aneurysm to locate the exact anatomical location, and other miscellaneous diseases such as Guillain-Barré Syndrome (GBS) and transverse myelitis.

Table 2
Study details

#	First author (year)	No. of patients (% male)	Age (years)*	Neurological signs and symptoms (N)	Neurological diagnosis (N)	Brain imaging results (N)	EEG results (N)	COVID-19 severity (N)	Treatment
(31)	Miller, E (2020)	2 (100)	0.795 (0.02-11)	Non-specific: Fever (2), generalized weakness (1)	Status epilepticus (1), acute symptomatic seizure (1)	N/A	Near continuous sharply contoured slowing with rare embedded sharp waves, maximal right parietal region, frequent runs of the non-evolving rhythmic delta of varying amplitudes, anterior (at times right frontal or bi-frontal predominance) or anterior/posterior, excess overriding beta activity, mild to moderate encephalopathy with the absence of posterior dominant rhythm (in one patient)	Mild (2)	N/A
(32)	Patterson, R (2020)	1 (0)	16	Non-specific: Headache, fever PNS: Bilateral failure of abduction CNS: Diplopia, weakness of left orbicularis oculi	Pseudotumor cerebri (1)	MRI: dilated optic nerve sheaths and narrowed but patent transverse sinuses; consistent with raised intracranial pressure. No parenchymal changes or thrombosis of the head & neck vessels.	N/A	Moderate (1)	Therapeutic puncture, acetazolamide, colchicine, myocarb
(33)	Emami, A (2020)	2 (50)	2.9	Non-specific: Fever (2) PNS: Bilateral upward plantar reflexes (1) CNS: Seizure (2), altered mental status (2)	Status epilepticus (1), tonic-clonic seizure (1)	CT scan: right occipital mass and intracerebral hemorrhage (1); MRI: right occipital mass (suspected ganglioglioma) and intracerebral hemorrhage	Generalized slowing (in one patient)	Mild (1), Critical (1)	Phenobarbital, levetiracetam, valproic acid, phenytoin, midazolam, thiopental, fentanyl

*Data are presented in median (range) when there is more than one patient

*Both investigations are done on the same patient

EEG, electroencephalogram; CSF, cerebrospinal fluid; LOS, length of stay; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; CT, computed tomography; PRES, posterior reversible encephalopathy syndrome; N/A, not available

#	First author (year)	No. of patients (% male)	Age (years)*	Neurological signs and symptoms (N)	Neurological diagnosis (N)	Brain imaging results (N)	EEG results (N)	COVID-19 severity (N)	Treatment
(34)	Beslow, L (2020)	6 (50)	5.835 (0.01-16)	Non-specific: Fever (3), headache (1), hypotonia (1) PNS: Nystagmus (1), otalgia (1), gait disturbances (1), oculomotor abnormalities (1), CNS: Encephalopathy (1), jitteriness (1), chorea (1), seizure (1), meningitis (1)	Acute ischemic stroke (6)	MRI: thalamocapsular infarct (1); Left basal ganglia infarct, Left middle cerebral artery stenosis (1); midbrain infarct (1); bilateral posterior cerebral artery infarcts (1); Left middle cerebral artery, left anterior cerebral artery, right anterior cerebral artery infarct (1); right transverse sinus and right sigmoid sinus thrombosis (1); MRA: vasculitis (1)	N/A	Asymptomatic (2), Mild (3), Critical (1)	N/A
(40)	Conto-Palomino, N (2020)	1 (0)	13	Non-specific: Headache, fever CNS: Hemiparesis, sensory disorder, difficulty in standing	Viral encephalitis (1)	CT scan: diffuse cerebral edema with a hyperdense right frontal subcortical image and meningeal thickening in the tentorial region and interhemispheric line	N/A	Mild (1)	Hydroxy 400 mill day oral azithromycin 1000 milligrams orally, a dexamethasone 10 milligrams intravenous
(41)	Gutierrez Amezcua, J (2020)	1 (100)	7	Non-specific: Fever, headache, dizziness CNS: Altered mental status, gaze deviation, fixed and dilated pupils, loss of brainstem reflex	Encephalopathy (1)	CT scan: diffuse cerebral edema with loss of gray-white differentiation	Left frontotemporal slowing, a loss of fast activity on the right with an increase in delta waves on the left, and bilateral voltage attenuation	Critical (1)	Levetiracetam
(42)	Savić, D (2020)	1 (0)	13	Non-specific: Fever, weakness CNS: Loss of consciousness	Pseudoaneurysm of the left middle cerebral artery (M2 segment) with partial thrombosis	CT scan: large left-side frontoparietal intracerebral hematoma with an intraventricular extension and a midline shift of 5 mm to the contralateral side and left-sided brain edema	N/A	Mild (1)	Surgery frontal craniotomy and ventriculostomy
(53)	Nathan, N (2020)	4 (100)	0.1875 (0.13–0.23)	Non-specific: Fever (4) CNS: Drowsiness (3) PNS: Hypotonia (3)	Encephalopathy (4)	N/A	N/A	Critical (4)	N/A

