Brain Neurorehabil. 2024 Mar;17(1):e2
https://doi.org/10.12786/bn.2024.17.e2
pISSN 1976-8753·eISSN 2383-9910

Brain & NeuroRehabilitation

Case Report

Check for updates

Quadriplegia, Dysphagia and Ataxia Manifested in a Child With COVID-19 Related Acute Necrotizing Encephalopathy: A Case Report

Young-Su Ku, Kyung-Lim Joa, Myeong-Ok Kim, Chang-Hwan Kim, Han-Young Jung

Received: Aug 17, 2023
Revised: Nov 7, 2023
Accepted: Nov 13, 2023
Published online: Jan 4, 2024

Correspondence to
Han-Young Jung
Department of Physical and Rehabilitation Medicine, Inha University College of Medicine, 100 Inha-ro, Michuhol-gu, Incheon 22212, Korea.
Email: rmjung@inha.ac.kr

HIGHLIGHTS

- Coronavirus disease 2019 (COVID-19) triggers diverse neurological problems.
- We report a case of COVID-19-ANE in a child with quadriplegia, ataxia and dysphagia.
- Intensive rehabilitation is vital for addressing neurological effects.

Brain Neurorehabil. 2024 Mar;17(1):e2
https://doi.org/10.12786/bn.2024.17.e2
pISSN 1976-8753·eISSN 2383-9910

Case Report

Check for updates

Quadriplegia, Dysphagia and Ataxia Manifested in a Child With COVID-19 Related Acute Necrotizing Encephalopathy: A Case Report

Young-Su Ku , Kyung-Lim Joa , Myeong-Ok Kim , Chang-Hwan Kim , Han-Young Jung

Department of Physical and Rehabilitation Medicine, Inha University College of Medicine, Incheon, Korea

Received: Aug 17, 2023
Revised: Nov 7, 2023
Accepted: Nov 13, 2023
Published online: Jan 4, 2024

Correspondence to
Han-Young Jung
Department of Physical and Rehabilitation Medicine, Inha University College of Medicine, 100 Inha-ro, Michuhol-gu, Incheon 22212, Korea.
Email: rmjung@inha.ac.kr

ORCID iDs
Young-Su Ku
https://orcid.org/0000-0003-0809-6919
Kyung-Lim Joa
https://orcid.org/0000-0002-3747-9831
Myeong-Ok Kim
https://orcid.org/0000-0002-5584-7714
Chang-Hwan Kim
https://orcid.org/0000-0002-8940-2246
Han-Young Jung
https://orcid.org/0000-0003-1428-9821

Funding
None.

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, presents primarily with respiratory symptoms. However, children with COVID-19 are usually asymptomatic or mild acute symptoms and also neurological manifestations have also been observed. We report the case of a 7-year-old girl who presented with high fever and altered mental status, leading to a diagnosis of COVID-19 and acute necrotizing encephalopathy (ANE). The patient received intensive medical care in the intensive care unit and subsequently underwent rehabilitation programs due to neurological functional sequelae. Neurological complications in COVID-19, including ANE, may result from potential viral nerve involvement, cytokine storms, and the blood-brain barrier disruption. Early rehabilitation plays a pivotal role in managing COVID-19-related neurological complications and enhancing patients' functional outcomes. Further research is essential to gain a better understanding of the mechanisms and treatment strategies for neurological manifestations in pediatric COVID-19 patients, particularly those with multisystem inflammatory syndrome in child.

Keywords: Child; SARS-CoV-2; Encephalopathy; Quadriplegia; Ataxia

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The most common symptoms of COVID-19 infection are fever, malaise, shortness of breath, cough, diarrhea, and abdominal pain [1]. However, various neurological symptoms related to COVID-19 have also been observed at onset or during the course of the disease. Headache and dizziness are common nonspecific neurological manifestations in COVID-19 patients [2]. Furthermore, numerous studies have reported severe neurological complications, including encephalopathy, meningoencephalitis, ischemic stroke, cerebral venous thrombosis, seizures, acute necrotizing encephalopathy (ANE), Guillain-Barré syndrome, cerebellitis, reversible splenial lesion, microhemorrhages, and posterior reversible encephalopathy syndrome [3]. Among hospitalized COVID-19 patients, neurological complications range from 6% to 36% [4]. Neurological symptoms mostly appear in adults and are rare in children [5]. According to a recent study, nonspecific neurological symptoms were reported in 16% of pediatric patients with COVID-19, and specific neurological manifestations, including encephalopathy and meningeal signs, were reported in 1% [6].

