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Neurological Manifestations of COVID-19 and Monkeypox in Pediatric patients & their management- A state of art systematic review

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Title

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Title: Neurological Manifestations of COVID-19 and Monkeypox in Pediatric patients and their management- A state of art systematic review.

Abstract

Background:

There is an increasing number of cases being reported of neurological manifestations of COVID-19 infection and Monkeypox, both during the course of the infection or as a presenting symptom. We aim to review the neurological manifestations of COVID-19 and Monkeypox in Pediatric patients and their management.

Methods:

We conducted a systematic review which included cohort studies and case series or reports involving a pediatric population of patients with a confirmed COVID-19 or Monkeypox infection and their neurological manifestations. We searched the following electronic databases: PubMed, EMBASE, Scopus.

Results:

From 1136 articles identified, 127 studies were included. Headache, stroke, GBS, seizure, nerve palsies and MISC-C were the most common neurological symptoms caused by COVID-19 while encephalitis was commonly seen in Monkeypox patients. Rare neurological manifestations of COVID-19 included cerebral venous sinus thrombosis, plexopathies, demyelinating disorders, encephalitis etc and rare neurological manifestations of Monkeypox included headache.

Conclusion:

Our review highlights the importance of investigating possible neurological manifestations and closely monitoring these patients to develop a better understanding of the treatment strategies that can be adopted.

1. Background

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in Wuhan, China in December 2019. Ever since the initial outbreak, non-respiratory manifestations have been reported across all age groups. (22) COVID-19 presents with different clinical features in adults and children.(128) In children the clinical presentation is mild, mostly with an influenza-like pattern.(129) Neurotropic and neuroinvasive capabilities of other coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have been previously described. (130) The neurologic manifestations of SARS-CoV-2 are now being increasingly recognized.(29)

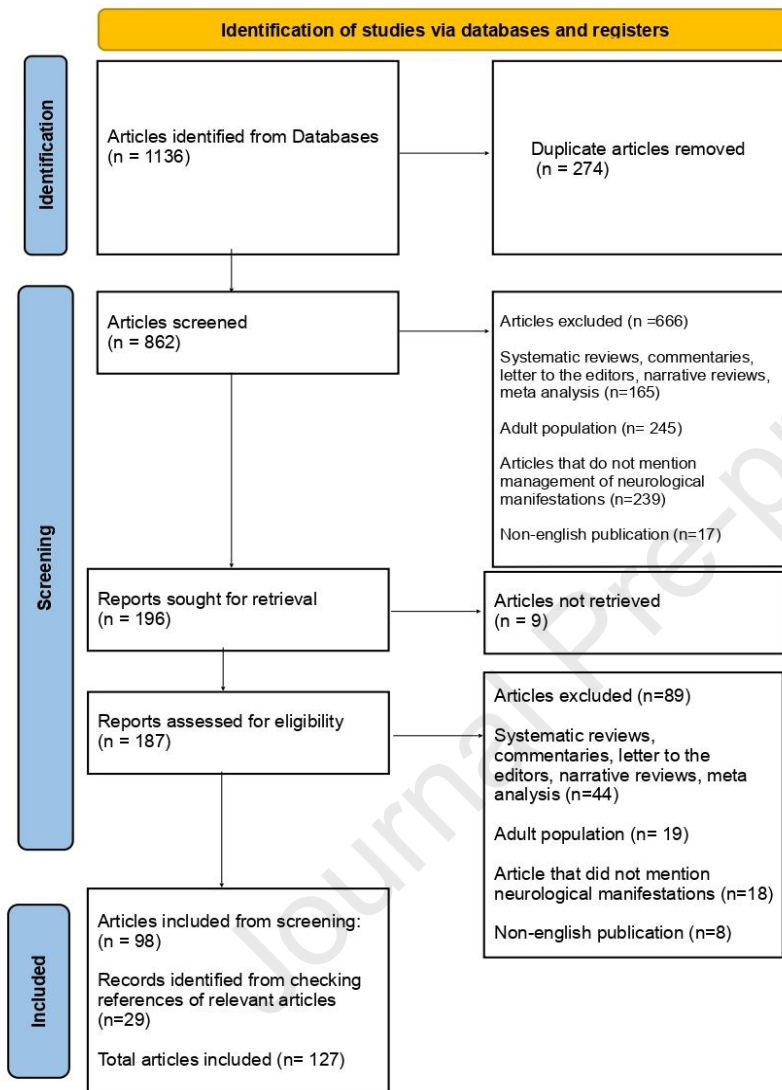
Neurological problems reported in COVID-19 patients include febrile seizures, convulsions, loss of consciousness, encephalomyelitis, and encephalitis.(131) Laboratory studies have revealed that the main host-cell receptor of SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2) (132) and given that ACE2 is expressed in both neurons and glial cells, direct viral invasion of the central nervous system (CNS) is a possible mechanism for neurological manifestations of COVID-19.(133)

The re-emergence of monkeypox, a viral disease, was confirmed in May 2022 when initial clusters were found in the United Kingdom.(134) Till date, over 455 confirmed cases have been reported. The clinical presentation was similar to that of the ordinary and modified forms of smallpox.(105) No deaths were recorded in vaccinated patients while in unvaccinated patients, the crude case-fatality rate was 11%, with the highest being among the pediatric population at 15%.(105) Neurological symptoms in pediatric patients were not uncommon.

This article reviews the neurological manifestations of COVID-19 and Monkeypox in Pediatric patients and their management.