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EEG, electroencephalogram; CSF, cerebrospinal fluid; LOS, length of stay; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; CT, computed tomography; PRES, posterior reversible encephalopathy syndrome; N/A, not available

#	First author (year)	No. of patients (% male)	Age (years)*	Neurological signs and symptoms (N)	Neurological diagnosis (N)	Brain imaging results (N)	EEG results (N)	COVID-19 severity (N)	Treatment
(54)	McAbee, G (2020)	1 (100)	11	Non-specific: Generalized weakness	Viral encephalitis (1)	CT scan: normal	Frontal Intermittent delta activity	Mild (1)	N/A
(55)	Burr, T (2021)	1 (0)	1.92	Non-specific: Fever CNS: Altered mental status, seizure, hyperkinetic movements	Autoimmune encephalitis (1)	MRI: normal	N/A	Mild (1)	IV methylprednisolone (30 mg/kg) and IVIG (2 g/kg) administered for the 1st 4 days of encephalitis
(56)	Chacón-Aguilar, R (2020)	1 (100)	0.07	Non-specific: Lethargy PNS: Hypotonia, areflexia CNS: Altered mental status	Acute symptomatic seizure (1)	N/A	Continuous patterns with sleep-wake cycles	Mild (1)	Empirical: antibiotic
(57)	Di Nicola, P (2020)	1 (0)	0.049	Non-specific: Fever, generalized weakness CNS: Seizure	Encephalopathy (1)	MRI: normal	Cortical depression without seizures	Critical (1)	Broad-spectrum empirical: antimicrobials, caffeine
(58)	Chegoni, M (2020)	1 (0)	2	Non-specific: Fever CNS: Convulsion	Status epilepticus (1)	MRI: Normal	Generalized slowing without recurrence of seizures	Mild (1)	IV lorazepam, levetiracetam, acetaminophen, Ceftriaxone, foscarnet
(59)	Paybast, S (2020)	1 (0)	14	PNS: Hyporeflexia, lower limb weakness, hypoesthesia CNS: Quadriparesis, ataxia	Guillain-Barré Syndrome (1)	N/A	N/A	Asymptomatic (1)	IVIG 20 g/kg for five days
(60)	Khalifa, M (2020)	1 (100)	11	Non-specific: Fever, hypotonia PNS: Areflexia, symmetrical lower limb weakness, hypoesthesia, gait disturbances	Guillain-Barré Syndrome (1)	MRI: enhancement of cauda equina	N/A	Moderate (1)	IVIG 1 g/kg for 2 days, acetaminophen, hydroxychloroquine, low molecular weight heparin
(61)	Frank, C (2020)	1 (100)	15	Non-specific: Fever, headache, retro-orbital pain, hyperhidrosis PNS: Areflexia, symmetrical lower limb weakness	Guillain-Barré Syndrome (1)	MRI: normal	N/A	Mild (1)	Methylprednisolone, azithromycin, albendazole 400 mg, 5 days
(62)	Shen, M (2021)	1 (100)	1.42	CNS: Right hemiparesis	Acute ischemic stroke (1)	MRI: acute left pontine infarct	N/A	Asymptomatic (1)	Aspirin daily

