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Multiple encephalopathy syndrome: a case of a novel radiological subtype of acute encephalopathy in childhood

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Abstract. – INTRODUCTION: This report presents the case of a novel subtype of acute encephalopathy syndrome in childhood found in a patient with influenza type A infection; the patient exhibited evident magnetic resonance imaging (MRI) findings.

CASE REPORT: A 4-year-old boy was transferred to our hospital for prolonged (lasting 60 min) status epilepticus with influenza encephalopathy. Mild brain hypothermia therapy was applied for 72 h, followed by targeted temperature management for 96 h with mechanical ventilation in the intensive care unit. Moreover, methylprednisolone pulse therapy and immunoglobulin therapy were administered. One month after the treatment, his physical status recovered such that he was able to run, take food orally, communicate verbally, and successfully return to kindergarten. Interestingly, serial MRI studies revealed findings that were compatible with 1) acute necrotizing encephalopathy (ANE), 2) mild encephalitis/encephalopathy with a reversible splenial lesion (MERS type II), 3) acute cerebellitis, and 4) acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) on days 2, 4, 7, and 16, respectively.

CONCLUSIONS: To the best of our knowledge, these significant MRI findings associated with acute encephalopathy have never been reported. Thus, herein, we propose the new term radiological "multiple encephalopathy syndrome (MES)" based on our case of acute encephalopathy in childhood.

Key Words:
Acute encephalopathy, Biphasic seizures, Late reduced diffusion, Acute necrotizing encephalopathy, Cerebellitis, Cerebellopathy, Mild encephalopathy, Reversible splenial lesion, Multiple encephalopathy syndrome.

Introduction

Acute encephalopathy (AE) is a rapidly developing pathophysiological brain process that may be expressed as either subsyndromal delirium, delirium, or coma. The guidelines for AE in infancy and childhood developed by the Japanese Society of Child Neurology propose that the impairment of consciousness in AE persists for at least 24 h, with 11 points or less on the Glasgow coma scale[1]. Moreover, it is often associated with viral infections, especially influenza A and human herpesvirus 6. AE manifests as fever, seizures, and impaired consciousness and may lead to neurological sequelae or death. AE can be classified into four types based on the underlying pathomechanism: hypercytokinemia (e.g., acute necrotizing encephalopathy [ANE]), excitotoxicity (e.g., acute encephalopathy with biphasic seizures and late reduced diffusion [AESD]), metabolic abnormalities, and miscellaneous type (e.g., clinically mild encephalitis/encephalopathy with a reversible splenial lesion [MERS], other/unclassified encephalopathy)[1]. The treatment and prognosis of AE can vary depending on the underlying pathomechanisms. This is the first report of a pediatric patient who presented with radiological multiple encephalopathy in childhood (R-MEC) in the form of ANE, clinically MERS type 2, AESD, and acute cerebellitis, suggesting that encephalopathy syndromes are not always independent of each other, but may co-exist.

Case Report

A 4-year-old boy presenting with fever was diagnosed with influenza A infection and started

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on oseltamivir therapy by a local doctor. Approximately 6 h after the onset of fever, his consciousness level declined to mild impairment. On day 2, he presented with a seizure lasting around 60 min and was transferred to the intensive care unit of our hospital. On admission, his body temperature was 40°C, his blood pressure was 100/30 mmHg, and his heart rate was 120 bpm. He presented several episodes of partial and generalized febrile seizures. The disturbance of consciousness persisted after the cessation of the seizures, leading to a diagnosis of AE associated with influenza A infection. The patient was administered oxygen *via* tracheal intubation, to control his respiratory and general status. Electroencephalography revealed widespread high-amplitude slow-wave activity.