2. Methodology

This review is reported according to recommendations of the Preferred Reporting Items for Systematic reviews and Meta-analyses statement. (135)



2.1 Search strategy

A thorough literature search was conducted on three major electronic healthcare databases for relevant studies from inception to October 2022 : PubMed, Embase, and Scopus. The terms used in the search strategies were as follows: ((neurological manifestation) OR (nervous system) OR (neurological symptom)) AND ((therapy) OR (treatment) OR (management)) AND ((paediatric) OR (child) OR (children)) AND ((covid-19) OR (SARS-COV-2) OR (Monkeypox)). References

of all relevant articles, narrative reviews and systematic reviews have also been considered during data extraction .

2.2 Inclusion and exclusion criteria

All articles which contained information about neurological manifestations of either COVID-19 OR Monkeypox in pediatric patients and their outcomes were included.

The results of the initial search were imported into the Rayaan software (136) and all the duplicates were resolved. A three-step screening approach to exclude all irrelevant articles based on title, abstract, and full-text was implemented. All reported neurological findings, including manifestations of both central nervous system and peripheral nervous system have been taken into consideration.

All systematic reviews, meta-analysis, narrative reviews, conference abstracts, commentaries, letters to editors, animal studies and non-english articles were excluded. Articles where full texts couldn't be fetched, or which included the adult population were also excluded.

2.3 Data extraction and quality assessment

For each relevant study, the following information were recorded: author, demographic information, number of cases, study design, age, sex, any existing comorbidities, main neurologic symptoms, investigations performed, treatment and outcomes.

Quality of the non-randomized studies was evaluated using the Newcastle-Ottawa Scale (137) while quality of case series and case reports was evaluated using the Joanna Briggs Institute checklist.(138)

3. Results

<Table 1.0: Neurological Symptoms of COVID-19 and monkey pox>

4. Discussion

4.1 Common Neurological Manifestations of COVID-19

4.1.1 Headache

23 studies have reported headache as a manifestation of COVID-19 and in all studies, headache was the patient's presenting complaint. In one study the patient presented with thunderclap headache and photophobia [45] while in others headache was associated with GI symptoms [86], convulsions and seizures [122,103,69], confusion and altered mental status[28,75,90,96] and myalgia. [5] In almost all cases, treatment of the primary cause resulted in recovery from headache. In other cases, oral acetaminophen was prescribed [86]. An Indian study done by Sharma S et al, evidenced a Computed Tomography (CT) finding of ill defined cerebellar hemispheric hypodensity with compression of the fourth ventricle, resulting in obstructive hydrocephalus in both cases.[90]

4.1.2 Stroke

5 studies have reported stroke in COVID-19 patients. E Gulko et al reported a patient who presented with fluctuating headache, speech difficulty and right upper and lower limbs extensor weakness. The CT scan was suggestive of ischemic infarct while magnetic resonance imaging (MRI) suggested multiple infarcts in the middle meningeal artery and magnetic resonance angiography (MRA) showed left middle cerebral artery (MCA) thickening. [57] Essajee F et al reported a case of left sided weakness and lethargy with miliary tuberculosis (TB). CT brain revealed pan-hydrocephalus with infarction involving the right internal capsule, lentiform nucleus and thalamus along with multiple filling defects. [59] Steroid therapy with methylprednisolone and dexamethasone [57,58] with antitubercular regimen to treat the TB coinfection were prescribed.[59] All patients gradually recovered and were advised physical therapy for improvement.

4.1.3 Guillain-Barre syndrome (GBS)

A total of 9 cases of GBS have been reported in patients with COVID-19. There were variable clinical presentations in these cases. While most cases had typical manifestations of GBS [118,117,116,11,21,33], in others non-projectile vomiting with abdominal pain [79] and otalgia,odynophagia and facial palsy were also noted. [7] All patients were treated with 5 cycles of intravenous immunoglobulins with doses as per the body weight. Significant improvement was seen on these patients and they were discharged with routine follow up.

4.1.4 Seizure

49 studies have reported seizure as a neurological manifestation of COVID-19. Some patients had a previous history of epilepsy. [2,12,7,112,123,124,16] A 7 year old with a history of right temporal lobe epilepsy presented with high grade fever and abdominal pain, diagnosis of encephalomyelitis. [12] In majority of the patients seizure were preceded by fever. [12,100,112,16,20,27,29,23,47,71,74,91] Episodes of seizures related to Multisystem Inflammatory Syndrome in Children (MISC) were also seen.[23,24,47,101,73] Vergera D et al reported a 14 year old female with PRRT2 mutation and history of focal seizure presented with new onset tonic clonic seizures with impaired consciousness in between episodes. MRI revealed increased T2 signals at bilateral hippocampus, a diagnosis of super refractory status epilepticus(SRSE) was made [2].

Khan A et al reported a case of 11 year old female presented with generalized tonic clonic seizure, brain MRI revealed features of acute cerebellitis, patient was treated with antibiotics and antiviral drugs, the patient was stable after 4 months. [12] Majority of the patients recovered and were discharged with proper medications or rehabilitation services while three patients died [41,2,76] while some patients chose passive euthanasia. [38]

4.1.5 Nerve palsy

7 cases reported nerve palsy as a manifestation of COVID-19. Three cases reported facial nerve palsy [3,13,63], one reported abducens nerve palsy [26,53,47] and another case reported oculomotor nerve palsy [84]. All patients received a short course of corticosteroids and were discharged with proper follow up.