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*Both investigations are done on the same patient

EEG, electroencephalogram; CSF, cerebrospinal fluid; LOS, length of stay; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; CT, computed tomography; PVE, posterior reversible encephalopathy syndrome; N/A, not available

#	First author (year)	No. of patients (% male)	Age (years)*	Neurological signs and symptoms (N)	Neurological diagnosis (N)	Brain imaging results (N)	EEG results (N)	COVID-19 severity (N)	Treatment
(63)	de Ruijter, N (2020)	1 (100)	15	Non-specific: Headache, nausea, photopsias PNS: Visual loss	Neuromyelitis optica spectrum disorder (1)	MRI: Normal brain appearance; Orbit: a bilateral edematous optic nerve lesion (right more than left), characteristic for bilateral optic neuritis	N/A	Mild (1)	Intravenous methylprednisolone (1g/day days)
(64)	Dugue, R (2020)	1 (100)	0.115	Non-specific: Fever CNS: Seizure, gaze deviation (sustained upward gaze)	Acute symptomatic seizure (1)	N/A	An excess of sharp temporal transients for age and intermittent vertex delta slowing with normal sleep-wake cycling	Mild (1)	N/A
(65)	Khan, A (2021)	1 (100)	11	Non-specific: Fever PNS: Visual loss	Myelin oligodendrocyte glycoprotein (MOG) antibody disease	MRI: bilateral asymmetrical optic neuritis, right > left, involving the intraorbital and intracanalicular portion on the right side and intraorbital portion on the left side; enhancement of the optic nerve sheath in the right orbit; chiasmatic, retrochiasmatic portion, as well as optic tracts, were normal in signal intensity and appearance on both sides	N/A	Mild (1)	Intravenous methylprednisolone 30mg/kg by oral prednisone 1mg/kg/day

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*Both investigations are done on the same patient

EEG, electroencephalogram; CSF, cerebrospinal fluid; LOS, length of stay; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; CT, computed tomography; PRES, posterior reversible encephalopathy syndrome; N/A, not available