Most children infected with COVID-19 had mild clinical symptoms without fever, but serious cases with multiple organ failure have been reported. Although neurological symptoms reported in children were very rare, recent reports described neurological involvements associated with COVID-19 infection in children diagnosed with multisystem inflammatory syndrome in child (MIS-C) [6]. This was thought to be related to the cytokine storm [2,6]. We report a case of a child with quadriplegia, ataxia and dysphagia due ANE associated with COVID-19.

In the previous article, children with ANE-associated neurological sequelae were managed with pediatric rehabilitation programs and showed remarkable improvement in outcomes [7]. Therefore, it is expected that children with COVID-19 associated neurological sequelae would have similar benefits to pediatric rehabilitation programs for those with ANE. We will describe clinical & neurological signs and symptoms, theoretical pathophysiology, and pediatric rehabilitation strategies.

CASE DESCRIPTION

The patient, a previously healthy 7-year-old, presented to the emergency room with a high fever (up to 42°C) that had persisted since the previous day and a change in mental status (glasgow coma scale score 8) during the day. Laboratory results revealed neutrophilia with elevated C-reactive protein and procalcitonin levels. Interleukin-6 levels were also elevated (1,308.0 pg/mL). The coagulation profile showed abnormalities, with a prothrombin time of 43.9 seconds, international normalized ratio of 5.03, and activated partial thromboplastin time of 104.9 seconds. D-dimer levels were also elevated (13.03 μg/mL). Cardiac makers were abnormal as well, with troponin-I at 0.900 ng/mL, creatine kinase at 1779 IU/L, and N-terminal pro-brain natriuretic peptide at 1,031 pg/mL. SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR) was performed on a nasopharyngeal swab, confirming the diagnosis of COVID-19 (**Table 1**).

Magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid (CSF) analysis were conducted to investigate the cause of the altered consciousness. CSF analysis revealed normal protein and glucose levels, with no presence of white blood cells. Brain MRI revealed hyperintense areas in bilateral thalamus, bilateral subinsular white matter, posterior basal ganglia, internal capsule posterior limb, upper midbrain, and pons in fluid-attenuated inversion recovery (FLAIR) images (**Fig. 1**). Electroencephalography indicated a few low voltage spike or sharp wave discharges in the right temporal area with slightly suppressed background activity, suggesting diffuse cerebral dysfunction and partial seizure.

Table 1. COVID-19 reverse transcription-polymerase chain reaction (nasopharyngeal swab) findings

COVID-19	Positive
E gene (Ct)	18.57
RdRp/S gene (Ct)	18.99
N gene (Ct)	19.21

COVID-19, coronavirus disease 2019; Ct, cut-off cycle threshold.

