International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Neurological Complications with Delayed Onset in Post-COVID-19 Pediatric Patients

Aida Bushati[1,2], Kristi Aleksi[2], Afërdita Tako[1], Armand Shehu[1]

[1]Service of Pediatrics, Mother Teresa University Hospital Center, Tirana, Albania

[2]Faculty of Medicine, University of Medicine, Tirana

Abstract: ***Background: Post-COVID-19 neurological complications are central and/or peripheral neurological disorders manifested after the onset of SARS-CoV-2 infection, caused by hitherto vague neuropathogenetic mechanisms. Aims: To explore the acute neurological complications with delayed clinical onset after SARS-CoV-2 infection in pediatric patients. Methods: We collected our data from the database of patients' charts in Mother Teresa University Hospital Center, Tirana, Albania during a twelve-month period. Results: In total 8 children were included in the study. Neurological conditions identified as post-COVID-19 were post-viral encephalitis (n=5), Guillain-Barré syndrome (n=2) and intraparenchymal hemorrhage (n=1). The clinical onset of these conditions varied from 4 to 8 weeks after SARS-CoV-2 infection. The clinical presentation, laboratory, and imagining test results, as well as treatment were diverse among patients and disorders. The mortality was zero. The morbidity should be estimated in longer terms. Conclusions: Our study emphasizes that COVID-19 is a struggling systemic disorder, and suggests that SARS-CoV-2 is a possible trigger factor of both central and peripheral post-COVID-19 neurological conditions in children. Awareness concerning the matter, prevention of SARS-CoV-2 infection, follow-up of post-COVID-19 patients and collaboration among health professionals are of particular importance, therefore recommended.***

Keywords: neurological complications; COVID-19; SARS-CoV-2; pediatrics

Abbreviations: **ACE-2** = angiotensin-converting enzyme 2; **ASLO** = anti-streptolysin O; **CD =** cluster of differentiation; **CDC =** Centers for Disease Control and Prevention; **COVID-19** = coronavirus disease 2019; **CSF** = cerebrospinal fluid; **CT** = computed tomography; **EEG** = electroencephalography; **EMG/ENG** = electromyography/electroneurography; **IgG** = immunoglobulin G; **IVIG** = intravenous immunoglobulin**; MERS-CoV** = Middle East respiratory syndrome–related coronavirus; **MRI** = magnetic resonance imaging; **RNA**= ribonucleic acid; **RT-PCR** = reverse transcription-protein chain reaction; **SARS-CoV =** severe acute respiratory syndrome coronavirus;

1. Introduction

Early January 2020 found the world in panic after the reporting of a cluster of patients in China diagnosed with atypical pneumonia caused by a hitherto unknown pathogen [1]. The disease became widely known as *coronavirus disease 2019* (COVID-19), the etiology of which is the notorious *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), a beta-coronavirus of the family Coronaviridae, whose genome is an RNA with a positive sense strand [2]. This virus has main structural and molecular characteristics similar to other viruses of the same family, such as structural proteins S (spike), M (membrane), E (envelop) which are responsible for the binding to the ACE-2 receptors of the host cell, the assemblage and stabilization of the virion membrane, and protein N (nucleocapsid) which interacts with the viral genome [3]. The clinical manifestation of COVID-19 varies among patients, from asymptomatic to severe forms ending in exitus lethalis [4]. Among the epidemiological reports of both confirmed infection and death cases, significantly lower statistics were evident in children compared to adults during the course of the pandemics [5]. Of particular clinical interest are acute post-COVID-19 neurological conditions. According to the CDC, *post-COVID-19 condition* refers to the wide range of health consequences that are present four or more weeks after SARS-CoV-2 infection [6]. The mechanisms by which the virus manages to affect the central and peripheral nervous systems are yet to be explicated but four hypotheses have been addressed to date: a) direct viral invasion, b) inflammatory vascular damage, c) disorders of the immune system and autoimmunity, and d) effects of severe systemic COVID-19 and/or its treatment [7]. Despite being associated primarily with infection of the lower respiratory tract, SARS-CoV-2 is not the only human coronavirus accused of neurotropism; other human coronaviruses, including SARS-CoV and MERS-CoV, are implicated with the infection of neural tissue [8-10].