#	First author (year)	No. of patients (% male)	Age (years)*	Neurological signs and symptoms (N)	Neurological diagnosis (N)	Brain imaging results (N)	EEG results (N)	COVID-19 severity (N)	Treatment
(66)	Dominguez, J (2020)	2 (100)	8.5 (4–13)	Non-specific: Fever (1), headache (1), weakness (1) CNS: Loss of sensory disorder (1), drowsy (1), gaze deviation (1), absent patellar reflex (1), flaccid paralysis (1), strabismus (1)	Acute disseminated encephalomyelitis (1), Guillain-Barré Syndrome (1)	CT scan: normal (1); multifocal, hyperintense white matter lesions in the frontal region right temporal.	N/A	Asymptomatic (1), Mild (1)	Ceftriaxone 1000 mg IV q8h, acyclovir 300 mg IV q8h, methylprednisolone 30 mg IV q12h for 5 days, Immunosuppressants 400 mg IV q12h for 5 days
(67)	Seth, V (2020)	1 (100)	15	Non-specific: Headache CNS: Photophobia, irritable, agitated	Encephalitis (1)	CT scan: normal; MRI: normal	N/A	Mild (1)	Intravenous acyclovir and paracetamol
(68)	Mirzaee, S (2020)	1 (100)	12	Non-specific: Headache CNS: Seizure, dysarthria	Focal cerebral arteriopathy (1)	MRI: acute infarction without microhemorrhages along with focal irregular narrowing and banding of the proximal M1 segment of the left middle cerebral artery with a slightly reduced distal flow	N/A	Mild (1)	Diazepam
(69)	Kaur, H (2020)	1 (0)	3	Non-specific: Weakness CNS: Decreased sensation, hemiparesis, absent gag reflex, quadriparesis, areflexia, no pain response	Transverse myelitis	MRI: swelling of the cervical spinal cord with T2-hyperintense edema on the transverse aspect of the spinal cord, extending from the lower medulla to the midthoracic level	N/A	Asymptomatic (1)	Intravenous methylprednisolone (30 mg/kg and immunoglobulin G/kg total plasma volume; 1.0-1.5 volume per session) rituximab infusion (mg/m ²)
(70)	Bhatta, S (2020)	1 (100)	11	CNS: Seizure (stretching and tightening of all four limbs, uprolling of eyes, frothing from the mouth, teeth clench, and tongue bite without urinary or bowel incontinence)	Tonic-clonic seizure (1)	CT scan: normal	N/A	Asymptomatic (1)	Lorazepam, Levetiracetam
(71)	Swarz, J (2020)	1 (100)	4.5 (0.01-9)	Non-specific: Fever CNS: Decreased consciousness	Encephalopathy and status epilepticus (1)	CT scan: normal; MRI: normal	Continuous delta slowing throughout the right hemisphere without epileptiform features	Critical (1)	Lorazepam, antibiotic

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*Both investigations are done on the same patient

EEG, electroencephalogram; CSF, cerebrospinal fluid; LOS, length of stay; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; CT, computed tomography; PRES, posterior reversible encephalopathy syndrome; N/A, not available

#	First author (year)	No. of patients (% male)	Age (years)*	Neurological signs and symptoms (N)	Neurological diagnosis (N)	Brain imaging results (N)	EEG results (N)	COVID-19 severity (N)	Treatment
(72)	Davide, S (2021)	1 (0)	4	PNS: Conjugate eye deviation	Focal epilepsy	N/A	Temporo-occipital right region sub-continuous slow spikes-slow waves complexes	Asymptomatic (1)	Midazolam
(73)	Vivanti, A (2020)	1 (100)	0	Non-specific: Irritability, axial hypertonia CNS: Opisthotonos	Cerebral vasculitis (1)	N/A	N/A	Severe (1)	N/A
(74)	Gulko, E (2020)	1 (0)	13	Non-specific: Headache, weakness PNS: Speech difficulty	Focal cerebral arteriopathy (1)	MRA: Focal moderate stenosis within the M1 segment of the left middle cerebral artery. Vessel wall imaging targeted to the left middle cerebral artery M1 segment demonstrated wall thickening and marked, concentric contrast enhancement at the site of stenosis; CT-scan: Left frontal hypodensity	N/A	Mild (1)	N/A
(75)	Lorenz, N (2020)	1 (0)	0	Non-specific: Fever, lethargy PNS: Smell disturbances (anosmia), taste disturbances (ageusia) CNS: Encephalitic syndrome (lethargic but severely hyperexcitable, high pitched crying)	Encephalitic syndrome (1)	N/A	N/A	Mild (1)	Oral caffeine
(76)	Tan, Y (2020)	1 (0)	2	Non-specific: Fever CNS: seizure	Febrile seizure (1)	N/A	N/A	Mild (1)	N/A
*Data are presented in median (range) when there is more than one patient									
*Both investigations are done on the same patient									
EEG, electroencephalogram; CSF, cerebrospinal fluid; LOS, length of stay; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; CT, computed tomography; PARS, posterior reversible encephalopathy syndrome; N/A, not available									

According to CNS or PNS manifestations, the neurological diagnosis was mainly of the CNS side (38/42) (Fig. 2). Brain disorders predominated in this category (22/38), with the most common diagnosis being acute symptomatic seizure (n = 6) and encephalomyelopathy (n = 6). However, the single most common neurological diagnosis belonged to the vascular disorders (11/38), namely stroke, with seven patients diagnosed with COVID-19. In the PNS classification, all patients were affected by GBS (4/4).

