



MRI Findings of COVID-19 Associated Acute Necrotizing Encephalopathy in Two Pediatric Patients: Case Report and Literature Review

소아에서 발생한 COVID-19 연관 급성 괴사성 뇌병증의 MRI 소견: 2건의 증례 보고 및 문헌 고찰

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Acute necrotizing encephalopathy (ANE) is a rare immune-mediated complication of a viral infection commonly involving the bilateral thalamus and has been reported mainly in children. Here, we describe the MRI findings of coronavirus disease 2019 (COVID-19)-associated ANE in two pediatric patients, including a 7-year-old girl with fever and mental change, and a 6-year-old girl with fever and generalized seizures. Brain MRI revealed symmetrical T2 fluid attenuated inversion recovery high-signal intensity lesions in the bilateral thalamus with central hemorrhage. In one patient, the thalamic lesions showed a trilaminar pattern on the apparent diffusion coefficient map. This report emphasizes the importance of creating awareness regarding these findings in patients with COVID-19, particularly in children with severe neurological symptoms. Furthermore, it provides a literature review of several documented cases of COVID-19 presenting with bilateral thalamic hemorrhagic necrosis, suggesting a diagnosis of ANE.

Index terms COVID-19; Coronavirus Disease 2019; Acute Necrotizing Encephalopathy; Pediatric; Brain Magnetic Resonance Imaging

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INTRODUCTION

Since the end of 2019, 600 million confirmed cases and six million deaths worldwide have been attributed to Coronavirus disease 2019 (COVID-19) (1). Moreover, with the recent spread of the omicron variant, the number of confirmed COVID-19 pediatric patients has increased rapidly.

Most infected patients develop a mild to moderate illness; however, a few present with serious symptoms that require immediate treatment or hospitalization. The most common symptoms of COVID-19 are respiratory or cardiac; however, neurological symptoms such as headache, dizziness, and confusion have also been reported (1). COVID-19-associated acute necrotizing encephalopathy (ANE) has been reported in adults and children (2-11). Herein, we report the brain MRI findings and the clinical course of ANE, a rare complication of influenza and other viral infections, in two pediatric patients with COVID-19. Given the recent increase in the incidence of COVID-19 among pediatric populations, this report will be helpful in considering ANE in pediatric patients with neurological abnormalities associated with COVID-19.

CASE REPORTS

CASE 1

A 7-year-old girl with fever and mental change was referred to our hospital by the emergency department. The fever started one day before admission and reached a maximum of 42°C (107.6°F). At presentation, the patient was in a stuporous mental state (Glasgow Coma Scale: eye 2, verbal 2, motor 4), with a body temperature of 38.9°C, and a blood pressure of 111/64 mmHg. The patient had no pertinent medical or family history. A real-time reverse transcriptase-polymerase chain reaction (RT-PCR) with a nasopharyngeal swab was used for screening COVID-19, and a positive result was obtained. On laboratory examination, inflammatory markers such as C-reactive protein and procalcitonin were increased to 1.09 mg/dL (normal range: 0–0.5 mg/dL) and 27.2 mg/dL (normal range: 0–0.5 mg/dL), respectively. Cerebrospinal fluid (CSF) analysis was limited due to a traumatic lumbar puncture; however, tests for tuberculosis, *Streptococcus pneumoniae*, enterovirus, herpes simplex virus 1 and 2, respiratory syncytial virus, and *Cryptococcus* antigen were negative. Test results for the presence of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) in the CSF could not be obtained. Although the patient had no definitive respiratory symptoms, chest radiography revealed mild haziness in both lung fields.

One day after admission, the patient experienced a generalized tonic-clonic seizure with eyeball deviation. Electroencephalogram suggested diffuse cerebral dysfunction. A brain MRI obtained two days after admission revealed markedly symmetrical edematous lesions in the bilateral thalamus. Multifocal high-intensity lesions were observed in the bilateral subinsular white matter, posterior basal ganglia, posterior limb of the internal capsule, subcortical and deep white matter of the bilateral cerebral hemispheres, upper midbrain, and pons on fluid attenuated inversion recovery (FLAIR) images (Fig. 1A). On T2* gradient echo images, the centers of the thalamic lesions were hypointense, suggesting a hemorrhage (Fig. 1B). The centers of the bilateral thalamic lesions were hyperintense on diffusion-weighted imag-

ing (DWI, $b = 1000$) and surrounded by an isointense rim (Fig. 1C). On apparent diffusion coefficient (ADC) maps, the thalamic lesions showed a trilaminar pattern (Fig. 1D). The central cores of the lesions were slightly hyperintense than the brain parenchyma, and the interme-

Fig. 1. COVID-19-associated acute necrotizing encephalopathy in a 7-year-old girl.