2. Materials and Methods

Study Design

This is a retrospective, descriptive study.

Data Collection

For this study we reviewed all the patients' charts from the database of Pediatric neurology service and Pediatric intensive care unit in Mother Teresa University Hospital Center, Tirana, Albania from April 1, 2020 to March 31, 2021.

Inclusion and Exclusion Criteria

We recorded the demographics, clinical phenotypes, laboratory and imaging results, treatment protocols, and outcome data of patients from 1 month to 14 years old, with normal psychomotor development, diagnosed with a post-COVID-19 neurological condition, with history of a documented laboratory-confirmed SARS-CoV-2 infection at least four weeks prior to the neurological onset, with no history of other bacterial and/or viral infection during the intermediate period. Patients with comorbidities were excluded from the study.

3. Results

After carefully reviewing all the charts, 8 patients fulfilled the criteria to be enrolled in the study. The cluster consisted of 3 females and 5 males from 5 to 13 years old. Their mean age was 8.25 years. The age mode was 5 years. The time of COVID-19 onset varied from approximately 4 to 8 weeks prior to the neurological condition. The time mode of COVID-19 onset was approximately 4 weeks. In total, three conditions believed to be related to COVID-19 were identified as follows and detailed below:

- Post-viral encephalitis (n=5)
- Guillain-Barré syndrome (n=2)
- Intraparenchymal hemorrhage (n=1)

Table 1 summarizes the main characteristics of our patients.

Table 1: Main characteristics

Sex	
Female	3/8 patients
Male	5/8 patients
Age intervals	
<1 year	0/8 patients
1-5 years	3/8 patients
6-10 years	2/8 patients
11-14 years	3/8 patients
Mean age	8.25 years
Age mode	5 years
Range	5-13 years
Approximate time of COVID-19 onset prior to the neurological disorder	
4 weeks	7/8 patients
8 weeks	1/8 patient
Time mode	4 weeks
Range	4 -8 weeks
Neurological conditions	
Post-viral encephalitis	5/8 patients
Guillain-Barré syndrome	2/8 patients
Intraparenchymal hemorrhage	1/8 patients

Post-Viral Encephalitis

Out of the total number of patients, 5 were diagnosed with *post-viral encephalitis* approximately 4 weeks after SARS-CoV-2 infection. Severity of past COVID-19 was mild in 3 children and moderate in the remaining two. Signs of presentation were as follows: seizures in 2 patients, hallucinations in one patient, difficulty in gait and balance in one patient, lack of concentration in one patient. Clinical phenotypes are described in Table 2. Apropos of laboratory and imaging examinations, summarized in Table 3, RT-PCR test for SARS-CoV-2 in nasopharyngeal swab resulted negative in all patients at the time of hospitalization. The complete blood count and blood biochemistry tests showed diverse results with nonspecific findings. Immunophenotyping of peripheral blood was normal in 4 patients, but it showed elevated CD4 population and decreased CD56 population in one child. Antibody investigation was applied; anti SARS-CoV-2 IgG antibodies were present and ASLO antibodies were absent in all patients. Other antibody titers are described in Table 3. Cerebrospinal fluid (CSF) samples obtained by lumbar puncture were examined, they resulted with no microorganisms. Other findings are described in Table 3. EEG was applied in all children; it showed unremarkable findings in 2 patients, slow bifrontal theta waves at a poorly structured basal rhythm in one patient and epileptiform discharges in 2 patients. Head MRI showed no significant changes in 2 patients and T2 hyperintense signals in subcortical location in the remaining three. The administered medications included intravenous immunoglobulin (IVIG), Cyclophosphamid, Dexamethasone, Methylprednisolone, Phenobarbital and/or Valproic acid for seizures, and Risperidone for hallucinations. Plasmapheresis was applied in only one patient.