https://doi.org/10.12786/bn.2024.17.e2

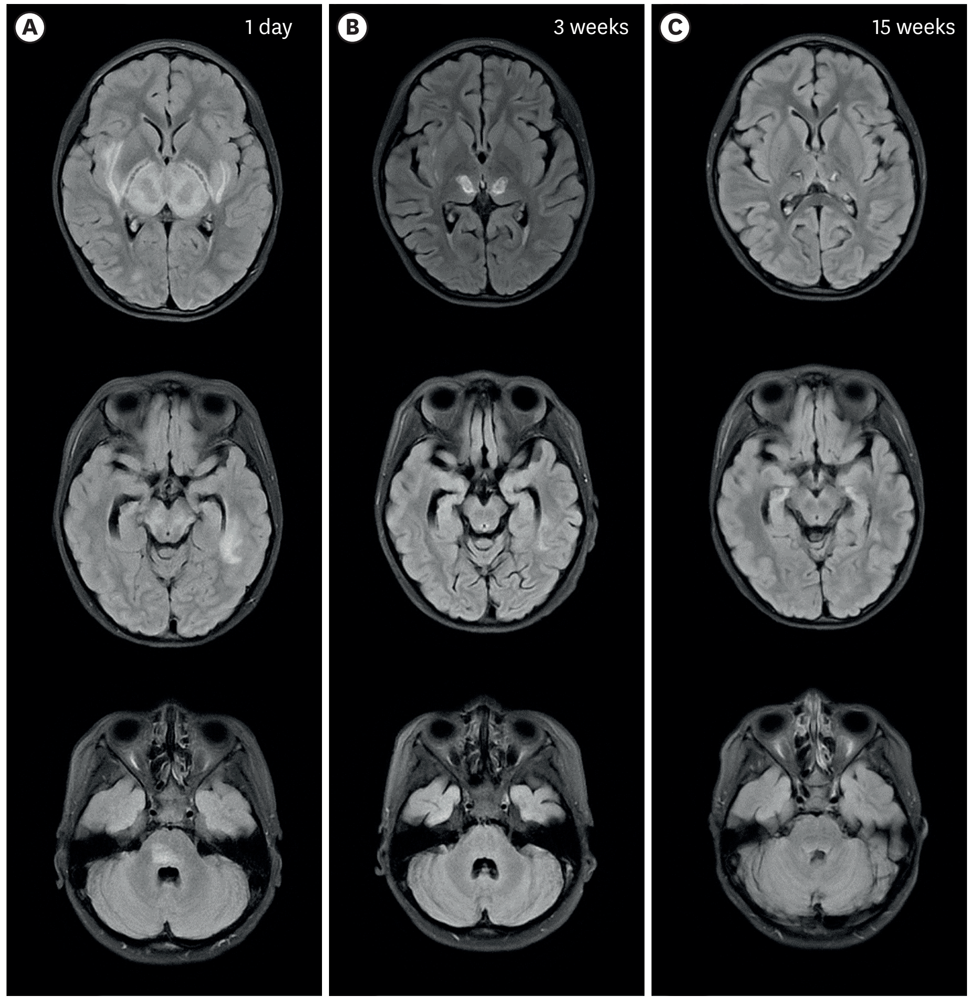

Fig. 1. Magnetic resonance imaging findings of the patient: high signal intensity was observed in the bilateral thalamus, subinsular white matter, posterior basal ganglia, internal capsule posterior limb, upper midbrain, and pons in axial fluid-attenuated inversion recovery images. (A) One day after onset, (B) 3 weeks after onset, (C) 15 weeks after onset.

She was admitted to the intensive care unit (ICU) to stabilize her vital signs, as she presented with hypotension and sepsis. Her symptoms included fever, hypotension, cardiac dysfunction, coagulopathy, elevated inflammatory markers in laboratory tests, and neurological involvement, leading to a diagnosis of MIS-C associated with COVID-19 (**Table 2**). Her treatment plan included essential medical interventions, such as intravenous immunoglobulin and methylprednisolone pulse therapy, along with antibiotic treatment. Three weeks after acute care, she was transferred to the department of rehabilitation medicine for functional assessments and proper rehabilitation programs. At that time, she was alert mentality but had quadriparesis, intentional tremor of both hands and legs and truncal ataxia. She took L-tube feeding and was unable to speak due to severe dysarthria. Manual muscle test (MMT) grade in both upper and lower extremities was poor, and the berg balance scale (BBS) was 0. The Videofluoroscopic Swallowing Study (VFSS) revealed drooling, poor chewing, and poor bolus formation attributed to clumsy tongue movement. Consequently, no pharyngeal phase of swallowing was observed. Based on the initial functional assessments, she underwent a multidisciplinary rehabilitation program that included physiotherapy to restore her quadriparesis and ataxia, incorporating methods such

https://doi.org/10.12786/bn.2024.17.e2

Table 2. World Health Organization case definitions of multisystem inflammatory syndrome in children and all 6 criteria be met in a reported case (bold)

Case definitions of multisystem inflammatory syndrome in children
1. Age 0 to 19 years
2. Fever for ≥ 3 days
3. Clinical signs of multisystem involvement (at least 2 of the following)
✓ Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
✓ **Hypotension or shock**
✓ **Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP)**
✓ **Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)**
✓ Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4. Elevated markers of inflammation (e.g., ESR, CRP, or procalcitonin)
5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
6. Evidence of SARS-CoV-2 infection
Any of the following:
✓ **Positive SARS-CoV-2 RT-PCR**
✓ Positive serology
✓ Positive antigen test
✓ Contact with an individual with COVID-19

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription-polymerase chain reaction; COVID-19, coronavirus disease 2019.

as neurodevelopmental treatment and functional electrical stimulation. Additionally, she received occupational therapy to improve hand tremors, cognitive function, and dysphagia, as well as speech therapy to treat her severe articulation disorder.