A-D. Brain MRI obtained two days after admission.

A. T2 FLAIR images demonstrate symmetrical edematous lesions in the bilateral thalami and multifocal high-signal intensities in the bilateral subinsular region, posterior basal ganglia, posterior limb of the internal capsule, bilateral cerebral white matter, midbrain, and pons.

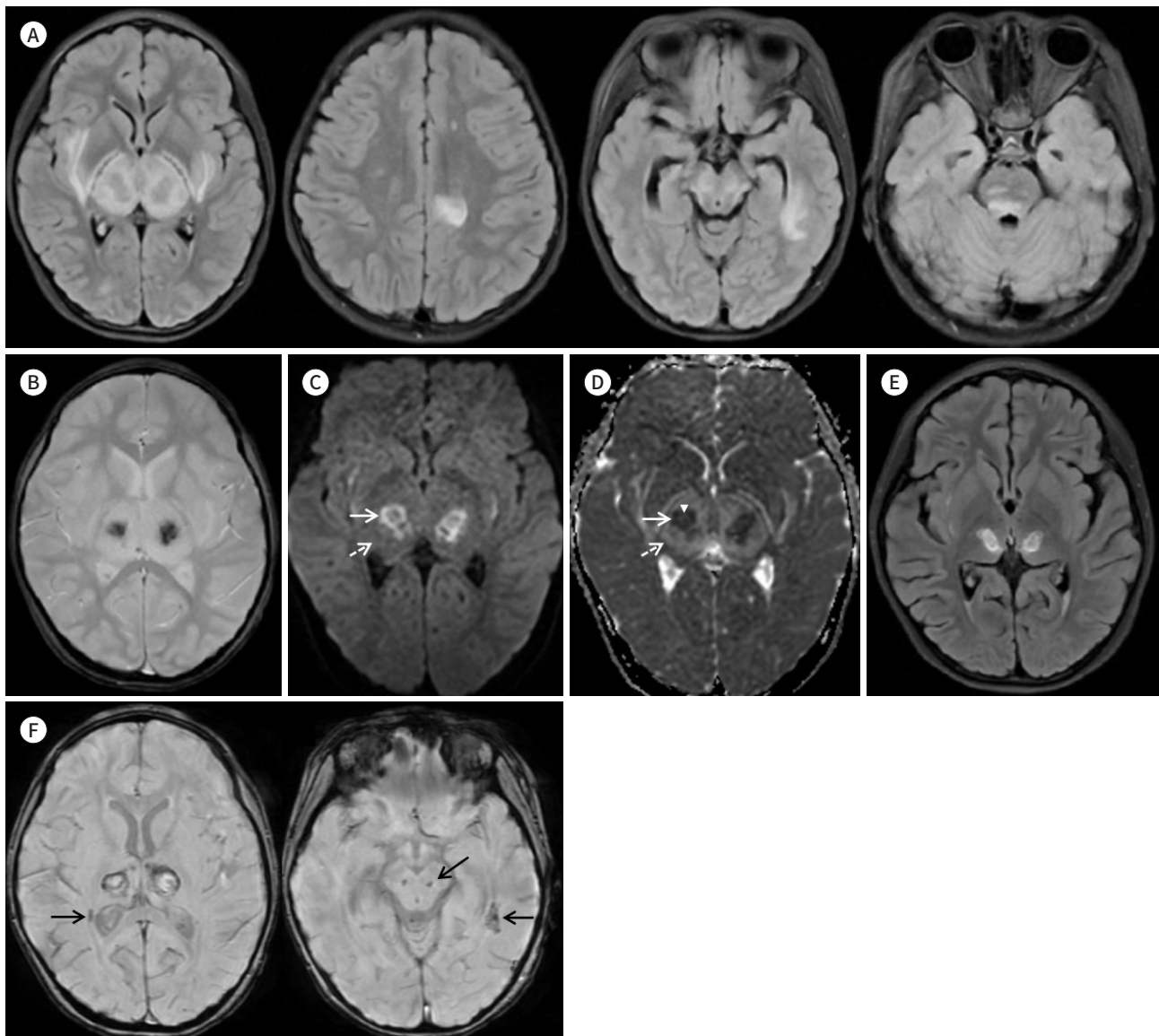
B. Hypointense lesions are observed at the center of the thalamic lesions in the T2* gradient echo image, suggesting a hemorrhage.