Guillain-Barré syndrome

Out of the total number of patients, 2 were diagnosed with Guillain-Barré syndrome; one patient approximately 4 weeks and the other approximately 8 weeks after SARS-CoV-2 infection. Severity of past COVID-19 was mild in one child and moderate in the remaining child. Sign of presentation was weakness of lower limbs in both children. Clinical phenotypes are described in Table 2. As for laboratory and imaging tests, summarized in Table 3, RT-PCR test for SARS-CoV-2 in nasopharyngeal swab resulted negative in both patients at the time of hospitalization. The complete blood count and blood biochemistry tests showed diverse results, with significant hyperglycemia in one patient. Immunophenotyping of peripheral blood was normal in both patients. Serology tests were applied; anti SARS-CoV-2 IgG antibodies were present and ASLO antibodies were absent in both children. CSF samples resulted transparent, with no microorganisms detected, elevated glycorrhachia in only one patient, elevated protein level in both, normal white blood cell count and no red blood cells. EMG/ENG was also applied; it showed reduction of neural signal conduction. Spinal contrast-enhanced MRI was applied on both and showed enhancement of nerve roots in cauda equina and conus medullaris. The administered medications included IVIG and Dexamethasone.

Intraparenchymal hemorrhage

Out of the total number of patients, only one was diagnosed with *intraparenchymal hemorrhage* with onset approximately 4 weeks after SARS-CoV-2 infection onset. Past COVID-19 was severe and the child underwent therapeutic anticoagulation. Sign of presentation was lipothymia. Clinical phenotype is described in Table 2. Apropos of laboratory and imaging examinations, summarized in Table 3, RT-PCR test for SARS-CoV-2 in nasopharyngeal swab resulted negative at the time of hospitalization. The complete blood count and blood biochemistry tests showed no significant findings. Immunophenotyping of peripheral blood was normal. Serology tests were applied; anti SARS-CoV-2 IgG antibodies were present. CSF sample was xanthochromic with no microorganisms, normal glycorrhachia, elevated protein level, elevated white blood cell and red blood cell count. EEG showed interhemispheric asymmetry with excess of slow waves in the right side. Head CT confirmed the diagnoses by showing the hyperdense hematoma in the right parietal lobe of the cerebrum with perihematoma oedema. Funduscopic examination was reported normal. The patient underwent surgical evacuation of hematoma through craniotomy.

Outcome

Throughout the hospitalization period, laboratory and imaging examination were applied to all patients. In all cases, clinical improvement was evidenced. The mortality was zero, whereas the morbidity should be estimated in longer terms.

Table 2: Summary of clinical phenotypes

No./ Sex/ Age	Diagnosis	COVID-19 onset prior w/severity	Specific central and peripheral neurological signs/symptoms						Nonspecific signs/ symptoms
			Altered level of conciousness	Motor/ sensory disorder	Seizure	Cognitive impairment	Behavioral changes	Psychiatric symptoms	
1/F/5	PVE	4/mild	confusion, disorientation	ataxia, difficulty in gait and balance	+*	–	agitation	–	fatigue, vertigo, headache, nausea
2/F/5	PVE	4/mild	confusion, disorientation	ataxia, difficulty in gait and balance*	–	–	irritation	–	fatigue, headache
3/M/5	PVE	4/mild	confusion	stereotypical leg movements, difficulty in gait and balance	–	–	agitation	hallucinations*, compulsive behavior	nausea, fatigue, fever (1 episode)
4/M/11	PVE	4/moderate	disorientation	ataxia, difficulty in gait and balance, mild hyperreflexia	–	lack of concentration*, memory loss	agitation, aggression	hallucinations	fatigue, fever (1episode)
5/F/13	PVE	4/moderate	confusion, disorientation	ataxia, difficulty in gait and balance	+*	–	agitation, aggression	–	fatigue, nausea
6/M/7	GBS	4/mild	–	hyporeflexia, difficulty in gait and balance, paresthesia in lower limbs, no cranial nerve deficits	–	–	–	–	weakness of lower limbs*, myalgia, artralgia
7/M/11	GBS	8/moderate	–	hyporeflexia, difficulty in gait and balance, paresthesia in lower limbs, no cranial nerve deficits	–	–	–	–	weakness of lower limbs*, myalgia, artralgia
8/M/9	IPH	4/severe	lipothymia*, disorientation, lethargy, syncope (1 episode)	mild left hemiparesis, left hemisensory impairment	+	–	–	–	headache, vomiting, fatigue, fever

