Difficulties in Diagnosis Acute Necrotizing Encephalopathy of Childhood: A Case Report

Setyo Handryastuti, MD, PhD,1 Sisca Silvana, MD,2 Reyhan Eddy Yunus, MD, MSc,3 Iqbal Taufiqurrachman, MD,1 and Achmad Rafli, MD1

Abstract
Acute necrotizing encephalopathy of childhood (ANEC) is a rare condition of encephalopathy which commonly occurs in healthy children. This case report will discuss the diagnostic approach in a female child, three years old, with neurologic deficits. The diagnostic approach of ANEC consists of clinical manifestation, laboratory examination, cerebrospinal fluid (CSF) analysis, and neuroimaging interpretation. The patient had high liver enzyme, normal CSF analysis with appearances of edema, hemorrhage and necrosis in serial brain magnetic resonance imaging (MRI).

Keywords
acute necrotizing encephalopathy of childhood, ANEC, encephalopathy

Introduction
Acute necrotizing encephalopathy of childhood (ANEC) is a rare and specific type of encephalopathy commonly occurring in Japan, Taiwan, and Korea.1,2 It occurs mainly in healthy children.3 Microorganisms such as influenza A virus, rubella virus, coxsackie 9, measles, herpes simplex virus (HSV), human herpes virus-6 (HHV-6), HHV-7, enterovirus, novel reovirus (MRV2Tou05), rotavirus, mycoplasma have been reported as the etiology of ANEC.2,4 The most common viral infection associated with ANEC is HHV-6 infection.4

Viral infection plays an essential role at the beginning of ANEC pathogenesis.4 Besides the external factors, individual vulnerability and alteration of genes might be involved in the pathogenesis of ANEC.4 Despite the most common etiology of ANEC is microorganisms, the mechanism of ANEC is not inflammatory encephalitis.4 Based on pathological examinations, the inflammation of the brain is minimal and not related to the abnormality of the brain parenchymal, even the polymerase chain reaction (PCR) from cerebrospinal fluid (CSF) sample positive for some viruses.4

In contrast, the other literature describes that proinflammatory cytokines such as IL-6, IL-1, and tumor necrosis receptor-1 were involved in the process of ANEC development.2 The common hypothesis that elaborates the pathogenesis of ANEC is cytokine storm. It is caused by the excessive immune response to viral infections.4

The neurological manifestations of ANEC are similar to other neurological diseases such as seizures, altered consciousness and focal neurological deficits. Therefore, the diagnosis of ANEC is troublesome and challenging. In order to supply the clinical diagnosis from the clinical findings, supporting examinations such as imaging and laboratory examinations are needed.

Case Description
A female child, three years old, 16 kg, had complaints of vomiting, weakness, and convulsion-like tremor at the right angle of the mouth a week before the admission. After a week in hospital...
care, the patient was discharged. A week later, the patient’s head tilted to the right while talking, and the patient was less active than before. Therefore, the patient was admitted to the hospital again to be evaluated with brain magnetic resonance imaging (MRI) and brain tissue biopsy.

The patient was diagnosed with tuberculoma based on first brain MRI, brain tissue biopsy and got regimens of antituberculosis therapy. A week after the patient got the anti-tuberculosis therapy, the patient’s condition worsened. The patient was consulted to the pediatric neurologist with general weakness, altered consciousness, and hand tremor.

The patient was admitted with fever (39 °C), Glasgow Coma Scale (GCS) was 7 (E2V2M3); pupils were asymmetric with slow response to the light, tetraparesis (the motoric strength were 1 of 5), increasing physiological reflexes; positive Babinsky with clonus, spastic, and hand tremorShe had high transaminases enzyme without proof of cytomegalovirus (CMV), HSV-1, HSV-2 syphilis, and tuberculosis infection.

First brain MRI (two weeks before admission) (Figure 1), showed hypointense lesion and hyperintense spots in T1W1, which became hyperintense dominance on T2W1 with perifocal edema. The size of the lesion is 7,8 × 8,1 × 7,9 cm in the corpus callosum and frontal lobe bilateral (with right dominance). The lesion adheres to the falx cerebri and bilateral lateral ventricle with compression to the anterior horn of the bilateral lateral ventricle. Another smaller lesion with the same characteristics was found in the left parietal lobe that adheres to the falx cerebri and bilateral lateral ventricle. This condition suggests glioblastoma with a differential diagnosis of necrotizing toxoplasma encephalitis. The brain tissue biopsy showed a gemicytotic cell adjacent to the edematous loose neutrophil stromal. A few parts of the tissue consisted of extensive necrotic tissue, which forms caseous necrosis with lymphocytes, macrophage, and epithelioid-like cell infiltration. The conclusion was a chronic inflammation in brain tuberculosis. The biopsy specimen was sent for a second opinion. The result showed a necrotic mass and inflammatory cells, suggesting an inflammatory process without malignancy or tuberculosis.