C. On diffusion-weighted imaging ($b = 1000$), the center of the thalamic lesions appears hyperintense (arrow), and the peri-central lesions are isointense (dashed arrow).

D. Trilaminar patterns are visible on the ADC map. The slightly hyperintense central core of the lesion (arrowhead) indicates hemorrhagic necrosis. The surrounding intermediate rim shows a decreased ADC value (arrow), suggesting cytotoxic edema, whereas the outermost rim exhibits an increased ADC value (dashed arrow), indicating vasogenic edema.

E, F. A follow-up brain MRI was performed 18 days after admission. **(E)** FLAIR image shows markedly decreased edema in both thalami. **(F)** On susceptibility-weighted imaging, preexisting FLAIR hyperintense lesions in the midbrain and both cerebral hemispheres demonstrate newly visible petechial hemorrhages (arrows).

ADC = apparent diffusion coefficient, FLAIR = fluid attenuated inversion recovery



diate rims were markedly hypointense, suggesting diffusion restriction. The outermost rims were hyperintense, suggesting vasogenic edema. The lesions showed no definite enhancement after the administration of gadolinium contrast. Given the findings of hemorrhagic lesions in the bilateral thalami and multiple FLAIR hyperintense lesions in the bilateral cerebral white matter, posterior basal ganglia, and brain stem in the setting of COVID-19 infection, COVID-19-associated encephalopathy, such as ANE, was suspected.

The patient developed complications, such as multisystemic inflammatory syndrome and disseminated intravascular coagulation, during hospitalization, which were treated with systemic steroids (methylprednisolone), intravenous immunoglobulins, and antibiotics. Thirteen days after admission, a nearly alert mental state was attained (Glasgow Coma Scale: eye 4, verbal 2, motor 6), without fever or seizures. Moreover, inflammatory markers and platelet counts were normal. A follow-up brain MRI (18 days after admission) showed markedly decreased edema in the bilateral thalami, bilateral cerebral white matter, and brainstem (Fig. 1E). Petechial hemorrhages were observed in pre-existing FLAIR hyperintense lesions in the midbrain and bilateral periventricular white matter on susceptibility-weighted imaging (SWI) (Fig. 1F). These findings indicated an improvement in ANE. On hospitalization day 22, the patient was transferred to the rehabilitation medicine department because of dysarthria and dysphagia.

CASE 2

A previously healthy 6-year-old girl presented to the emergency department with three episodes of generalized-type seizures with eyeball deviation, fever up to 41.4°C (106.5°F), and vomiting that had begun an hour ago. The patient was disoriented with an impaired memory of time and place. The Glasgow Coma Scale was eye 4, verbal 4, and motor 6; however, eye contact was difficult, motor response was slow, and only the left hand could be raised. RT-PCR testing for SARS-CoV-2 by nasal swabs yielded positive results. The CSF glucose level was mildly decreased (46% of blood glucose). CSF tests for tuberculosis, *Streptococcus pneumoniae*, enterovirus, and herpes simplex virus 1 and 2 were all negative. Test results for the presence of SARS-CoV-2 in CSF could not be obtained. Electroencephalogram results were normal. There were no definite respiratory symptoms or abnormalities on a chest radiograph.

MRI of the brain revealed symmetrical T2 FLAIR hyperintense lesions in the bilateral thalami, midbrain, and pons (Fig. 2A). SWI revealed internal hemorrhages in the thalamic and pontine lesions (Fig. 2B). DWI was not performed on this patient. Considering the bilateral symmetric FLAIR hyperintense lesions in the thalamus, midbrain, and pons accompanied by hemorrhage, ANE associated with COVID-19 was considered.