After completing four weeks of comprehensive rehabilitation programs, significant improvements were observed in her cognitive and speech & language function compared to before. Her receptive vocabulary test scores were in the 90–100%ile range, and her expressive vocabulary scores fell within the 80–90%ile range in the receptive and expressive vocabulary test. She persisted in experiencing symptoms of dysarthria, and her performance on The Korean standard picture of articulation and phonological test yielded a score of 34.9%. Furthermore, her full-scale IQ on the Korean Wechsler Intelligence Scale for Children-Fifth Edition was measured at 92, with an estimated IQ of 105. MMT grade of all limbs changed from poor to fair, and the BBS was 54 (**Table 3**). During the follow-up VFSS, the patient still showed weak bolus formation, premature bolus loss, and mild aspiration (penetration-aspiration scale [PAS] 7) when taking liquids. However, there was no aspiration observed during the intake of semisolid and solid substances (PAS 1). She started oral feeding with a soft meal and a liquid mixed with a viscosity controlling agent. She was able to walk for a short distance but had ataxic gait pattern on her left leg. Intentional tremors showed both hands with worse on the left side.

She was discharged six weeks after the onset and continued her rehabilitation programs in an outpatient clinic. After 15 weeks of the onset, MMT grade improved from fair to good, and the BBS was 56, but she still experienced mild intentional tremors in her left hand, mild left limb ataxia, and mild dysarthria.

DISCUSSION

COVID-19 infection typically presents with respiratory symptoms; however, it can also lead to neurological complications. ANE is a rare symptom of certain viral infections, such as

Table 3. Results of functional assessments

	3 weeks after onset	7 weeks after onset	15 weeks after onset	11 months after onset
MMT				
Rt U.E	P	F	G	G
Lt U.E	P	F	G	G
Rt L.E	P	F	G	G
Lt L.E	P	F	G	G
Grasp power (Kg)				
Rt	0	4	8	10
Lt	0	4	4	3
Box & Block test				
Rt	NT	26	28	36
Lt	NT	25	19	26
Perdue pegboard test				
Rt	NT	NT	6	8
Lt	NT	NT	NT	1
KS-PAPT (%)	NT	34.9	100	100
REVT (%ile)				
RV	80	90–100	-	-
EV	NT	80–90	-	-
BBS	0	54	56	56
MBI	0	60	65	71

MMT, manual muscle test; Rt, right; Lt, left; U.E, upper extremity; L.E, lower extremity; BBS, berg balance scale; MBI, modified Barthel Index; KS-PAPT, The Korean standard picture of articulation and phonological test; REVT, receptive and expressive vocabulary test; RV, receptive vocabulary; EV, expressive vocabulary; P, poor; F, fair; G, good; NT, not testable.

influenza, and generally affects the bilateral thalamus, along with other regions such as the brainstem, cerebral white matter, and cerebellum. While the exact mechanism by which SARS-CoV-2 invades the nervous system remains incompletely understood, several theories have been proposed [8].

First, there may be direct viral nerve involvement with nerve damage from SARS-CoV-2 via the olfactory nerves, infection of vascular endothelium. Another possibility is an antiviral immune response that could trigger a cytokine storm, resulting in blood-brain barrier disruption. Cytokines that migrate across this disrupted blood-brain barrier can trigger dysregulation and excessive immune responses in the brain that cause immune-mediated tissue damage. It can also cause edema and necrosis as a secondary effect [2].

