



Case Report

Journal Homepage: <http://crp.tums.ac.ir>

Acute Necrotizing Encephalopathy Following Presumed COVID-19 Infection: The First Iranian Report in Children



Meisam Babaei¹, Susan Hosseini², Maryam Tavakoli³, Mahnaz Banaei⁴, Maryam Bagheri^{5*}

1. Department of Pediatrics, North Khorasan University of Medical Sciences, Bojnurd, Iran.

2. Pardis Pathobiology and Genetics Laboratory, Mashhad, Iran.

3. North Khorasan University of Medical Sciences, Bojnurd, Iran.

4. Hazrat Ali Asghar Children's Hospital, Iran University of Medical Sciences, Tehran, Iran.

5. Student Research Committee, North Khorasan University of Medical Sciences, Bojnurd, Iran.

Use your device to scan and read the article online



Citation Babaei M, Hosseini S, Tavakoli M, Banaei M, Bagheri M. Acute Necrotizing Encephalopathy Following Presumed COVID-19 Infection: The First Iranian Report in Children. Case Reports in Clinical Practice. 2022; 7(5): 234-237.

Running Title Acute Necrotizing Encephalopathy Following Presumed COVID-19 Infection



Article info:

Received: August 9, 2022

Revised: August 21, 2022

Accepted: September 23, 2022

Keywords:

Acute necrotizing encephalopathy; COVID-19; Children; SARS-CoV-2

ABSTRACT

In the fifth's SARS-CoV-2 infection peak, although extended vaccination, still there is some reports of neurologic complications of covid-19 in children like adult. Though often we expose to benign neurologic features but sometimes there is unusual clinicoradiologic presentation. Thus, report of uncommon neurologic manifestations can help us to better understand of main pathophysiology in pediatric brain involvement. In this report, we present a five-year-old previously healthy girl that arrive to our hospital with fever, vomiting and loss of consciousness, on lumbar puncture there was mild protein elevation without pleocytosis and nasopharyngeal swab PCR for COVID-19 was positive. Brain imaging 10 hours after admission, revealed findings suggestive of acute necrotizing encephalopathy (ANE). In spite of extensive brain involvement, after prompt initiation of high dose methylprednisolone and IV immunoglobulin, there was dramatic improvement after 3 months' follow-up. To our knowledge, this is the first Iranian report and the second report on the world.

Introduction

S

ARS-CoV-2 infection is benign in most pediatric patients [1]. However, its clinical course in children is highly variable, with many asymptomatic or monosymptomatic cases [2]. It has been established that the SARS-CoV-2 virus has neuroinvasive properties [3]. Two mechanisms were

proposed to explain how SARS-CoV-2 may induce neurological damage: direct viral infection of nervous system through ACE2 receptors and inflammatory injury mediated by cytokines release; also, neurological manifestations may be part of a MIS-C [4]. Regarding neurological involvement in COVID-19, severe neurological manifestations (encephalopathy, meningoencephalitis, stroke, seizure, Guillain-Barre syndrome, acute disseminated encephalomyelitis)

* Corresponding Author:

Dr. Maryam Bagheri

Address: Department of Pediatrics, Emam Ali Hospital, Chamran Street, Bojnurd, North Khorasan, Iran

E-mail: M.babaei@nkums.ac.ir



have been reported mainly in adults [5], while a few cases have been described in children.

Acute necrotizing encephalopathy is one of the uncommon and possibly rare manifestations after COVID-19 infection that present in adult [6] and pediatric [7]. Herein, we report the first Iranian but the second one's in the world, that prompt treatment, despite extensive brain involvement, led to dramatic improvement at the follow-up study.

Case presentation

A previously healthy 5-year-old girl, brought to our hospital with history of fever, recurrent vomiting, and loss of consciousness since three days before admission; initial examination revealed mild fever, moderate tachycardia and other vital signs were normal. The patient GCS(glasgow coma scale) was 7, and she had third and sixth nerve palsy, deep tendon reflexes were brisk, also bilateral babinski sign was observed. In general assesment, we didn't see any abnormal signs. Blood sample was sent for early evaluation and urine

toxicology for complete assesment, also brain CT scan was done and showed mild symmetric hypodensity on both thalamus. 10 hours after admission, brain MRI was done and showed increased symmetric and heterogenic signal intensity in thalamus, basal ganglia and brain stem include midbrain and pons (Fig. 1).

After this, the patient underwent lumbar puncture, then on CSF(cerebrospinal fluid) analysis, cell count and glucose were normal except mild protein elevation. On laboratory exam, revealed mild leukopenia with severe lymphopenia in addition to mild elevation of liver enzymes; other laboratory tests had been explained in detail (Table 1).

In the second days of admission, we begin to start a high dose methylprednisolon and IV immunoglobulin in combination, because based on clinical and radiological findings and also initial results of CSF exam, the patient is suspect to acute necrotizing encephalopathy diagnosis.