The results of the blood test that was performed on admission were as follows (Table I): white blood cell count, 6,000/μL; hemoglobin, 11.6 g/dL; platelet count, 45,000/μL; aspartate transaminase, 225 IU/L; lactate dehydrogenase, 683 IU/L; uric acid, 17.6 mg/dL; urea nitrogen, 63 mg/dL; creatinine, 1.25 mg/dL; creatinine kinase, 6,179 IU/L; C-reactive protein, 10.37 mg/dL; and procalcitonin, >1,500 pg/mL. Furthermore, a cerebrospinal fluid (CSF) analysis yielded the following findings: cell count, 26 μL; protein level, 82 mg/dL; and glucose level, 125 mg/dL. His blood amino acid and uric acid levels were close to normal. The serum/CSF values measured using the Bioplex Pro Human Chemokine Panel Assay (Bio-Rad, Richmond, CA, USA) on admission were as follows: interferon-γ, 40.65/31.55 pg/mL; interleukin 1β (IL-1β), 18.8/3.29 pg/mL; IL-6, 879.5/146.2 pg/mL; IL-10, 237.64/38.28 pg/mL; migration inhibitory factor (MIF), 7,380.35/55,442.41 pg/mL; and tumor necrosis factor-α, 24.52/35.23 pg/mL.

The patient was administered 30 mg/kg/day pulse methylprednisolone (3 days), 400 mg/kg/day immunoglobulin (5 days), and mitochondrial rescue treatment intravenously. Mild brain hypothermia therapy (BHT) was initiated for a target temperature of 34°C-35°C (72 h) under mechanical ventilation with sodium thiopental and midazolam. This was followed by targeted temperature management (TTM) to maintain the body temperature at 36°C-37°C for 96 h. On day 6, a partial seizure of the right arm occurred after sodium thiopental and midazolam administration was stopped for withdrawal of the mechanical ventilation. Midazolam treatment was then reinitiated, and levetiracetam was added.

We performed serial magnetic resonance imaging (MRI) studies during his intensive clinical course. The MRI scans acquired on day 2 showed reduced diffusion in the bilateral thalamus and mid-pons with T1 and T2 prolongation, reduced diffusion in the corpus callosum, deep frontoparietal white matter with mild T2 prolongation, and reduced diffusion in the bilateral hippocampus; on day 4, the lesions in the corpus callosum and deep white matter had disappeared, with T1 shortening in the bilateral thalamus and additional lesions with reduced diffusion signals in the cerebral cortex, subcortical white matter, and cerebellar cortex. The MRI scans performed on day 7 showed prominent lesions in the subcortical white matter, and, on day 17, diffusion-weighted imaging (DWI) revealed cerebral atrophy, hippocampal atrophy, and thalamic lesions with hyperintensity.

Reduced diffusion in the thalamic regions was observed on day 2 *via* MRI-DWI, indicating ANE (Figure 1A-D). A lesion was also evident in the splenium of the corpus callosum (Figure 1D), with symmetrical deep lesions observed in the white matter around the bilateral ventricles (Figure 1E, F), indicating MERS type 2. On day 4, DWI showed cerebellitis/cerebellopathy (Figure 1G, H) and delayed reduced diffusion in the parietal cortex (Figure 1K, L), which is an initial sign of AESD. On day 7, DWI showed delayed reduced diffusion in the subcortical white matter, mainly within the parietal lobe (bright tree appearance) (Figure 1R), indicating AESD. Midazolam treatment was terminated on day 8, after which seizures did not reoccur. Therefore, the patient was extubated. DWI showed a lesion in the substantia nigra (Figure 1T, U) and global brain atrophy with lateral ventricle enlargement (Figure 1V-X) on day 16.

Although the patient showed mild neurological symptoms, his motor activity had improved progressively at the time of discharge. The patient was discharged 1 month after admission. After discharge, he could communicate well verbally, ingest food orally, and walk and run slowly. When the patient was discharged, he had a score of 2 on the Pediatric Cerebral Performance Category (PCPC) Scale; in contrast, by the time we examined him in the outpatient clinic, he had recovered to a score of 1 on the PCPC Scale. Three months after the onset of symptoms, he returned to his kindergarten and enjoyed a sports festival.