COVID-19, coronavirus disease 2019; **F**, female; **GBS**, Guillain-Barre syndrome; **IPH**, intraparenchymal hemorrhage; **M**, male; **No**., number; **PVE**, post-viral encephalitis; **y**, year; **w**, week;
+ present, **–** absent, *****presentation sign

Table 3: Summary of laboratory and imaging findings

	Diagnosis	RT-PCR SARS-CoV-2	CBC & blood biochemistry	Immunopheno-typing	Serology	CSF	Electrodiagnostic tests	Imaging tests
Patient 1	PVE	–	nonspecific findings	low increase of CD4; low decrease of CD56; normal CD3, CD8, CD19	anti-SARS-CoV-2 IgG+; ANA– ; anti-dsDNA–; MPO –; ASLO–	turbid; glucose 70 mg/dL; protein 58 mg/dL; WBCs 436/mm^3; no RBCs; sterile	**EEG**: epileptiform discharges	**head MRI:** subcortical T2 hyperintensities
Patient 2	PVE	–	nonspecific findings	N	anti-SARS-CoV-2 IgG+; ASLO–	clear; glucose 67 mg/dL; protein 21 mg/dL; WBCs 2/mm^3; no RBCs; sterile	**EEG**: unremarkable	**head MRI**: no significant changes
Patient 3	PVE	–	nonspecific findings	N	anti-SARS-CoV-2 IgG+; ASLO–	clear; glucose 78 mg/dL; protein 49 mg/dL; WBCs 92/mm^3; no RBCs; sterile	**EEG**: unremarkable	**head MRI**: no significant changes
Patient 4	PVE	–	nonspecific findings	N	anti-SARS-CoV-2 IgG+; ASLO–	turbid; glucose 62 mg/dL; protein 44 mg/dL, WBCs 341/mm^3; no RBCs; sterile	**EEG**: slow bifrontal theta waves at a poorly structured basal rhythm	**head MRI:** subcortical T2 hyperintensities
Patient 5	PVE	–	nonspecific findings	N	anti-SARS-CoV-2 IgG+; ANA+; anti-dsDNA–; MPO–; NMDAR–; anti-HSV1 IgM–; anti-HSV2 IgM–	turbid; glucose 60 mg/dL; protein 153 mg/dL, WBCs 572/mm^3; no RBCs; sterile	**EEG**: epileptiform discharges	**head MRI:** subcortical T2 hyperintensities
Patient 6	GBS	–	nonspecific findings	N	anti-SARS-CoV-2 IgG+; ASLO–	turbid; glucose 74mg/dL; protein 173 mg/dL, WBCs 8/mm^3; no RBCs; sterile	**EMG/ENG**: reduction of neural signal conduction	**spinal contrast MRI**: enhancement of nerve roots in cauda equina and conus medularis