The patient was still treated with anti-tuberculosis, corticosteroid, anti-convulsant, antipyretic, 20% mannitol for high intracranial pressure management.

On the 3rd day of the hospitalization, the GCS was improved (E4V2M3). The second brain MRI was done (Figure 2). The lesions found in the subcortical and juxtacortical of the bilateral fronto-temporo-parietal, right occipital, bilateral parieto-occipital lobes, the trunk of the corpus callosum, bilateral head of the caudate nucleus, part of the putamen and bilateral of the globus pallidus. These lesions were followed by the relatively stable early subacute of the hemorrhage component at the lesion, located at the bilateral head of the caudate nucleus, part of the putamen, and bilateral globus pallidus. There was also the addition of cortical laminar necrosis in the frontal and bilateral parietal lobes. On the third week of hospitalization, the clinical condition remained.

Examination of serum showed the negativity of anti-Histoplasma, aspergillus, autoimmune panel for encephalitis, and Ab MOG. The patient showed improvement with GCS 13 (E4V4M5) and slight tetraparesis after five months of discharge.

Discussion
Acute necrotizing encephalopathy of childhood (ANEC) is a rare case with common neurological manifestation with an uncertain mechanism. Based on report from Wu X, et al (2015), the mechanism of ANEC is led from cytokine storm. The accumulation of proinflammatory cytokines from excessive immune response will cause the systemic inflammatory response syndrome (SIRS), which manifests as acute renal failure, liver dysfunction, disseminated intravascular coagulation and shock. In addition, this condition will lead to brain injury caused by increased vessel wall permeability without any vessel disruption.

Initially, ANEC was reported as a disease with geographic predilection. However, the relationship between gene
susceptibility and ANEC (missense mutations in the gene encoding the nuclear pore protein Ran Binding Protein 2 or RANBP2) shows that ANEC is a disease with an inherited disposition. In addition, Shinohara et al found another gene associated with ANEC, which is the carnitine palmitoyl transferase II (CPT II) gene. The alteration of CPT II will decrease its enzymatic activities that reduced the utilization of energy by mitochondrial oxidation during high-grade fever and cause the increase of vascular wall permeability and development of brain edema.4

Acute necrotizing encephalopathy of childhood (ANEC) is a rare case, which is the first case in our institution. The first diagnosis was tuberculoma based on brain MRI and biopsy. However, the condition was not improved after the therapy. Then, the finding’s change on the second brain MRI was not the course of the tuberculoma. The approach diagnosis for ANEC was based on specific criteria by Mizuguchi, which consist of symptoms of viral infection followed by encephalopathy with rapid onset of impaired consciousness and immediate onset of convulsion, without pleocytosis in CSF, evidence of symmetric multifocal brain lesions, increase of serum aminotransferase, and there is no explanation for another diagnosis with similar presentation.5

The clinical manifestation of ANEC consists of fulminant symptoms such as the immediate onset of convulsion, altered consciousness, vomiting, and impaired hepatic function.2 In ANEC survivors, there are three stages during the clinical courses: prodromal stage, acute encephalopathy, and recovery stage.4 The prodromal symptoms were caused by different viral infections.4 These symptoms are fever, upper respiratory

Figure 1. Axial view of brain MRI.

Figure 2. (Left) Transversal, (Right) Coronal View of Brain MRI.
Data from 10 of 12 subjects diagnosed with ANEC who had the CSF analysis describes normal cell count, no growth of bacteria in CSF culture, and negative viral infection in CSF analysis. The CSF analysis of this patient has similar characteristics from subjects in the literature which meet one of the criteria of ANEC.

The evidence of symmetric multifocal brain lesions is one of the criteria of ANEC. The primary appearance of ANEC in neuroimaging is the multifocal, symmetric brain lesion in gray and white matter. The lesions can spread into the thalamus, brainstem, the white matter of the cerebrum and cerebellum. Bashiri F, Al S, et al (2020) reported that 5 of 12 subjects with ANEC (41.7%) had brainstem involvement.

However, the neuroimaging appearance of ANEC is characterized by dynamic changes within the clinical course. These dynamic changes are caused by pathophysiological changes from the edema, hemorrhage, and necrosis of the brain tissue. The neuroimaging appearance of the patient could be improved or regression. On the MRI T1-weighted imaging (T1WI), the acute necrotizing encephalopathy was found with the hyperintense structure in the center surrounded by the hypointense structure. In contrast, the T2-weighted imaging (T2WI) will show the hypointense structure, surrounded by a hyperintense structure.