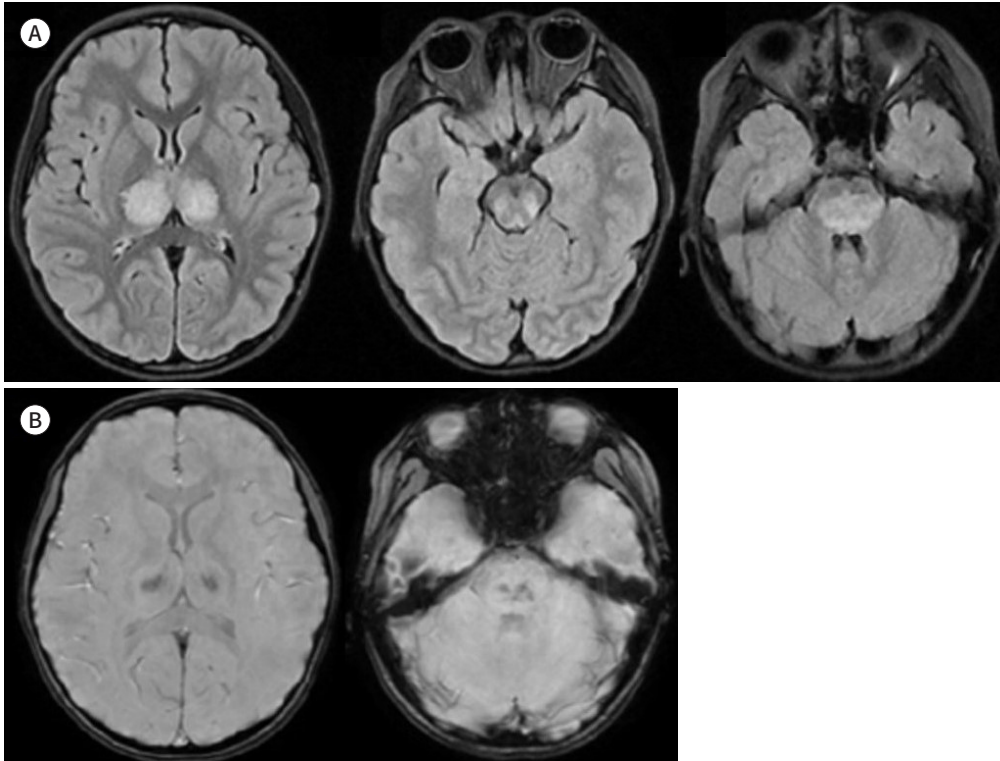
Steroid pulse therapy for 2 weeks, along with empirical antibiotics and acyclovir, was initiated. Brain MRI performed at 2 weeks of hospitalization showed interval resolution of hyperintense lesions in the bilateral thalami, midbrain, and pons on FLAIR. Petechial hemorrhage in the bilateral thalami and pons also decreased. No further seizures occurred after admission, and the patient's general condition improved. The patient was discharged after tapering steroid therapy, and motor and verbal abilities as well as cognition remained intact.

This study was approved by the Institutional Review Board, which waived the requirement for informed patient consent (IRB No. 2022-04-027).

Fig. 2. COVID-19-associated acute necrotizing encephalopathy in a 6-year-old girl.

A. On the initial brain MRI, symmetrical hyperintense lesions are seen in the bilateral thalami, midbrain, and pons on the T2 fluid attenuated inversion recovery images.

B. Susceptibility-weighted imaging demonstrates internal hemorrhage in the thalamic and pontine lesions.



DISCUSSION

We report the development of ANE in two pediatric patients who presented with severely altered mental status and seizures during the COVID-19 infection. Similar to previously reported ANE cases, the patients showed symmetrical hemorrhagic lesions in the thalami and multiple lesions in the bilateral cerebral white matter and brain stem on brain MRI. One patient showed a characteristic trilaminar pattern on the ADC maps. Based on the clinical and radiologic findings, COVID-19-related ANE was diagnosed.