4.1.6 MIS-C

18 reported cases present with symptoms suggestive of MIS-C or Pediatric Inflammatory Multisystem Syndrome (PIMS). In a study by Hacoheh et al, 4 patients were identified with symptoms of encephalopathy, cerebellar signs, meningism. [96] MRI Brain of all 4 patients showed splenic signal changes. They were treated with dexamethasone, anakinra and IVIG. All patients showed good prognosis with resolution of encephalopathy. Another study by Varol et al identified 2 patients with Reversible splenic lesion syndrome (RESLES). [101] They presented with fever, blurred vision, ataxia, encephalopathy, hallucinations. Contrast enhanced MRI showed non specific lesions in the splenic region of corpus callosum. One patient improved with dexamethasone and IVIG while the other patient improved with plasma exchange therapy. A study by Olivetto et al reported 7 patients with acute encephalopathy symptoms such as drowsiness, mood changes, photophobia, oculomotor apraxia, speech disorder, limb pain. [103] All showed diffuse EEG slowing with periodic posterior complexes. They received MIS-C therapy with intravenous methylprednisolone and all patients showed full recovery.

4.2 Rare Neurological Manifestations of COVID-19

4.2.1 Central Nervous System

There were 4 cases with viral encephalitis as the primary manifestation. In a study by Urso et al, patients presented with altered mental status. [8] Patient was treated with dexamethasone and antibiotics with full recovery. Another study by Freij et al reported a case of viral encephalitis with tuberculosis as comorbidity [42] where the patient presented with confusion and cognitive defects. Despite treatment with antibiotics, dexamethasone and remdesivir, the patient died. Another case presented with vertigo and drop attacks. Patient had a fatal prognosis despite

treatment with antibiotics, IVIG, mannitol, dexamethasone and plasmapheresis. [61] Additionally, 1 study reported partially treated meningitis, 3 studies reported acute disseminated encephalomyelitis, 1 study reported meningoencephalitis, and 2 studies reported acute hemorrhagic necrotizing encephalitis.

Demyelinating disorders were reported in 8 studies. A study by Khair et al exemplified this with 5 cases as post or para covid demyelinating manifestations. [3] Patients presented with primarily walking difficulty and limb weakness. 2 patients were diagnosed with ADEM, 2 with multiple sclerosis and 1 with anti-MOG antibody demyelinating disorder. All cases were treated with methylprednisolone with IVIG in 2 cases with recovery and improvement. Another cohort study described by Figen et al describes 14 patients presenting with symptoms such as headache, epilepsy, hallucinations, neck stiffness. [112] The most common cranial MRI finding was RESLES. In six of these cases, diffusion restriction was detected in the posterior part of the splenium in diffusion-weighted MRI sequences. In one patient who presented with hallucinations and seizures, cranial MRI showed symmetrical signal changes in the cerebellar hemispheres, periaqueductal region, mesencephalon, bilateral hypothalamic region, bilateral thalamus, lentiform nucleus, caudate nucleus, deep white matter, and subcortical area with no diffusion restriction or contrast enhancement. These entities were considered as ADEM-like lesions. The clinical state of the patient first improved, but five days later, seizures were observed again. Although the lesions had completely disappeared according to the cranial MRI examination, new pathological signal changes were in the bilateral parieto occipital and bilateral frontoparietal regions without contrast enhancement or diffusion restriction. These new lesions were evaluated as posterior reversible encephalopathy syndrome. In another patient, ADEM- like lesions were found to increase and accompanied by necrotic areas.

There were 2 reports of cerebral venous sinus thrombosis described by Silvestri et al and Blazkova et al. In the first study patients presented with dysarthria and paresthesia of the right arm and cheek. MRI Brain showed extensive thrombotic casting in the superior sagittal sinus, transverse-sigmoid sinuses of both sides and jugular veins and in cortical veins afferent to the superior sagittal sinus and CT brain revealed presence of massive cerebral thrombosis and revealed mild cerebral edema. [45]The second reported patient with seizures, and facial spasm. Investigations also revealed subdural hematoma and cerebral venous sinus thrombosis in

transverse sinuses reaching to sigmoid sinuses, confluens sinuum, and sagittal superior sinus.

[49] Both patients were treated with anticoagulants such as enoxaparin and low molecular weight heparin as well as dexamethasone with overall improvement. Other occlusive phenomenon that were reported were of right cerebral artery ischemia and 2 reports of acute ischemic stroke due to acute intracranial large vessel occlusion (LVO). Right cerebral artery occlusion was described by Scala et al. [77] The patient had malignant cerebral edema, brain was swollen and pale, with congested cortical veins. Presenting symptoms were left-sided hemiplegia, dysarthria, and lateral nystagmus. CT and MRI of the head showed a large right MCA ischemia and a second CT scan demonstrated malignant cerebral edema. He was treated with bridging systemic thrombolysis followed by endovascular thrombectomy and sedated for 12 hrs. The neurologic exam at discharge was Glasgow Coma Score (GCS) of 14 with the persistence of left-sided severe hemiparesis. Androgen insensitivity syndrome (AIS) due to large vessel occlusion was described by Brain et al in two cases. [110] First is an 8 year old Native American female with new onset right hemiplegia and language impairment. She presented with bilateral middle cerebral artery distribution strokes. Emergent mechanical thrombectomy of the left middle cerebral artery with successful clot retrieval was done but she experienced a re-occlusion of that artery 5 hours after intervention. Evidence of cerebral arteritis on catheter angiography and vessel wall imaging was also found. Second report is of a 16 year old African American male who presented 7 days after dense right hemiparesis and global aphasia. He had complete left MCA territory infarction, irregularity of left M1 suggestive of arteritis, and occlusion of left MCA bifurcation. MRI showed worsening edema and increased midline shift. They were treated with heparin, lovenox. 2 months later, on follow up there was persistent dysarthria, aphasia, right facial palsy, right upper extremities weakness.