The typical appearance of neuroimaging in ANE is the concentric or laminar structure, tricolor pattern, or target-like appearance. The center of the lesion is hyperintense, and the surrounding lesion is hypointense because of cytotoxic edema in the center and vasogenic edema in the periphery. Besides that, the small petechial hemorrhage also seen in the MRI T2WI.

The first patient’s brain MRI was not considered as ANEC. The lesions are located on the corpus callosum, bilateral frontal lobe (with right dominance), cerebral falk, bilateral lateral ventricles, and nodules in the left frontal, bilateral parietal, and left temporal lobes. These found still do not fulfill the criteria of ANEC, which must be symmetrical multifocal lesions.

The diagnosis of the ANEC considered after the second brain MRI, which showed the lesion at subcortical and juxta-cortical located in the bilateral fronto-temporo-parietal, right occipital, bilateral parieto-occipital lobes, and bilateral head of the caudate nucleus, in the part of the putamen and the bilateral of globus pallidus without mass effect. From these descriptions of the lesion, the patient’s brain MRI shows a symmetrical multifocal lesion. The other findings also support the diagnosis, which is an early subacute of hemorrhage component in the lesion of the bilateral head of caudate nucleus with cortical laminar necrosis at the frontal and the bilateral of parietal lobes. Hemorrhage and cortical laminar necrosis are the typical appearances of ANEC.

The last criteria for ANEC is no explanation for another diagnosis with a similar presentation. Differential diagnoses of ANEC were acute disseminated encephalomyelitis (ADEM), Japanese encephalitis (JE), and leishmaniasis. The basic difference between ADEM with this patient is no pleocytosis in CSF analysis. Finding lesions in the brain on the brain infection, gastroenteritis, and skin erythema. A retrospective review from the 12 patients with ANEC showed the preceding symptoms were fever, upper respiratory tract infection, diarrhea, vomiting, headaches, and chest infection. In this case, the only symptom which occurs in this patient is vomiting.

In line with the progression of ANEC lesion, impaired brain function is involved, which present with altered consciousness, convulsion, and focal neurological deficit. Bashiri F et al (2020) reported the presenting symptoms in 12 children with ANEC, which were altered consciousness (8/12), convulsion (8/12), and ataxic gait (1/12). In this case, the clinical manifestations of the patient are atypical from ANEC, such as general weakness, hand tremor, a convulsion-like mouth tremor and asymmetric of the pupils.

After acute encephalopathy, the patients with ANEC will enter the recovery stage. In this stage, the patient will survive with sequelae of neurological deficit or got full recovery from those disturbances. In this case, the neurological deficits were improved.

The laboratory findings of ANEC are varied. Several patients (41.7%) had thrombocytopenia and leukocytosis. One of the most helpful laboratory parameters to guide the diagnosis is the increase of AST and ALT. High liver enzyme was detected in 66.7% of patients diagnosed with ANEC. In addition, 6 of 12 subjects diagnosed with ANEC reported was positive for influenza A from the nasopharyngeal aspirate. In line with this evidence, the supporting data from the patient for the diagnosis of ANEC is high liver enzymes, which are ALT 493 u/L and AST 865 u/L, which were decreased during the hospitalization. The RT-PCR test of the nasopharynx specimen showed no evidence of any infection by viral or even bacteria. A high level of liver enzyme in the patient’s laboratory findings fulfill the criteria of ANEC.
MRI can exclude JE. Leishmaniasis can be excluded, because there were no hypoglycemia, hyperammonemia, or even metabolic acidosis.

The etiology and pathogenesis of acute necrotising encephalopathy of childhood (ANEC) remains unknown. Although influenza A virus, mycoplasma, herpes simplex virus, and human herpes virus-6 have been reported as common causative agents, it is now believed that this disease is most likely immune-mediated or metabolic. It has been reported that cytokines, such as tumor necrosis factor receptor-1, interleukin-1, and interleukin-6, could mediate the disease. There is no data lymphoma, toxoplasmosis, ANHLE cause ANEC.5,7

In conclusion, the diagnosis of ANEC is challenging because ANEC is a rare case with similar clinical manifestation to other neurological disease. Therefore, the diagnostic approach must consist of clinical symptoms of viral infection followed by acute encephalopathy, an increase of serum aminotransferase, no pleocytosis in CSF, neuroimaging showed symmetric multifocal lesion, and excluding the differential diagnosis. If the first brain MRI is not a conclusive finding for ANEC, then the serial brain MRI is needed.

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ORCID iDs
Setyo Handryastuti https://orcid.org/0000-0001-6968-9780
Reyhan Eddy Yunus https://orcid.org/0000-0001-9046-6303

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