The most common COVID-19 specific sign and symptom was fever (n = 29), followed by cough (n = 9), and vomiting (n = 8) (Fig. 3). As for COVID-19 neurological signs and symptoms, seizure and altered consciousness were the most common signs and symptoms, with nine cases each followed by headache (n = 8) and irritability and hemiparesis (n = 7) (Fig. 4). Out of the 18 PCR testing done from the CSF sample, five were positive for COVID-19 while two out of three rectal samples were positive for COVID-19 (Table 3). The median age of all the patients was 3.5 years old (0–16 years old). Out of 37 patients

with known outcomes, 34 patients were alive (91.9%). Length of stay was known in 31 patients and six days (0–30 days) was the median length of stay. Patients mostly presented with moderate COVID-19 severity (24/42), followed by asymptomatic (8/42) and mild presentation (7/42).

Table 3
Individualized patient characteristics

Variables	# Patients with available data	Median (Range)	N (%)
Age (years)	42	3.5 (0–16)	N/A
Male gender	42	N/A	26 (61.9)
CNS diagnosis	42	N/A	37 (88.1)
First onset of symptom before first neurologic manifestation (days)	18	2.5 (0–10)	N/A
COVID-19 tests			
Serologies	9	N/A	
IgM positive			0 (0)
IgG positive			3 (33.3)
IgM and IgG positive			2 (22.2)
Not specified*			4 (44.4)
Polymerase chain reaction (PCR)			
Positive from the cerebrospinal fluid sample	18	N/A	5 (27.8)
Positive from nasopharyngeal sample	35	N/A	33 (94.3)
Positive from rectal sample	3	N/A	2 (67.7)
Outcome (alive)	37	N/A	34 (91.9)
Length of stay (days)	31	6 (0–30)	N/A
COVID-19 severity			
Asymptomatic		N/A	8 (19.0)
Mild		N/A	5 (11.9)
Moderate		N/A	24 (57.1)
Severe		N/A	2 (4.8)
Critical		N/A	3 (7.1)
*Presented as serologies positive			
CNS, central nervous system; N/A, not available			

Table 4 presented a pooled analysis of laboratory values. Pediatric COVID-19 patients with neurological manifestations had lymphopenia, elevated C-reactive protein (CRP), procalcitonin, ferritin, creatinine kinase, blood urea nitrogen, D-dimer, and erythrocyte sedimentation rate (ESR).

Table 4
Laboratory values

Variable	# Patients with available data	Reference range	Median (range)
Hematology			
Hemoglobin (g/dL)	14	11.5–14.5	11.75 (7.2–15.0)
White blood cell count ($10^3/\mu\text{l}$)	18	4–12	7.745 (2.0–20.6)
Lymphocyte (%)	8	25–33	22.65 (11.6–49.4)
Neutrophil (%)	6	57–67	57.7 (22–83.7)
Platelets ($10^3/\mu\text{l}$)	12	150–400	340.5 (81–406)
Inflammatory markers			
C-reactive protein (mg/L)	24	Male 0.6–7.9 Female 0.5–10.0	7.55 (0–556)
Ferritin (ng/mL)	5	10–60	87.3 (19.9–4220)
Procalcitonin (ng/mL)	7	≤ 0.15	0.21 (0.1–1.31)
Lactate dehydrogenase (U/L)	5	150–500	390 (128–1019)
Creatine kinase (U/L)	5	5–130	246.8 (43.7–482)
Lactate (mg/dL)	3	7–14	5 (4.32–7.0)
Liver and kidney functions			
Creatinine (mg/dL)	3	0.3–0.7	0.5 (0.47–0.5)
Alanine transaminase (U/L)	5	5–45	14 (8–20)
Aspartate aminotransferase (U/L)	5	15–50	22 (10–40.49)
Blood urea nitrogen (mg/dL)	2	7–18	48.1 (40.7–55.5)
Coagulation			
D-dimer (mg/L)	10	< 0.4	3.2 (0.29–619)
Fibrinogen (mg/dL)	3	220–440	418 (364.74–730)
Erythrocyte sedimentation rate (mm/h)	2	0–20	29 (13–45)
The reference range used in this table is according to normal values of children who are 3.5 years old (the median age of this study). These values are obtained from the Nelson Textbook of Pediatrics (77).			