ANE is a rare complication of a viral infection that is frequently reported in children under five years of age (12). Although its pathophysiology is not completely understood, ANE is considered a parainfectious or inflammatory encephalitis, and its association with viral infections is well known. The causative pathogen is rarely detected in the CSF (13). An immune-mediated process that causes overproduction of cytokines (cytokine storm) in the brain has been reported as the underlying cause of ANE (14, 15). Excess cytokines cause damage to the vascular endothelium in multiple organs and increase vessel wall permeability. Intracranial cytokine storms result in the breakage of the blood-brain barrier without direct viral invasion or demyelination (14, 15). Cytokine storms can also affect other organs, leading to systemic inflammatory response syndrome, which may be accompanied by multiorgan failure, disseminated intravascular coagulation, or shock (14, 15).

ANE is associated with viral infections such as influenza, parainfluenza, herpes viruses 6 and 7, herpes simplex virus, measles, rubella, varicella, coxsackie A9, rotavirus, reovirus, and dengue (16). Recently, several cases of ANE have been reported in adults and children with COVID-19 (2-11).

The clinical course of ANE is characterized by a prodromal febrile illness followed by neurological deficits such as altered consciousness or seizures (14). This disease is highly fulminant and is associated with a high mortality rate. Survivors may experience severe neurologic sequelae (14, 17). For successful outcomes, early diagnosis and prompt use of immunomodulatory therapies, including steroid pulse therapy, intravenous immunoglobulin, and antiviral agents, are crucial (12, 15). The first case of COVID-19-related ANE was reported in a 58-year-old female in March 2020. The authors described similar brain MRI features of ANE as those reported in the present study, such as bilateral thalamic lesions with hemorrhage, and multiple lesions in the medial temporal lobes and subinsular region (2). To our knowledge, nine additional cases of COVID-19-associated ANE have been reported to date, including six pediatric cases (2-11). These case reports describe the MRI findings of bilateral thalamic lesions with hemorrhagic necrosis. Other sites include the cerebral hemispheres, basal ganglia, and brainstem. A characteristic diffusion-restricted pattern was present in the affected area in 8 of the 10 cases. Testing for the SARS CoV-2 virus in the CSF was negative in 8 of 10 cases, and no additional testing for the SARS CoV-2 virus was performed in the remaining two cases. Table 1 summarizes the imaging features and clinical course of the reported cases.

The characteristic radiological feature of ANE is symmetrical thalamic involvement with central hemorrhage or necrosis. Diffusion-restricted features of the trilaminar pattern have also been reported and are correlated with neuropathological findings (15, 17, 18). A central portion with a high ADC value indicates hemorrhagic necrosis. The adjacent pericentral portion (intermediate rim) with a very low ADC value and the peripheral outer lesion (outermost rim) with a high ADC value indicate cytotoxic edema and vasogenic edema, respectively (15, 17, 18). Similar to these findings, bilateral thalamic lesions with distinct layers were observed in one of our patients (Fig. 1D). Furthermore, despite the lack of documentation in the literature, we identified three distinctive layers on the ADC map in a 2-year-old girl reported by Karavas et al. (11).

Although no positive PCR results for SARS-CoV-2 were obtained in the CSF of our patients, we diagnosed ANE because of the presence of SARS-CoV-2 infection and characteristic MRI findings similar to those reported in the literature. In the current COVID-19 pandemic era, the number of COVID-19 patients, including children, is increasing worldwide. As a higher incidence of ANE has been reported in the pediatric population, clinicians and radiologists should consider this condition in pediatric patients presenting with neurological abnormalities concomitant with COVID-19.

Author Contributions

Conceptualization, C.Y.Y., L.H.Y.; investigation, C.Y.Y., L.H.Y.; methodology, C.Y.Y., L.H.Y.; writing—original draft, C.Y.Y.; and writing—review & editing, L.H.Y., L.M.K., K.Y.H.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Table 1. Reported Cases of COVID-19-Associated Acute Necrotizing Encephalitis in the English Literature