Discussion

This was the first case of MES showing MRI findings consistent with 1) ANE, 2) MERS type

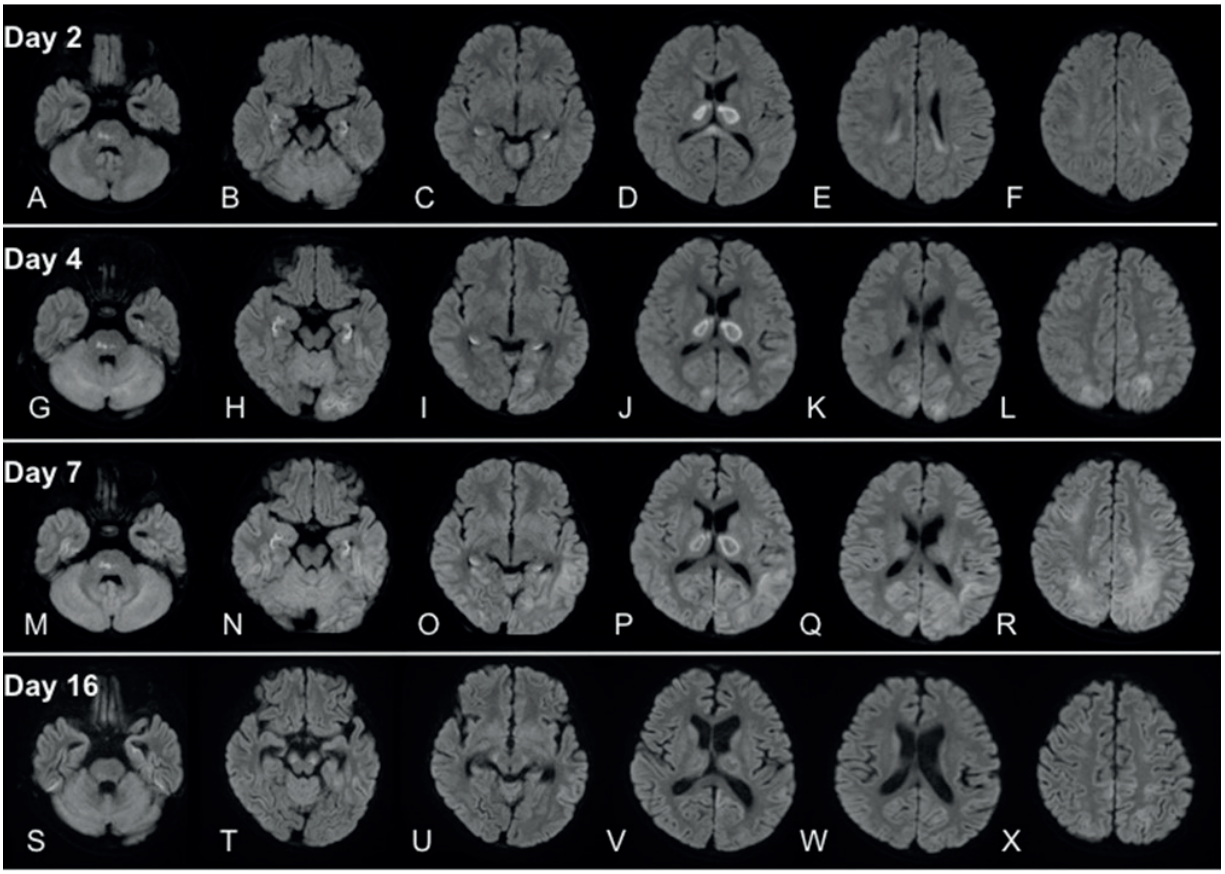

Figure 1. Reduced diffusion in the thalamic regions.

2, 3) cerebellitis/cerebellopathy, and 4) AESD. Most cases of ANE diagnosed by MRI have a mortal outcome, and even if the patients survive, they have severe neurological sequelae. AESD is also associated with impaired motor development and language delay in many cases. To the best of our knowledge, extremely severe MRI findings associated with AE have never been reported. Here we propose the term MES to denote the simultaneous occurrence of multiple features of the spectrum of AE in childhood. We did not obtain parental consent for genetic testing in this case. Although the possibility of unknown or very rare metabolic abnormalities cannot be ruled out, mass screening tests in Japan have already identified a large number of inborn metabolic errors. Furthermore, many of the cases of ANE, AESD, and MERS that have been reported in the past are not caused by inborn metabolic errors.