Lastly, Table 5 presented a comparison of CSF analysis between the CNS group and the PNS group. Patients with CNS disorders were younger (2.785 years old; 0–16 years old) compared to those with PNS manifestations (12.5 years old; 4–15 years old). The median for the onset of lumbar puncture from the first symptom was two days (0–18 days) in the CNS group, while it took three days (1–10 days) in the PNS group. None of the PNS group tested positive for COVID-19 from the CSF sample, while five pediatric patients were positive for COVID-19 via CSF analysis. In the CNS group, CSF monocytes (55%; 11–80%), CSF polymorphonuclear cells (15%; 0–96%), CSF red blood cells (282 cells/mm³; 2–4000 cells/mm³), and opening pressure (34.5 cm/H₂O; 25–100 cm/H₂O) were elevated. Meanwhile, in the PNS group, all the parameters were mostly normal except for positive albumin-cytological dissociation.

Table 5
Cerebrospinal fluid analysis according to central or peripheral nervous system involvement

Variable	Reference range	Central nervous system disorder (n); median (range)*	Peripheral nervous system disorder (n); median (range)*
Total	N/A	38	4
Age	N/A	2.785 (0–16)	12.5 (4–15)
Male sex	N/A	23	2
Onset from first symptom to lumbar puncture (days)	N/A	2 (0–18); n = 21	3 (1–10)
CSF PCR results for COVID-19	Negative	Positive: 5; Negative: 12; Not checked: 21	Negative: 1; Not checked: 3
Total cells (count/ μ L)	0–20	6.5 (0–55); n = 16	5 (5–5); n = 2
Normal value (n)		20; n = 23	4
Increased (n)		3; n = 23	0
CSF lymphocytes (%)	40–80	41.5 (20–89); n = 4	91; n = 1
Normal value (n)		3; n = 6	3
Increased (n)		1; n = 6	1
Decreased (n)		2; n = 6	0
CSF monocytes (%)	15–45	55 (11–80); n = 3	9; n = 1
Normal value (n)		3; n = 6	3
Increased (n)		2; n = 6	0
Decreased (n)		1; n = 6	1
CSF polymorphonuclear cells (%)	0–6%	15 (0–96); n = 9	N/A
Normal value (n)		10; n = 16	2; n = 2
Increased (n)		5; n = 16	0; n = 2
Decreased (n)		1; n = 16	0; n = 2
CSF protein (mg/dL)	5–40	40 (0.3–97); n = 13	34.7 (25–316.7); n = 3
Normal value (n)		16; n = 22	2
Increased (n)		5; n = 22	1
Decreased (n)		1; n = 22	0
CSF glucose (mg/dL)	40–80	60 (3.1–92); n = 13	65 (64–66), n = 3
Normal value (n)		18; n = 22	4
Increased (n)		3; n = 22	0
Decreased (n)		1; n = 22	0
CSF red blood cells (RBC/ mm^3)	0	282 (2–4000); n = 9	N/A
Normal value (n)		7; n = 16	2; n = 2
Increased (n)		9; n = 16	0; n = 2
Decreased (n)		0; n = 16	0; n = 2
Opening pressure (cm/ H_2O)	11.5–28	34.5 (25–100); n = 4	N/A
Normal value (n)		4; n = 7	1; n = 1
Increased (n)		3; n = 7	0; n = 1
Decreased (n)		0; n = 7	0; n = 1
Positive oligoclonal bands	Negative	0; n = 3	0; n = 1
The reference range used in this table is according to normal values of children who are 3.5 years old (the median age of this study). These values are obtained from The Harriet Lane Handbook (78) and Mosby's Manual of Diagnostic and Laboratory Tests (79).			
*When n is not defined, n has the same value as the total sample			
CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RBC, red blood cells; N/A, not available			