Various psychiatric manifestations were reported as well. This included 3 reports of delirium, 1 report of hallucination as a presenting symptom, neuropsychiatric syndrome with myoclonus, 1 report of functional tic like movement. 2 cases of delirium reported by Bauer et al [18] and SARS-COV2 induced hallucination described by Pleszko et al [59] were treated with antipsychotic medication and improved. Buts et al did retrospective chart review of 34 consecutive pediatric patients presenting with sudden onset tic-like movements, seen over 6 months out of which only 15% had past history of covid in the patient or a 1st degree relative[98]. Clonus described in a patient by Della Corte et al was treated with clonazepam and

intravenous methylprednisolone for five days followed by oral prednisolone. This was followed by five days of IVIG with significant improvement.[53]

Transverse myelitis was observed in 3 research studies described by Nejad et al, Poyrazoğlu HG et al and Najafinejad, M et al. Najafinejad, M described 91 confirmed cases out of which 83 recovered and 8 died. The patients described in the other studies recovered after treatment with methylprednisolone, plasma exchange and IVIG. [71,88,93]

Less frequently manifestations such as Wernicke's encephalopathy, atypical Lemierre, atypical kawasaki, miller fischer syndrome, loss of taste and smell, acute flaccid paralysis, pseudotumor cerebri, and exacerbation of opsoclonus myoclonus syndrome was reported in pediatric population. [35,16,54,90,30]

4.2.2 Peripheral Nervous System

There were 5 cases which described neuropathy as a neurological manifestation of COVID-19. These were brachial plexopathy, ulnar neuropathy, sciatic neuropathy, demyelinating polyneuropathy and cranial nerve X palsy leading to polyneuropathy. There was one case of chronic inflammatory demyelinating polyneuropathy and one case of myopathy. Avila-Smirnow et al described 3 cases of neuropathy, presented with limb weakness or tingling. [5] All cases had generally good prognosis upon treatment with antibiotics. [5]

2 studies that reported vestibular neuritis. Both presented with vertigo and nystagmus were observed on examination. The first case was treated with an intravenous course of prednisone. [31] Second patient underwent vestibular rehabilitation and had resolution of symptoms.[109]

4.3 Neurological Manifestations of Monkeypox

We describe cases of human monkeypox infection in 2 case reports (106, 127) and a 282 patients cohort study. (105) All patients were unvaccinated.

Adler H et al describes a 2 year old female who presented with lymphadenopathy and concomitant lesions across her body but later developed headache and malaise and was discharged without any antiviral therapy or treatment on 22nd day of admission. (127)

Sejvar et al reports a 6 years old female who presented with fever, sore throat, malaise, anorexia, and headache. A provisional diagnosis of encephalitis was made. Diagnosis of monkeypox infection was confirmed by a polymerase chain reaction (PCR) Brain MRI showed diffuse cortical, thalamic, and brainstem edema, meningeal enhancement, and left thalamic and right parietal signal abnormality. Following treatment with intravenous ceftriaxone, acyclovir, phenobarbital, and midazolam for 2 weeks, she was discharged without any neurological deficits. (106)

Ježek Z et al conducted a cohort study with 282 patients, out of which 262 were of pediatric age group. Most common neurological manifestation in this cohort was headache, mostly preceded by fever.(105)

4. Conclusion

This systematic review highlights that neurological manifestations commonly occur in pediatric patients with both COVID-19 and Monkeypox. Headache, stroke, GBS, seizure, nerve palsies and MISC-C were the most common neurological symptoms caused by COVID-19 while headache and encephalitis were commonly seen in Monkeypox patients. Neurological manifestations may often even be presenting symptoms of both viral infections. Hence, it is important to investigate possible neurological manifestations in all patients and closely monitor these patients to develop a better understanding of the treatment strategies that can be adopted.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Novonil Deb, Poulami Roy, Anuradha Biswakarma, Therese Mary, Javeria Khan, Sanah Mahajan, Aatam shah contributed to revising and final approval of the version to be published. All authors agreed and confirmed the manuscript for publication.