MRI findings of ANE include bilateral symmetrical signal changes and necrosis in the central thalamus, sometimes with hemorrhagic components and/or involvement of the brain stem, cerebral white matter, and cerebellum. The lesion appears T2 FLAIR hyperintense signal with internal hemorrhage on MRI [9]. In some case reports, RT-PCR for SARS-CoV-2 targeting the N gene was positive in CSF study, although it is rare [10].

COVID-19 gives rise to frequent neurological complications, putting patients at risk and potentially affecting their functional capacity and quality of life. Therefore, early rehabilitation plays a crucial role in preventing further complications, regaining their functional abilities, and improving neurological issues caused by the virus. While evidence and treatment guidelines are currently limited, recent studies have highlighted the effectiveness of rehabilitation in addressing the condition [11]. Given the potential increase in COVID-19-related disabilities, quick action from rehabilitation specialists is vital to reducing disability and optimizing acute hospital settings [12].

In a retrospective study of COVID-19-associated ANE in children, a mortality rate of 66.67% was reported, with only one patient regaining consciousness after undergoing rehabilitation following ICU care [13]. Another case report involving a 9-year-old male patient showed quadriparesis and a lack of head and trunk motor control at the time of discharge [14]. While there are some reports of neurological sequelae after COVID-19-associated ANE, as mentioned in the papers above, there is a lack of studies providing long-term follow-up on functional improvement after rehabilitation. We report on a patient with post-acute neurological sequelae who showed improvement during rehabilitation with long-term follow-up and functional assessment. In this case, we present a case of a previously healthy child with ANE meeting the criteria for MIS-C associated with COVID-19, who subsequently experienced neurological sequelae after acute treatment. The World Health Organization defines long COVID as symptoms lasting at least two months after a probable or confirmed diagnosis of COVID-19, including neurological symptoms [15]. According to the American Academy of Physical Medicine and Rehabilitation consensus guidelines, rehabilitation strategies are helpful for people with long COVID, depending on their sequelae, and comprehensive rehabilitation programs for those with long COVID should be different from adult rehabilitation programs [16]. The patient showed significant functional improvement after undergoing comprehensive and intensive rehabilitation programs. In this case, MIS-C affected multiple organ systems, including the brain, triggered by systemic inflammation leading to a cytokine storm and damage to the blood-brain barrier. The cytokine storm also caused a hypercoagulable state and vascular thrombosis, resulting in cerebral ischemia. Moreover, existing literature supports the notion that reactive oxygen species played a pivotal role in the histological, inflammatory, and cellular changes, ultimately contributing to neurological damage witnessed in this case [17].

The patient displayed various brain region impacts, such as the bilateral thalamus, subinsular white matter, basal ganglia, internal capsule, midbrain, and pons, leading to dysphagia, dysarthria, and thalamic ataxia. Speech and swallowing involve intricate coordination between different brain areas and muscular structures, including the medulla oblongata, primary motor and sensory cortices, frontoparietal operculum, insula, anterior cingulate cortex, and others [18,19]. The severe oral phase of dysphagia and dysarthria in our patient may be linked to the involvement of the subinsular white matter and corticobulbar tract. The disruption of the dentato-rubro-thalamo-cortical tract affected the smooth coordination between the cerebellum, thalamus, and cerebral cortex, resulting in involuntary tremors and difficulties in controlling voluntary muscle movements [20]. In the reported patient, notably, the larger lesion in the right thalamus likely contributed to the more severe tremor and ataxia experienced on the left side of the body.

With the prevalence of SARS-CoV-2 and the increasing number of children with MIS-C, further studies are essential to better understand pediatric patients at risk of neurological symptoms and the mechanisms behind nervous system involvement, and it is important to investigate the treatments, including pediatric rehabilitation programs.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-1720. PUBMED | CROSSREF