In Japan, the use of a novel treatment for pediatric AE that combines BHT and TTM is gradually increasing. The patient survived and had no severe sequelae; moreover, the successful treatment method of cerebral hypothermia used in this case may be of interest to many pediatric neurologists.

A previous case of ANE was associated with poor neurological prognosis and was characterized by thalamic lesions detected on brain MRI. Elevated blood levels of cytokines, such as IL-6, may play a central role in the pathogenesis of ANE[2], and the use of corticosteroid and immunoglobulin therapy to suppress inflammatory cytokines may be useful for managing this condition[3]. However, AESD is not considered to be associated with hypercytokinemia.

MERS complicated with ANE has not been previously reported. MERS is an encephalopathy/encephalitis characterized by lesions in the splenium of the corpus callosum. Cases of MERS with bilaterally symmetrical white matter lesions (mainly in the deep white matter, around the ventricles) are classified as type 2[1]. MERS is a clinically mild disease that rarely leads to neurological sequelae. It is often associated with viral infections, such as influenza, rotavirus, mumps, and Kawasaki disease, and rarely with bacterial infec-

Table I. Laboratory data of blood, urine, and spinal fluid at the time of patient admission.

Peripheral blood test		
White blood cell count	6,000/μL	
Red blood cell count	432×10^6/μL	
Hemoglobin	11.6 g/dL	
Hematocrit	35.10%	
Platelet count	45,000/μL	
Blood chemistry test		
Aspartate transaminase	224 IU/L	
Alanine aminotransferase	85 IU/L	
Lactate dehydrogenase	683 IU/L	
Total bilirubin	0.3 mg/dL	
Total protein	5.3 g/dL	
Albumin	3.1 g/dL	
Ammonia	70 μg/dL	
Uric acid	17.6 mg/dL	
Urea nitrogen	63 mg/dL	
Creatinine	1.25 mg/dL	
Na	145 mg/dL	
K	3.4 mg/dL	
Cl	111 mg/dL	
Ca	5.6 mg/dL	
p	17.6 mg/dL	
Amylase	455 U/L	
Glucose	125 mg/dL	
Creatinine kinase	6,179 IU/L	
Total cholesterol	126 mg/dL	
Triglyceride	127 mg/dL	
C-reactive protein	10.37 mg/dL	
Ferritin	588.4 ng/ml	
Procalcitonin	>1,500 pg/mL	
β2-microglobulin	4.5 mg/L	
Cerebrospinal fluid: CSF		
Cell count	26 μL	
Protein level	82 mg/dL	
Glucose level	125 mg/dL	
Blood coagulation test		
Prothrombin time %	45%	
Fibrinogen	311 mg/dL	
Fibrin degradation product	9.9 μg/mL	
D-dimer	2.8 μg/mL	
Antithrombin-3	63%	
Urine test		
Soluble interleukin-2 receptor	1,270 U/mL	
β2-microglobulin	4,709 mg/L	
Cytokine profile: The serum/CSF values measured using the Bio-plex Pro Human Chemokine Panel Assay (Bio-Rad, Richmond, CA, USA)		
	serum	CSF
Interferon-g	40.65 pg/mL	31.55 pg/ml
Interleukin (IL)-1β	18.8 pg/mL	3.29 pg/mL
IL-6	879.5 pg/mL	146.2 pg/mL
IL-10	237.64 pg/mL	38.28 pg/mL
Migration inhibitory factor (MIF)	7,380.35 pg/mL	55,442.41 pg/mL
Tumor necrosis factor-α	24.52 pg/mL	35.23 pg/mL

tions, such as acute focal bacterial nephritis[1,4,5]. Its immunopathology may result from a dysregulated and excessive immune response as a result of these infections. Although there is no direct evidence linking hypercytokinemia to infection-induced MERS, hyper inflammation can be observed in severe MERS, and ANE-associated hypercytokinemia may have a similar effect.