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Journal Pre-proof									
Journal	Author	Study Type	No of total people involved	Number of relevant cases	Demographics	Age/Sex	Main Neuro symptom	Treatment	Outcome
American Journal of neuroradiology	E Gulko et al	Case report	1	1	USA	13yr/F	Stroke	Steroids	Full recovery
The Lancet Child and Adolescent Health	Lokesh Tiwari et al	Case report	1	1	India	9yr/F	Stroke	IVIG, methylprednisolone, dexamethadone, remdesivir, low molecular weight heparin	Improvement
BMJ journals	Farida Essajee et al	Case report	1	1	South Africa	2yr/F year	Stroke	Prednisolone, aspirin	Improvement
Annals of Neurology	Lauren A. Beslow et al	Cohort study	971	8	Multiple countries	-	Stroke	-	-
American Journal of neuroradiology	E Gulko et al	Case report	971	8	USA	13yr/F	Stroke	Steroids	Full recovery
The Lancet Child and Adolescent Health	Lokesh Tiwari et al	Case report	1262	10.1	India	9yr/F	Stroke	IVIG, methylprednisolone, dexamethadone, remdesivir, low molecular weight heparin	Improvement
BMJ journals	Farida Essajee et al	Case report	1553	12.2	South Africa	2yr/F year	Stroke	Prednisolone, aspirin	Improvement
Annals of Neurology	Lauren A. Beslow et al	Cohort study	1844	14.3	Multiple countries	-	Stroke	-	-
STROKE									
Annals of Medicine and Surgery	El Mezzouic	Case report	1	1	Morocco	3yr/F	GBS	IVIG	Full recovery
Indian Journal of Critical Care Medicine	Mehra, B. et al	Case report	1	1	India	3yr/F	GBS	IVIG	Full recovery
Journal of medical virology	Akçay N et al	Case series	2	1	Istanbul	6yr/M	GBS	IVIG	Improvement
Neurosciences	Al Haboob et al	Case report	1	1	Saudi Arabia	11yr/M	GBS	IVIG	Improvement
Journal of NeuroVirology	Krueger et al	Case series	4	1	Brazil	15yr/M	GBS	IVIG	Improvement
Italian journal of pediatrics	Iacono A et al	Case report	1	1	Italy	5yr/M	Facial nerve palsy	Prednisone	Full recovery
Radiology Case Reports	Zain, S. et al	Case report	1	1	USA	23 mo/F	Facial nerve palsy	Prednisone	Full recovery
Brain and development; journal of japanese society of child neurology	Christos Theophanous et al	Case report	1	1	USA	6yr/M	Facial nerve palsy	IV acyclovir, IVIG	Improvement
Pediatric neurology	Baccarella A et al	Case series	2	1	USA	9yr/M	Abducens nerve palsy	Not mentioned	Full recovery
				1		6yr/M	Abducens nerve palsy	Not mentioned	Full recovery
Journal of infection and public health	Elena N et al	Case report	1	1	France	10yr/M	Oculomotor nerve palsy	Prednisone, calcium, vitamin D	Full recovery
Headache									
Cureus	Khair AM et al	Case Series	5	1	USA	13yr/F	Headache	IV methylprednisolone, steroids	Improvement
				2	USA	13yr/F	Headache	Plasma exchange, steroids, rituximab	Improvement
Journal of clinical medicine	Totan M et al	Cohort study	71	47	Romania	121mo/52.22 % F	Headache	-	-

Child	Case								Full
Journal of Tropical Pediatrics	Khan, A. et al	Case series	3	1	USA	15yr/F	Headache	IV dexamethasone, oral steroids	Full recovery
JAMA Neurology	Larovere, K.L. et al	Cohort study	1695	365	USA	-	Headache	-	-
Hospital pediatrics	Agha R et al	Cohort study	22	1	USA	11yr/M	Headache	-	Improvement
Frontiers in pediatrics	Antonella Riva et al.	Cohort study	237	155	Italy	3.2yrs/48% F	Headache	-	-
BMC Pediatr.	Freij, B.J. et al	Case report	1	1	USA	5yr/F	Headache	IV dexamethasone, remedesivir	Death
Archives of Pediatric Infectious Diseases	Talebian, A. et al	Case report	1	1	Iran	10yr/F	Headache	Oral Acetazolamide	Full recovery
Pediatric Neurology	Sadeghizadeh, A. et al	Case report	2	1	USA	10yr/F	Headache	IVIg, methylprednisolone, aspirin, oral prednisolone	Full recovery
				2	USA	6yr/M	Headache	Epinephrine, milrinone, methylprednisolone, IVIG, oral prednisone	Full recovery
Frontiers in Neurology	Silvestri, P. et al	Case report	1	1	Italy	15yr/M	Headache	Enoxaparin, dexamethasone	Full recovery
Neurology, American Academy of Neurology	Sejal M. Bhavsar et al	Case report	1	1	USA	16yr/M	Headache	Vancomycin, ceftriaxone	Full recovery
Arch. Argent. Pediatr.	Gentile, A. et al	Cohort study	2690	2690	Argentina	-	Headache	-	Full recovery
Modern rheumatology	Salman, H. et al	Cohort study	17	4	Turkey	-	Headache	-	-
The Pediatric infectious disease journal	Yousefi K et al	Case report	1	1	Iran	9yr/M	Headache	Ceftriaxone, vancomycin, oral hydroxychloroquine sulfate, oral acetaminophen	Full recovery
Pediatric neurology	Sharma S et al	Case series	2	1	India	12yr/M	Headache	Steroids, acyclovir	Full recovery
				2	India	10yr/M	Headache	Steroids, acyclovir	Full recovery
International Journal of Pediatrics (United Kingdom)	Shahbaznejad, L. et al	Cohort study	29	14	Iran	-	Headache	-	-
Brazilian oral research	Santos TGFTD et al	Cohort study	54	21	Brazil	-	Headache	-	-
nature; scientific reports	Vibhu Parcha et al	Cohort study	12306	590	USA	-	Headache	-	-
Lancet Child Adolesc Health	Erika Molteni et al	Cohort study	1734	1079	UK	-	Headache	-	-
J Trop Pediatr	Beril Dilber et al	Cohort study	2530	966	Turkey	-	Headache	-	-
Pediatric Infectious Disease Journal	Hobbs, C.V. et al	Cohort study	1695	365	USA	-	Headache	-	-
Seizure									
Epileptic disorders : international epilepsy journal with videotape	Vergara D et al	Case report	1	1	Chile	14yr/F	Seizure	Midazolam IV, propofol	Death
Arch. Pediatr. Infect. Dis.	Karimi, A. et al	Case report	1	1	Iran	4yr/M	Seizure	Ceftriaxone, vancomycin	Full recovery
Journal of Tropical Pediatrics	Khan, A. et al	Case series	3	1	USA	11yr/F	Seizure	Ceftriaxone, vancomycin, methylprednisolone, IVIG, dexamethasone	Full recovery
				2	USA	7yr/F	Seizure	Norepinephrine, vancomycin	Full recovery