On her follow-up, nasal swap specimen for SARS-COV2 polymerase chain reaction (PCR) was positive but CSF PCR for herpes simplex1 and 2, ebstein bar

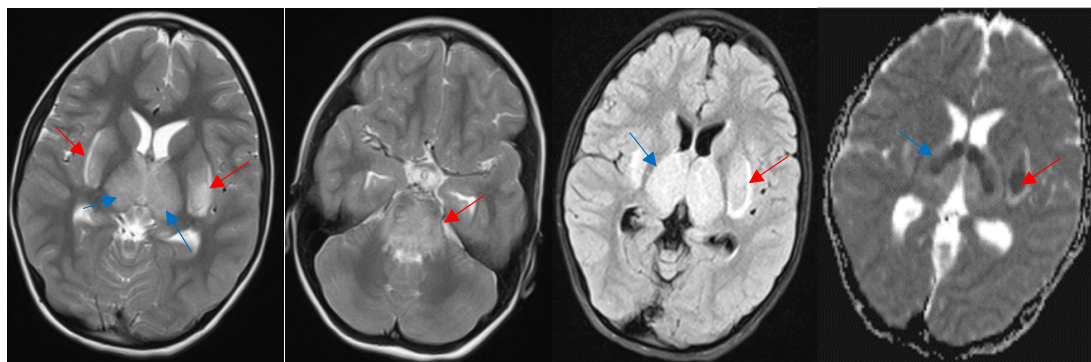


Fig. 1. Bilateral thalamic swelling with areas of high T2W (A, B) and FLAIR (C) heterogeneous signal intensity with basal ganglia involvement and restricted diffusion (D). Other areas of similar abnormal signal are also seen at the midbrain and pons (B).

Table 1. Main lab data

Lab data	
WBC	5000
Hb	12.7
Plt	113000
Ast	92
Alt	92
LDH	633
Ammonia	59
Lactate	1.3
CSF Analyze	Sugar=75
	Protein=58
	Cell=0
D-Dimer	1014
Crp	6.5
Esr	13
Nasal swap PCR for COVID-19	Pos.
CSF PCR for HSV, EBV, INFLU.COVID	Neg.



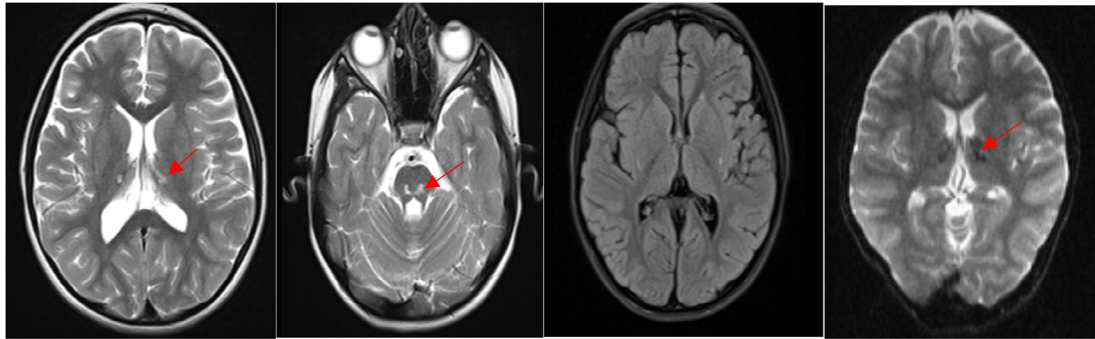


Fig. 2. After 3 months' follow-up, brain MRI revealed regressive course of the size of the previously noted bilateral thalamic, basal ganglia (A) and also brain stem (B, C) areas of signal changes and the surrounding edema. The lesions show facilitated diffusion at the current study (D).

virus, influenza virus, and also SARS-COV2 were negative, thus we discontinued IV acyclovir, and start to occupational and physical therapy furthermore supportive care.

The girl was conscious in forth days and extubate with succes, in the next day she interact to her mother. Two weeks after treatment the patient was alert and discharged by recommendation to occupational therapy. 3 month's later, her cognition was near normal, she walks with aid, and some neurologic impairment such as mild left side dytonia, and strabismus reside (Fig. 2).

Discussion

As regards pediatric COVID-19 cases, unlike the clinical presentation of adult patients, a systematic review showed that the most commonly reported symptoms are fever, cough, pharyngitis and rhinorrhea; other frequent symptoms are headache, myalgia, rash, conjunctivitis,

syncopal episodes and gastrointestinal manifestations such as vomiting, diarrhea, abdominal pain and difficulty in feeding [8, 9].

Despite common neurologic manifestation after COVID-19 exposure, there are some uncommon and rare neurologic presentation often in adults, But in children, it was less. In spite of two years after SARS-COV2 pandemic and extensive vaccination, there are increasing number of this report. This uncommon manifestation can be a part of multisystem involvement like MIS-C [10], or including isolated CNS involvement; such as our report that to our knowledge, is the first report in Iran and the second one's in the world.

Possible mechanisms that could be contribute to CNS injury after SARS-COV2 exposure include: direct viral injury to neural cells, vascular endothelial injury and inflammatory and autoimmune injury [4].