2. Harapan BN, Yoo HJ. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). J Neurol 2021;268:3059-3071. PUBMED | CROSSREF
3. Akçay N, Bakırtaş Palabıyık F, Şevketoğlu E. Bilateral lentiform and caudate nucleus lesions in a child with COVID-19: a case report. Biomed J 2022;45:957-960. PUBMED | CROSSREF
4. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. Rev Neurol 2020;70:311-322. PUBMED | CROSSREF
5. Lin JE, Asfour A, Sewell TB, Hooe B, Pryce P, Earley C, Shen MY, Kerner-Rossi M, Thakur KT, Vargas WS, Silver WG, Geneslaw AS. Neurological issues in children with COVID-19. Neurosci Lett 2021;743:135567. PUBMED | CROSSREF
6. Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological involvement in COVID-19 and potential mechanisms: a review. Neurocrit Care 2021;34:1062-1071. PUBMED | CROSSREF
7. Diwanmal S, Biradi M, Vanaki R, Yelamali B. Rehabilitation outcomes in acute necrotizing encephalopathy of childhood – a retrospective study. Indian J Physiother Occup Ther 2021;15:125-130. CROSSREF
8. Baig AM. Updates on what ACS reported: emerging evidences of COVID-19 with nervous system involvement. ACS Chem Neurosci 2020;11:1204-1205. PUBMED | CROSSREF
9. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology 2020;296:E119-E120. PUBMED | CROSSREF
10. Virhammar J, Kumlien E, Fällmar D, Frithiof R, Jackmann S, Sköld MK, Kadir M, Frick J, Lindeberg J, Olivero-Reinius H, Ryttlefors M, Cunningham JL, Wikström J, Grabowska A, Bondeson K, Bergquist J, Zetterberg H, Rostami E. Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. Neurology 2020;95:445-449. PUBMED | CROSSREF
11. Albu S, Rivas Zozaya N, Murillo N, García-Molina A, Figueroa Chacón CA, Kumru H. Multidisciplinary outpatient rehabilitation of physical and neurological sequelae and persistent symptoms of COVID-19: a prospective, observational cohort study. Disabil Rehabil 2022;44:6833-6840. PUBMED | CROSSREF
12. Raciti L, Calabrò RS. Neurological complications of COVID-19: from pathophysiology to rehabilitation. An overview. Acta Biomed 2021;92:e2021317. PUBMED | CROSSREF
13. Lin X, Wang Y, Li X, Abdalla M, Zhang F, Dong C, Lu W, Liu X, Zhang J, Ma K, Ma X, Jiang Q. Acute necrotizing encephalopathy in children with COVID-19: a retrospective study of 12 cases. Front Neurol 2023;14:1184864. PUBMED | CROSSREF
14. Lazarte-Rantes C, Guevara-Castañón J, Romero L, Guillén-Pinto D. Acute necrotizing encephalopathy associated with SARS-COV-2 exposure in a pediatric patient. Cureus 2021;13:e15018. PUBMED | CROSSREF
15. Stefanou MI, Palaiodimou L, Bakola E, Smyrnis N, Papadopoulou M, Paraskevas GP, Rizos E, Boutati E, Grigoriadis N, Krogias C, Giannopoulos S, Tsiodras S, Gaga M, Tsivgoulis G. Neurological manifestations of long-COVID syndrome: a narrative review. Ther Adv Chronic Dis 2022;13:20406223221076890. PUBMED | CROSSREF
16. Whiteson JH, Azola A, Barry JT, Bartels MN, Blitshteyn S, Fleming TK, McCauley MD, Neal JD, Pillarisetti J, Sampsel S, Silver JK, Terzic CM, Tosto J, Verduzco-Gutierrez M, Putrino D. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cardiovascular complications in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). PM R 2022;14:855-878. PUBMED | CROSSREF
17. Sarkar S, Karmakar S, Basu M, Ghosh P, Ghosh MK. Neurological damages in COVID-19 patients: mechanisms and preventive interventions. MedComm (2020) 2023;4:e247. PUBMED | CROSSREF
18. Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. Physiol Rev 2001;81:929-969. PUBMED | CROSSREF
19. Martin RE, MacIntosh BJ, Smith RC, Barr AM, Stevens TK, Gati JS, Menon RS. Cerebral areas processing swallowing and tongue movement are overlapping but distinct: a functional magnetic resonance imaging study. J Neurophysiol 2004;92:2428-2443. PUBMED | CROSSREF
20. Marek M, Paus S, Allert N, Mädler B, Klockgether T, Urbach H, Coenen VA. Ataxia and tremor due to lesions involving cerebellar projection pathways: a DTI tractographic study in six patients. J Neurol 2015;262:54-58. PUBMED | CROSSREF