Journal of Pediatric Neurology	Kamali Aghdam et al	Case report	1	1	Iran	65days/F	Seizure	Dizepam, phenytoin, vancomycin	Full recovery
JAMA Neurology	Larovere, K.L. et al	Cohort study	1695	100	USA	55% Males	Seizure	-	-
Frontiers in Pediatrics	Cheraghali, F. et al	Case report	1	1	Iran	34mo/M	Seizure	Dexamethasone, hydroxychloroquine, azithromycin, IVIG	No recovery
Frontiers in Pediatrics	García-Howard, M. et al	Case report	1	1	Spain	3mo/F	Seizure	Leviteracetam and hydroxychloroquine	Full recovery
Seizure: European Journal of Epilepsy	Kurd M et al	Cohort study	175	11	Israel	-	Seizure	-	-
Indian pediatrics	Raj SL et al	Case report	1	1	India	2yr/M	Seizure	Ceftriaxone, vancomycin, acyclovir, IVIG, remdesivir	Full recovery
Clinics (Sao Paulo, Brazil)	Pereira MFB et al	Cohort study	66	6	Brazil	-	Seizure	-	-
American journal of physical medicine & rehabilitation	Morrow AK et al	Case series	4	1	USA	18yr/F	Seizure	-	-
				2	USA	12yr/F	Seizure	-	-
				3	USA	15yr/F	Seizure	-	-
				4	USA	17yr/F	Seizure	-	-
Saudi medical journal	Alnajjar AA et al	Cohort study	62	3	Saudi Arabia	-	Seizure	-	-
Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology	Emami A et al	Cohort study	6147	5	Iran	-	Seizure	-	-
The Pediatric infectious disease journal	Akçay N et al	Case report	2	1	Turkey	9yr/M	Seizure	Methylprednisolone , IVIG	Improvement
				2		9yr/F	Seizure	Methylprednisolone , IVIG	Improvement
Frontiers in pediatrics	Riva A et al	Case report	1	1	Canada	10mo/M	Seizure	Tzobactam, tobramycin, trimethoprim/sulfamethoxazole, phenobarbital.	Death
Child Neurol. Open	Ninan, S. et al	Case report	1	1	USA	8yr/F	Seizure	Hypertonic saline, mannitol	Death
World J. Pediatr.	Moreno-Galarraga, L. et al	Case series	11	1	Spain	2mo/F	Seizure	Levetiracetam, hydroxychloroquine	Full recovery
European Journal of Paediatric Neurology	Laçinel Gürlevik et al	Case series	15	1	Turkey	3mo/F	Seizure	Midazolam infusion, Levetiracetam, phenobarbital.	Full recovery
Neurological Sciences	Manzo, M.L. et al	Case report	1	1	Italy	6yr/M	Seizure	IV methylprednisolone	Full recovery
Radiology, Radiological Society of North America	<u>Seyed Mohammad Mousavi Mirzaee et al</u>	Case report	1	1	Iran	12yr/M	Seizure	IV methylprednisolone	Improvement
Child's Nerv. Syst.	Sarigecili, E. et al	Case report	1	1	Turkey	7yr/M	Seizure	levetiracetam, methylprednisolone, IVIG, acyclovir, ceftriaxone, and clarithromycin	Full recovery
Case Rep. Clin. Pract.	Ferdosian, F. et al	Case report	1	1	Iran	7yr/M	Seizure	Nasogastric tube and Foley catheter insertion, oxygen supplementation by mask, and intravenous fluids for hydration, cefotaxime 1200mg 3 times per day, pantoprazole 20mg two times per day,	Full recovery

								250mg of intravenous acyclo-	
								Levetiracetam 500mg three times per day and phenytoin 60mg BD(seizures), Dexamethason, IVIG 15 gr for 5 days, vit C Daily, B-complex daily, and Remdesiver 60 mg daily(COVID 19).	
J. Child Neurol.	Sandoval, F. et al	Case series	91	3	Chile	-	Seizure	Antiepileptics	Full recovery
Pediatr. Infect. Dis. J.	Brum, A.C. et al	Case report	1	1	Argentina	17yr/M	Seizure	Ceftriaxone	Full recovery
International Journal of Surgery Case Reports	Rahmadhan, M.A. et al	Case report	1	1	Indonesia	15yr/M	Seizure	Dexamethasone, amiodarone	Death
The American journal of case reports	Farley M et al	Case report	1	1	Grenada	8yr/M	Seizure	Amoxicillin, Lorazepam, IVIG, ceftriaxone, hydroxychloroquine, Methylprednisolone	Full recovery
Seizure	Zombori L et al	Case report	1	1	United Kingdom	17yr/M	Seizure	Midazolam infusion, phenobarbitone	Improvement
The Pediatric infectious disease journal	Korkmazer B et al	Case report	1	1	Istanbul	10yr/M	Seizure	Favipiravir, phenytoin	Full recovery
Pediatric neurology	Martin PJ et al	Case report	1	1	Indiana	9days/M	Seizure	Antiepileptics	Full recovery
The Pediatric infectious disease journal	De Avila C et al	Case report	1	1	NC	14yr/F	Seizure	Antiepileptics	Full recovery
Acta paediatrica (Oslo, Norway : 1992)	Smarrazzo A et al	Cohort study	56	2	Italy	-	Seizure	Antiepileptics	Full recovery
Journal of child neurology	Cadet K et al	Cohort study	8854	3902	USA	-	Seizure	Antiepileptics	Full recovery
Eurosurveillance	Silvia Garazzino et al.	Cohort study	168	5	Italy	-	Seizure	Antiepileptics	Full recovery
Cureus	Sabita Bhatta et al	Case report	1		USA	11yr/M	Seizure	Levetiracetam	Full recovery
J Trop Pediatr	Beril Dilberl et al	Cohort study	2530	1338	Turkey	-	Seizure	Antiepileptics	Full recovery
International society for infectious disease	Minxian Suna et al	Cohort study	30	30	China	-	Seizure	Antiepileptics	Full recovery
Acta Pediatrics	Jonas F. Ludvigsson et al	Case series	4	1	Sweden	3mo/M	Seizure	Midazolam infusion, phenobarbital, levetiracetam	Full recovery
				2		21mo/M	Seizure	Midazolam infusion, phenobarbital, levetiracetam	Full recovery
				3		14yr/M	Seizure	Midazolam infusion, phenobarbital, levetiracetam	Full recovery
				4		12yr/M	Seizure	Mechanical ventilation	Full recovery
Acta Neurochirurgica	Blazkova, J et al	Case Report	1	1	Czech Republic	2mo/M	Focal seizures	Valproate, low molecular weight heparin	Improvement
CNS SYMPTOMS									
Neurol. Sci.	Urso, L. et al	Case report	1	1	Italy	5yr/F	Altered mental status	ceftriaxone, vancomycin, acyclovir, dexamethasone	Full recovery
Frontiers in Neurology	De Marcellus C et al	Case report	1	1	France	16yr/M	Neck stiffness, stupor	antithrombotic treatment intensification with high-dose methylprednisolone pulse course, tocilizumab (anti- IL-6 receptor), remdesivir, and full-dose enoxaparin.	Death