AESD complicated with ANE has been previously reported in Japan[6]. The initial symptoms of AESD are prolonged seizures (lasting 5 min or more) and disturbance of consciousness, followed by multiple partial seizures between days 3 and 9[1]. Although the prognosis of patients with AESD is not poor, neurological sequelae are often evident. Moreover, although the mortality rate of AESD is not very high, neurological sequelae, especially acute encephalopathy with frontal lobe predominance in infants (AIEF), delay not only their motor development, but also their intellectual and language development[7]. In the present case, DWI revealed a delayed reduction in diffusion in the subcortical cortex in the late seizure phase and in the subcortical parietal lobe on days 4 and 7; the patient experienced partial seizures on day 6, confirming that his condition was complicated with AESD. The pathogenesis of AESD is considered to be associated with the excitotoxicity associated with prolonged seizures. Because our patient manifested impaired consciousness starting on the afternoon of the day that preceded his admission to the hospital, and his seizure was noticed the following morning, he probably had experienced a long seizure.

Cerebellitis/cerebellopathy complicated by ANE has not been previously reported, although rare cases of MERS after cerebellitis/cerebellopathy have been described[8]. Cerebellitis/cerebellopathy is often caused by viral infections, such as varicella-zoster, and is associated with a poor neurological prognosis[9]. Occasionally, cerebellitis/cerebellopathy can progress rapidly to brain edema. Such cases exhibit severe neurological sequelae or fatal prognoses[10].

IL-6 is an important cytokine in AE, especially ANE and hemorrhagic shock and encephalopathy syndrome, and it may be a marker of clinical severity. A previous study[11] suggested that children with serum IL-6 levels >15,000 pg/mL are unlikely to survive. An increase in IL-6 levels (compared with the levels recorded at admission) was observed in our patient, which may have been controlled with corticosteroid treatment. IL-10, which is an anti-inflammatory cytokine associated with the poor prognosis of AE[12], was also elevated in our patient. In a previous study, the IL-10 CSF: serum ratio was significantly higher in patients with AE than it was in those with febrile convulsions[13]. If IL-6 and TNF- are cytokines that indicate immune overload, or a cytokine storm, IL-10 may be a suppressive cytokine on the overactive immune system. The fact that the IL-10 levels were elevated in our case could mean that IL-10 has an inhibitory effect on the cytokine storm caused by severe encephalopathy. MIF is a pro-inflammatory cytokine that activates the microglia in the CNS[14]. Activated microglia may be associated with the pathogenesis of AESD[15]. Moreover, MIF is considered a marker of poor prognosis. The level of MIF in our patient was extremely high, and the level of cerebrospinal MIF was greater than that of serum MIF, indicating that MIF was produced by central nervous cells. Hypothermia may inhibit microglial activation[16], and, in the present case, mild BHT and TTM were useful for managing AESD. Recently, an effective treatment strategy of mild BHT followed by TTM for treating cytokine-storm-type AE with hemorrhagic shock and encephalopathy syndrome has been gaining attention[17]. Our patient exhibited mild neurological symptoms at the time of discharge because of the presence of multiple concurrent encephalopathies (ANE, cerebellitis/cerebellopathy, and AESD), which are often associated with poor neurological prognosis; however, his motor abilities recovered well. The pathogenesis of AE is unclear, and effective treatments have not been established. However, a novel therapeutic approach using BHT followed by TTM for severe pediatric AE may have innovative therapeutic effects. We have demonstrated and reported the efficacy of this treatment in a previous study[17]. Further research on the pathophysiology of encephalopathy based on cytokine analysis is also needed.

Conclusions

Multiple radiological features of pediatric acute encephalopathy and a severe cytokine profile are present in this case. There have been no prior reports of such severe MRI images. Furthermore, the patient's survival with no severe sequelae, including the treatment method of cerebral hypothermia, is regarded as a very valuable outcome. This case report may have an impact on many pediatric neurologists.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

Dr. Fujita collected and analyzed the data and drafted and revised the manuscript. Dr. Imataka, Prof. Yoshihara, and Prof. Takanashi interpreted the data and critically revised the manuscript for important intellectual content. All authors have approved the final manuscript and agree to be accountable for all aspects of the work.

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Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Informed Consent

Written informed consent was obtained from the parents of the patient to publish this case report (including all data and images).

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