Variable	Reference range	Central nervous system disorder (n); median (range)*	Peripheral nervous system disorder (n); median (range)*
Positive albumin cytological dissociation	Negative	0	4
The reference range used in this table is according to normal values of children who are 3.5 years old (the median age of this study). These values are obtained from The Harriet Lane Handbook (78) and Mosby's Manual of Diagnostic and Laboratory Tests (79).			
*When n is not defined, n has the same value as the total sample			
CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RBC, red blood cells; N/A, not available			

Discussion

Our systematic review only includes 31 studies with 42 patients, a far cry from another systematic review that has been done with 26 studies and 3707 patients (19). However, Panda et al. only focus on reporting the neurological symptoms while this systematic review requires investigations of neurological symptoms, explaining the wide gap in the number of patients (19). Other systematic reviews that have also been done primarily focus on neurological manifestations in adults (14, 15, 17).

Encephalopathy is the most prominent and definite neurological complication, which some of the cases might be mediated by hypoxia and septic shock (19). This finding is similar to our result, where encephalomyelopathy and seizure are among the most common neurological diagnoses in COVID-19. The exact pathomechanism of SARS-CoV-2 infections on the nervous system has not been fully elucidated yet. Proposed mechanisms are direct infection injury via the hematogenous and neuronal pathway, hypoxia injury, immune injury, and angiotensin-converting enzyme-2 (ACE-2) (16). A high ACE-2 expression is found in the brainstem, cerebral cortex, amygdala, with the highest ACE-2 expression level at pons and medulla oblongata. The brainstem contains medullary respiratory centers, and this may explain the susceptibility of COVID-19 patients to respiratory distress (35).

Acute ischemic stroke is the most common diagnosis in this systematic review. Studies have shown an increase in the incidence of ischemic stroke by 2.5% in Italy and 3.7% in the Netherlands (36). This represents the cerebrovascular system's thromboembolic mechanism, found in COVID-19 patients, albeit more common in adult patients (18). Other possible pathways include the ACE-2 receptor and its subsequent effect on blood flow, hypoxia, vascular endothelial injury, and inflammatory insults (13, 20). The high cases of reported acute ischemic stroke in pediatric patients may reflect increased awareness of neurological complications of pediatric COVID-19 patients as acute ischemic stroke is uncommon in adult COVID-19 cases with a pooled prevalence of 2.1% (14, 17).

Seizure and altered mental consciousness are the two most common neurological manifestations. While seizure is not the most predominant symptom in other studies, it is more common in patients with severe COVID-19 disease, especially in multisystem inflammatory responses (37). This is why the authors excluded MIS-C in this systematic review because neurological manifestations are higher in MIS-C, which might skew the results (18, 20). Interestingly, most of the patients in this systematic review present with moderate severity, which might imply ongoing and evolving inflammation, leading to clinical deterioration. Hence, clinicians should keep a close observation of pediatric patients with neurological manifestations (38).