Sage Journals		Case	1	1	USA	5yr/M	Anisocoria,	ECMO, tocilizumab,	
	Shubhi Kaushik et al							heparin	Death
Clinical child psychology and psychiatry	Pleszkó A et al	Case report	1	1	Hungary	10yr/M	Hallucination	clonazepam, clobazam, alprazolam, clarithromycin, oral methyl prednisolone therapy	Full recovery
The Pediatric infectious disease journal	Regev T et al	Case report	1	1	Israel	16yr/M	Clonus	epinephrone and milrinone for warm shock. IVIG and high dose aspirin due to suspicion of Kawasaki disease. Additional IVIG dose and a 5 day course of pulse methylprednisolone	Improvement
Clinical neurology and neurosurgery	Della Corte M et al	Case report	1	1	Italy	12yr/M	Myoclonus	clonazepam 0.02 mg/kg/day, iv methylprednisolone 10 mg/kg/day for five days followed by oral prednisolone taper. At the end of iv steroid therapy, cycle of five days of ivig 0.4g/kg/day was started	Improvement
Journal of Tropical Pediatrics	Alvarado-Socarras et al	Case report	1	1	USA	21days/M	Hypotonia, drowsiness, poor suction	Ampicillin, gentamicin, acitaminophen, cefepime	Improvement
Wisconsin Medical Journal	Bauer, S.C. et al	Case series	2	1	USA	16yr/M	Altered mental status	Haloperidol 1-2mg, benzotropine, benzodiazepines, ketamine, dexmedetomidine, clonidine, olanzapine, quetiapine	Improvement
				2		17yr/M	Altered mental status	Quetiapine, melatonin, IM haloperidol, guanfacine extended release	Improvement
Pediatrics	McLendon LA et al	case report	1	1	USA	17mo/F	Upper Limb weakness, Gait disturbance	IVIg, IV methylprednisolone	Improvement
Brain & development	Bektaş G et al	Case series	2	1	Turkey	10yr/M	Visual hallucinations	IVIg, IV methylprednisolone	Improvement
				2		11yr/F	Personality changes	Milrinone, noradrenaline, IVIG, IV methylprednisolone	Improvement
The neurologist	Landzberg DR et al	Case report	1	1	USA	15yr/F	Horizontal Diplopia, Gait instability	Parenteral thiamine replacement	Improvement
Neuroradiology	de Miranda Henriques-Souza et al	Case report	1	1	Brazil	12yr/F	B/L motor weakness	Methylprednisolone	Improvement
BMC Pediatr.	Freij, B.J. et al	Case report	1	1	USA	5yr/F	Cognitive defect	Oral hydroxychloroquine, oral azithromycin, IV dexamethasone, remdesivir	Death
Frontiers in Neurology	Silvestri, P et al	Case report	1	1	Italy	15yr/M	Dysarthria and paresthesia	subcutaneous enoxaparin, dexamethasone	Improvement
International Journal of Infectious Diseases	Mierzewska-Schmidt et al	Case report	1	1	Poland	2mo/M	Nystagmus	morphine, midazolam, cefotaxime, vancomycin, and acyclovir	Death
Frontiers in Pediatrics	Knoflach, K et al	Case report	1	1	Germany	2yr/M	Abduction deficit with fixated turn of the head to the left side.	-	Improvement
Turk. J. Pediatr.	Yimenicioğlu, S et al	Case report	1	1	Turkey	15yr/M	Vertigo, Drop attacks	Vancomycin, ceftriaxone, favipiravir and acyclovir as well as iv immunoglobulin, Mannitol, dexamethasone, plasmapheresis	Death
Cureus	Khair AM et al	Case series	5	1	USA	16yr/F	Leg numbness	IVIg, IV methylprednisolone	Improvement
				2		8yr/M	Diplopia, imbalance, gait, ataxia	IVIg, IV methylprednisolone	Full recovery
				3		13yr/F	Walking difficulty	IVIg, IV methylprednisolone	Improvement
				4		14yr/F	Right leg weakness, left eye pain	IV methylprednisolone	-