Patient 7	GBS	–	glucose 186 mg/dL	N	anti-SARS-CoV-2 IgG+; ASLO–	turbid; glucose 113 mg/dL; protein 164 mg/dL; WBCs 12/mm^3; no RBCs; sterile	**EMG/ENG:** reduction of neural signal conduction	**spinal contrast MRI**: enhancement of nerve roots in cauda equina and conus medularis
Patient 8	IPH	–	nonspecific findings	N	anti-SARS-CoV-2 IgG+; ASLO–	xanthochromic; glucose 54 mg/dL; protein 189 mg/dL; WBCs 112/mm^3; RBCs 1352/mm^3; sterile	**EEG**: interhemispheric asymmetry with excess of slow waves in the right side	**head CT**: hyperdense hematoma in the right parietal brain lobe

ANA, antinuclear antibodies; **ASLO**, anti-streptolysin O; **CBC**, complete blood count; **CD**, cluster of differentiation; **CSF**, cerebrospinal fluid; **CT**, computed tomography; **dsDNA**, double stranded deoxyribonucleic acid; **EEG**, electroencephalography; **EMG/ENG**, electromyography/electroneurography; **GBS**, Guillain-Barré syndrome; **HSV**, anti-herpes simplex virus; **IgG**, immunoglobulin G; **IgM**, immunoglobulin M; **IPH**, intraparenchymal hemorrhage; **MPO**, Myeloperoxidase; **MRI**, magnetic resonance imaging; **N**, normal, **NMDAR**, N-methyl-D-aspartate receptor; **PVE**, post-viral encephalitis; **RBCs**, red blood cells; **RT-PCR**, real-time protein chain reaction; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **WBCs**, white blood cells; + present, – absent

4. Discussion

COVID-19 is a disorder which affects many systems of the body [11]. Subsequent neurological disorders are rarely reported in pediatric patients, and the incidence of these complications is not yet specified [12, 13].

After studying our cluster of patients, a possible bacterial, viral or other trigger factor of a different nature was excluded as neither the patients' medical history nor the results of laboratory tests evidenced one, therefore we suggest that there is an association between SARS-CoV-2 infection and these conditions. Regarding the patient with non-traumatic intraparenchymal hemorrhage after a severe COVID-19, anticoagulant therapy is certainly a risk factors. We noticed that there is no relationship between the severity of past COVID-19 clinical manifestation and the development of post-infectious neurological conditions.
As indicated in the literature, *post-infectious encephalitis* is an inflammatory brain disease characterized by neurological and neuropsychiatric symptoms, reported after infections from neurotropic viruses such as herpes simplex virus type I, Epstein-Barr virus or varicella-zoster virus [14-16]. Concurrently, *Guillain-Barré syndrome* is a type of immune-mediated peripheral neuropathy, and infections by Zika virus, influenza A virus, cytomegalovirus, Epstein-Barr virus and hepatitis E virus are known as antecedent events [17]. Lately, the development of both encephalitis and Guillain-Barré syndrome are reported after SARS-CoV-2 infection in children [13,18-20]. Meanwhile, *pediatric non-traumatic intraparenchymal hemorrhage*, also known as hemorrhagic stroke, is a type of intracranial hemorrhage with either an idiopathic etiology or as a consequence of intracerebral vascular anomalies, hypertension, neoplastic disease, systemic infection, brain inflammations such as meningitis and/or encephalitis [21]. Recent studies show a relation to SARS-CoV-2 infection, albeit infrequently compared to other complications [13].

5. Conclusion

COVID-19 is a convoluted and struggling systemic disorder. We strongly suggests that SARS-CoV-2 is a possible immunological trigger factor of both central and peripheral neurological conditions, thus COVID-19 is a possible antecedent event of acute post-infectious central and peripheral neurological disorders, not only in severe cases but unexpectedly also in children with mild symptoms. The paucity of data in the existing literature on post-COVID-19 neurological complications leaves the window open to ongoing and future research. Awareness concerning the matter, prevention of SARS-CoV-2 infection, follow-up of post-COVID-19 patients and collaboration among health professionals are of particular importance, therefore recommended.