Headache is the most common CNS symptom, and it is regarded as secondary to hypoxia (13, 14, 17, 19). However, the most common PNS symptom is anosmia and ageusia (13, 14, 17), which is not found in our result. Inflammation of the olfactory nerves might explain anosmia, while ACE-2 receptor damage on the tongue might explain ageusia. It is noteworthy that these studies include adults as their population, whereas it is more difficult to extract this information in children, especially those with severe symptoms (19). Qiu et al. look at the characteristics of adults and children presenting with olfactory or gustatory dysfunction. They find that 37% of the children present with olfactory or gustatory dysfunction with a median age of 16.6 years old, which shows that adolescents are more aware and more likely to report such symptoms than children (39). This study is not included in our systematic review because no further investigations are done on the patients.

Most of the patients are alive except for three patients. All three deaths can be explained by critical presentation, complications of surgery while, and cardiopulmonary arrest (40–42). Increased C-reactive protein, D-dimer levels, creatinine kinase, ferritin, procalcitonin, erythrocyte sedimentation rate, and decreased lymphocytes may portend poorer prognosis and hence leading to increased severity of disease and mortality (14, 43, 44).

One systematic review found that most patients who present with PNS manifestation have a normal cell count and high protein (22). This is different from our studies, where all CSF parameters are within normal except for positive albumin-cytological dissociation. Some of the possible explanations for this finding are that more samples in the PNS group (n = 55) and adult population are used in that systematic review. A different time course in obtaining the CSF sample may alter the CSF results, which may contribute to different results found in our study (45). Espindola et al. found that there is pleocytosis with predominant mononuclear cells in CNS disorders, a mild increase in total protein concentration and high neurofilament light (21), which is similar to what we find. There are only five samples that test positive for COVID-19 from CSF samples. This may be due to the low sensitivity of SARS-CoV-2 detection using PCR, the onset of

manifestation to lumbar puncture, as well as different pathomechanisms that may alter the results (19, 20). Therefore, any negative PCR results from CSF need to be interpreted with caution (46).

There are several limitations to our study. Firstly, many studies are excluded due to not meeting the criteria of investigations of neurological symptoms, or the corresponding authors do not provide essential data for this systematic review (23, 25, 26, 47–52). Despite many studies not being included in this systematic review, there is no guarantee that all those studies will end up included due to inclusion and exclusion criteria imposed. Secondly, our systematic review has a low sample, with most of the studies being case reports. This reflects the rarity of pediatric neurologic COVID-19 infections investigated by either laboratory or imaging studies. This systematic review gives insights into the clinical profiles and CSF analysis in pediatric COVID-19 patients with neurologic symptoms despite the low samples. Lastly, not all the data required in this systematic review are given in the corresponding paper. To our knowledge, this is the first systematic review to elucidate CSF analysis from pediatric COVID-19 patients with neurological symptoms.

Conclusion

This systematic review describes the demographic status, clinical manifestations, laboratory and imaging studies, including CSF analysis of new-onset and investigated pediatric COVID-19 patients. There is a male predominance with a majority of CNS diagnoses as well as a good prognosis. Results of CSF analysis show that CNS disorders present with elevated CSF monocytes, CSF polymorphonuclear cells, CSF red blood cells, and opening pressure. In contrast, patients with PNS disorders mostly have normal values except for albumin-cytological dissociation. Further studies are required to find the long-term consequences of neurological complications of COVID-19 as well as the dynamics of CSF results in pediatric COVID-19 patients.

Declarations

Conflicts of interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Availability of data and material

Data will be given upon reasonable request

Ethics approval

Not available

Consent to participate

Not available

Consent for publication

All authors have read and agreed on publishing this article

Authors' contributions

GSO and AJ did the conception of this systematic review while GSO registered the procedure on PROSPERO website. Data collections are done by GSO, SC, and JHW with disputes between the articles that were selected settled by AJ. GSO, SC, and JHW drafted the article while AJ did critical revision of the article. Final approval of the version to be published was granted by all authors.

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Figures

Figure 1

PRISMA flow chart of this study

Figure 2

Classification of COVID-19 induced neurological disorders

Figure 3

COVID-19 signs and symptoms distribution

Figure 4

Supplementary Files

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