In our case, base of initial clinical findings (focal deficit, loss of consciousness) and radiological findings (symmetric involvement in thalamus, basal ganglia, and brain stem), 2 folds increasing in liver enzyme, and positive findings in nasal swap for COID-19, most possible diagnosis was post-COVID-19 acute necrotizing encephalopathy; and other diagnosis such as Reye syndrome (ammonia and blood glucose were normal in this patient), hemolytic-uremic syndrome (platelet and urea were normal in this case), encephalitis (CSF PCR for viral markers was normal, without pleocytosis), probably ruled out [11, 12, 13]. On the other hand, in available studies (although often there are case reports or case series), age 4 or higher, less elevation of liver enzyme, low score on brain imaging, and prompt initiation of immunotherapy less than 24-48 hours, were accompanied with favorable outcome [14]; it seems, in our case because of factors that mentioned above and also early and concomitant initiation (less than 48 hour) of methylprednisolone and IVIG, there was a significant and hopeful improvement at the follow-up.

It should be noted that usually there is some lag before initiation of immnomodulator treatment, because of concerning about possible viral shedding and also delay on reaching to CSF PCR results. [15]

After 3 months' follow-up with occupational and speech therapy, the patient cognition was near normal, she could to walk with aid and also feed alone, although there was some right-hand dystonia and strabismus.

Thus, we believe that prompt initiation of steroid, particularly in combination with IVIG, if there is high suspicion for post-COVID ANE base on clinical, radiological, and laboratory findings, (probably because of autoimmune mechanisms) can be lifesaving and can lead to significant improvement; although it should be considered that this is a case report and needs to more extensive studies in the future.

Conclusion

In the base of recent reports of ANE following SARS-CoV2 in adult and children, it seems that COVID-19 should be added to other responsible virus in the literature, as presumed cause of acute necrotizing encephalopathy.

Ethical Considerations

Consent

Informed consent was obtained from parents.

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or nonprofit sectors.

Conflict of Interests

The authors have no conflict of interest to declare.

Acknowledgements

Not applicable.

References

- Bailey L.C, Razzaghi H, Burrows E.K, Bunnell H.T, Camacho P, Christakis D, et al . Assessment of 135 794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Across the United States. *JAMA Pediatr* 2021;1;175(2):176-84. <https://doi.org/10.1001/jamapediatrics.2020.5052>
- Kim L, Whitaker M, O'Halloran A, Kambhampati A, J Chai Sh., Reingold A. Hospitalization Rates and Characteristics of Children Aged < 18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69(32):1081-8. <https://doi.org/10.15585/mmwr.mm6932e3>
- Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the Nervous System. *Cell* 2020;183(1):16-27 el. <https://doi.org/10.1016/j.cell.2020.08.028>
- Lin J.E, Asfour A, Sewell T.B, Hooe B, Pryce P, Earley C, et al. Neurological issues in children with COVID-19. *Neurosci Lett.*2021;743:135567. <https://doi.org/10.1016/j.neulet.2020.135567>
- Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683-90. <https://doi.org/10.1001/jamaneurol.2020.1127>
- Dace Z, Gundega K, Krista S, Jaunozoliņa L, Karelis G. A fatal case of COVID-19-associated acute necrotizing encephalopathy. *Eur J Neurol.* 2021 Nov;28(11):3870-3872. <https://doi.org/10.1111/ene.14966>
- 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* 13(5): e15018.
- Manti S, Licari A, Montagna L, Votto M, Leonardi S, Brambilla I, et al. SARS-CoV-2 infection in pediatric population. *Acta Bio-Medica.* 2020;91(11-5): e2020003.
- Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr.* 2020;174(9):882-9. <https://doi.org/10.1001/jamapediatrics.2020.1467>
- Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ (Clinical research ed).* 2020;369:m2094. <https://doi.org/10.1136/bmj.m2094>
- Mizuguchi M, Abe J, Mikkaichi K, Noma S, Yoshida K, Yamanka T, Kamoshita S. Acute necrotizing encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. *J Neurol Neurosurg Psychiatry* 1995; 58:555-61. <https://doi.org/10.1136/jnnp.58.5.555>
- Kumar S, Misra U.K, Kalita J, Salwani V, Gupta R.K, Gujral R. MRI in Japanese encephalitis. *Neuroradiology* 1997; 39:180-84. <https://doi.org/10.1007/s002340050388>
- DeLong G.R, Glick T.H, Encephalopathy of Reye's syndrome: a review of pathogenetic hypotheses. *Pediatrics* 1982; 69:53-63. <https://doi.org/10.1542/peds.69.1.53>
- Wu X, Wu W, Pan W, Wu L, Liu K, Zhang H.L. Acute necrotizing encephalopathy: an underrecognized clinicoradiologic disorder. *Mediators Inflamm* 2015; 2015:792578. <https://doi.org/10.1155/2015/792578>
- Bashiri F.A, Johani S.AL, Hamad M.H , Kentab A.Y, Alwadei A.H , Hundallah Kh, et al. Acute Necrotizing Encephalopathy of Childhood: A Multicenter Experience in Saudi Arabia. *Front. Pediatr.*, 09 October 2020. <https://doi.org/10.3389/fped.2020.00526>