Conflicts of interest: No conflict of interest was declared by the authors.

Funding: No external funding was declared by the authors.

References

[1] who.int [Internet]. Pneumonia of unknown cause – China; 2020 Jan 5. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229
[2] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe Acute Respiratory Syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-COV-2. *Nat Microbiol*. 2020;5(4):536–544.
[3] Asghari A, Naseri M, Safari H, et al. The novel insight of SARS-COV-2 molecular biology and pathogenesis and therapeutic options. *DNA Cell Biol*. 2020;39(10):1741–1753.
[4] da Rosa Mesquita R, Francelino Silva Junior LC, Santos Santana FM, et al. Clinical manifestations of COVID-19 in the general population: Systematic review. *Wiener Klin Wochenschr*. 2020;133(7-8): 377–382.
[5] Wu Z, McGoogan JM. Characteristics of and important lessons from the corona-virus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323(13):1239–42.
[6] cdc.gov [Internet]. Post-COVID Conditions: Information for Healthcare Providers; 2021 Jul 9, Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html
[7] Schober ME, Pavia AT, Bohnsack JF. Neurologic manifestations of covid-19 in children: Emerging Pathophysiologic insights. *Pediatr Crit Care Med*. 2021;*22*(7):655–661.

[8] Arbour N, Talbot PJ. Persistent Infection of Neural Cell Lines by Human Coronaviruses. In: Enjuanes L, Siddell SG, Spaan W, editors. Coronaviruses and Arteriviruses. Advances in Experimental Medicine and Biology. Boston, MA: Springer;1998. p.575-581.
[9] Lau K-K, Yu W-C, Chu C-M, et al. Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis*. 2004;10(2):342–344.
[10] Algahtani H, Subahi A, Shirah B. Neurological complications of Middle East respiratory syndrome coronavirus: A report of two cases and review of the literature. *Case Rep in Neurol Med*, *2016*:1–6.
[11] Gavriatopoulou M, Korompoki E, Fotiou D, et al. Organ-specific manifestations of COVID-19 infection. *Clin Exp Med*, 2020;20(4):493–506.
[12] LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic Involvement in Children and Adolescents Hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome. *JAMA Neurol*. 2021;78(5):536.
[13] Panda PK, Sharawat IK, Panda P, et al. Neurological Complications of SARS-CoV-2 Infection in Children: A Systematic Review and Meta-Analysis. *J Trop Pediatr*. 2021:67(3)fmaa070.
[14] Hacohen Y, Deiva K, Pettingill P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. *Mov Disord.* 2014;29:90-96.
[15] Doja A, Bitnun A, Ford Jones EL, et al. Pediatric Epstein-Barr Virus—Associated Encephalitis: 10-Year Review. *J Child Neurol*. 2006;21(5):384-91.
[16] Nagel MA, Gilden D. Neurological complications of varicella zoster virus reactivation. *Curr Opin Neurol.* 2014;27(3):356-360.
[17] Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barré syndrome. *The Lancet*. 2021;397(10280):1214-1228.
[18] Kahwagi J, Diagne R, Fall M, et al. Post infectious encephalitis at Covid19: About one pediatric observation and review of the literature. *Rev Neurol (Paris).* 2021;177(1-2):132-134.
[19] Curtis M, Bhumbra S, Felker MV, et al. Guillain-Barré Syndrome in a Child with COVID-19 Infection. *Pediatrics*. 2021;147(4) e2020015115.
[20] Khalifa M, Zakaria F, Ragab Y, et al. Guillain-Barré Syndrome Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Detection and Coronavirus Disease 2019 in a Child.*J Pediatric Infect Dis Soc*. 2020;9(4):510–513.
[21] Lo WD. Childhood hemorrhagic stroke: an important but understudied problem. *J Child Neurol*. 2011;26:1174–1185.