				5		13yr/F	Right-sided		emen
Journal Pre-proof									
Journal of Tropical Pediatrics	Sofuoğlu, A.I et al	Case report	1	1	Turkey	11yr/F	Headache, neck stiffness, diplopia	Milrinone, noradrenaline, IVIG, IV methylprednisolone, Acetazolamide, topiramate	Full recovery
Academic Radiology, Vol 28, No 9, September 2021	Figen Palabiyik et al	Cohort study	45	14	USA	-	Headache, epilepsy, hallucination, neck stiffness, and inability to walk	-	-
International Journal of Pediatric Otorhinolaryngology	Rhiannon Halfpenny et al	Cohort study	50	18	UK	Median age 10 yrs	Dysphonia, dysphagia	Medication voice therapy	Full recovery
The Lancet Child and Adolescent Health	Ray, S.T.J. et al	Cohort study	22	52	UK	Median age 9 yrs	Encephalitis, Status Epilepticus, GBS, Chorea, Isolated Chorea, Acute Demyelinating Syndrome, Isolated Encephalopathy, TIA, Peripheral Nerve involvement, Hallucinations, Behavioral Changes	Inotropic support, Immunomodulation	Disability (10), Death(0)
Official Journal of the American Academy of Pediatrics	E. Ann Yeh et al.	Case report	1	1	USA	15yr/M	ADEM	-	Full recovery
Iran. J. Child Neurol.	Nejad Biglari et al	Case Report	1	1	Iran	11yr/F	Spinal cord swelling at T3-T6 segment	IVIG	Full recovery
Pediatric Neurology	Poisson, K.E. et al	Case Report	1	1	USA	8yr/F	Left Hemiparesis	IVIG, IV methylprednisolone	Death
Child's Nervous System	Scala, M.R. et al	Case Report	1	1	Italy	11yr/F	Malignant Cerebral Infarction	Decompressive right-sided hemicraniectomy	Full recovery
Neurology	Gaughan M et al	Case Report	1	1	USA	16yr/F	Encephalopathy-akinetic mutism, hallucinations	IVIG, IV methylprednisolone	Full recovery
The Turkish journal of pediatrics	Poyrazoğlu HG et al	Case Report	1	1	Turkey	10yr/M	ADEM & Transverse myelitis-weakness of lower limbs, headache	IVIG, IV methylprednisolone	Full recovery
Frontiers in Pediatrics	Najafinejad, M. et al	Cohort study	91	2	Iran	60.4% males	Transverse myelitis, viral encephalitis with possible parenchymal hemorrhagic components	-	83 fully recovered and 8 death
JAMA Neurology	Hacohen, Y. et al	Case series	4	1	UK	8yr/M	Encephalopathy, meningism, headache	IVIG	Full recovery
				2		9yr/M	Encephalopathy, meningism, headache	-	Improvement
				3		15yr/F	Encephalopathy, meningism, headache	Anakinra, dexamethasone, rituximan	Improvement
				4		15yr/F	Encephalopathy, meningism, headache	IVIG	Full recovery
Archives of disease in childhood	Buts S et al	Cohort study	34		UK	-	Sudden onset functional tic-like movements	-	-
Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis	Varol F et al	Case series	2	1	Turkey	14yr/M	RESLES	IVIG, IV methylprednisolone	Full recovery
				2		15yr/M	RESLES	Ceefotaxime, teicoplanin, IVIG, IV methylprednisolone	Full recovery
European Journal of Paediatric Neurology	Olivotto, S. et al	Case series	7	1	Iran	5yr/M	Acute encephalitis	IVIG, IV methylprednisolone	Full recovery

BMJ case reports	Giannantonio	Case							Full
Journal Pre-proof									
Multiple sclerosis and related disorders	Wiegand SE et al	Case report	1	1	USA	25mo/F	Opoclonus, ataxia	Lorazepam, levetiracetam loading dose, IVIG, dexamethasone	Improvement
Baylor University Medical Center Proceedings	Akbar, A. et al	Case report	1	1	USA	9yr/F	Lower limb weakness	IVIG	Improvement
JAMA Neurology	Hacohen, Y. et al	Case series	4	1	UK	8yr/M	Generalized muscle weakness	IVIG, dexamethasone, anakinra	Full recovery
				2		9yr/M	Proximal leg weakness	-	Full recovery
				3		15yr/F	Global proximal weakness	Dexamethasone	Improvement
				4		15yr/F	Global proximal weakness	IVIG	Full recovery
eNeurologicalSci	Aljomah, L. et al	Case series	5	1	Riyadh	31mo/M	encephalopathy, ataxia, headache, seizure, papilledema, ophthalmoplegia, hyporeflexia, and different clinical spectra, such as Miller Fisher syndrome, meningoencephalitis, and idiopathic intracranial hypertension	-	Full recovery
Egyptian Journal of Neurology, Psychiatry and Neurosurgery	Elshebawy, H. et al	Case series	42	14	Cairo, Egypt	-	Acute Inflammatory Demyelinating Polyneuropathy	-	-
Pediatrics	Dean A et al	Case report	1	1	USA	14yr/F	Stridor	Albuterol, prednisone, dexamethasone, methylprednisolone intravenously, IVIG	Full recovery
Sage Journals	Quentin Mat et al.	Case report	1	1	Belgium	13yr/F	Vertigo	Vestibular rehabilitation	Full recovery
Monkey Pox									
The Lancet	Hugh Adler et al.	Case series	7	1	UK	2yr/F	Headache	None	Fully recovery
The Journal of infectious diseases	James J Sejvar et al.	Case series	3	1	US	6yr/F	Encephalitis	Intravenous ceftriaxone, acyclovir, phenobarbital, and midazolam	Fully recovery
The Journal of Infectious diseases	Z Jezek et al.	Cohort study	282	262	Zaire	-	Headache	None	Fully recovery