Reference	Sex/Age	Clinical Manifestation	Radiologic Features	Outcome
Poyiadji et al., 2020 (2)	F/58 years	Cough, fever, altered mental status	Hemorrhagic lesions in the bilateral thalami, medial temporal lobes, and subinsular region	NA
Virhammar et al., 2020 (3)	F/55 years	Stupor, multifocal myoclonus after fever	Symmetrically increased signal intensities in the subinsular region and thalami in FLAIR with restricted diffusion in DWI	Recovered
Dixon et al., 2020 (4)	F/59 years	Background of aplastic anemia, presented with seizures, reduced consciousness after fever, cough, and headache	Symmetric swelling and hemorrhage in the brain stem, and amygdala. Microhemorrhage with restricted diffusion in the putamen, thalamic nuclei, subinsular region, splenium of the corpus callosum, cingulate gyri, and subcortical periorlandic region	Died
Ziemele et al., 2021 (5)	M/70 years	Headache, hypertension, generalized tonic-clonic seizure	Edematous lesions in the bilateral thalami, brain stem, and cerebellar peduncles with microhemorrhages, small necrotic cavities, and restricted diffusion in DWI	Died
Lazarte-Rantes et al., 2021 (6)	M/9 months	Fever, irritability, left clonic focal seizure, febrile status epilepticus	Necrosis of the bilateral thalami and cortico-subcortical junction in the parietal and occipital lobes. Diffusion restriction in the posterior limb of the internal capsule, posterior body of the corpus callosum, and corona radiata	Recovered, sequelae of quadriplegia, axial hypotonia, appendicular hypertonia, and global hyperreflexia
Khan et al., 2022 (7)	F/5 weeks	Decreased oral intake, irritability, progressive lethargy, episodic generalized seizures	Cytotoxic edema in the bilateral thalamic nuclei and adjacent posterior limb of the internal capsules sparing the pulvinar	Recovered, sequelae of cerebral palsy and developmental retardation
Mierzewska-Schmidt et al., 2022 (8)	M/2 months	Cough, sneezing, loss of appetite, fever	Bilateral symmetrical T2 hyperintensity in the basal ganglia, thalami, frontal and occipital gray and white matter with diffusion restriction and microhemorrhage	Brain death
Wertheimer et al., 2022 (9)	M/2 months	Irritability, nasal discharge, fever	Diffusion restriction and bilateral tumefactive hemorrhagic lesions in the thalamus as well as the basal ganglia	Recovered
Wang et al., 2022 (10)	F/2 years	Fever, cough, vomiting, decreased appetite, decreased urine output	Edema in the bilateral thalami, pons, and posterior limb of the bilateral internal capsule and external capsule, with peripheral diffusion restriction in lesions in the bilateral thalami and pons	NA
Karavas et al., 2022 (11)	F/2 years	General weakness, high fever	T2/FLAIR hyperintense lesions with diffusion restriction in the cerebellum and bilateral thalamus	NA

DWI = diffusion-weighted imaging, F = female, FLAIR = fluid attenuated inversion recovery, M = male, NA = not available

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소아에서 발생한 COVID-19 연관 급성 괴사성 뇌병증의 MRI 소견: 2건의 증례 보고 및 문헌 고찰

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급성 괴사성 뇌병증은 바이러스 감염의 드문 면역 매개 합병증이다. 일반적으로 양쪽 시상을 침범하며, 주로 어린이에서 보고된다. 저자들은 소아에서 발생한 코로나바이러스감염증과 관련된 급성 괴사성 뇌병증 2건을 보고하고자 한다. 7세 여아는 발열과 의식변화, 6세 여아는 발열과 전신성 간질로 내원하였다. 뇌 MRI에서 두 환자 모두 양쪽 시상에 중심부 출혈을 동반한 대칭적인 액체감쇠역전회 고신호강도 병변이 보였고, 한 환자에서는 걸보기확산계수에서 시상에 층상 병변이 보였다. 저자들은 이 보고를 통해 급성 괴사성 뇌병증의 특징적인 뇌 MRI 영상 소견을 인지함으로써 심각한 신경학적 증상을 나타내는 코로나바이러스감염증 환자의 경우 특히 소아에서 영상 소견을 바탕으로 한 빠른 진단이 필요함을 강조하고자 한다. 또한, 급성 괴사성 뇌병증을 시사하는 양측 시상의 출혈성 괴사로 나타났던 코로나바이러스 감염 증례에 대한 문헌을 검토하고자 한다.

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