Title
Hyper-Acute Necrotizing Encephalopathy-Like Syndrome in Early Pregnancy

Journal
The Neurohospitalist, 12(1)

ISSN
1941-8744

Authors
Holmes, Brandon B
Nolan, Amber
Wong, Charmian
et al.

Publication Date
2022

DOI
10.1177/19418744211008351

Peer reviewed

The Neurohospitalist
2022, Vol. 12(1) 90–95

DOI: 10.1177/19418744211008351
journals.sagepub.com/home/NHO
SAGE

Hyper-Acute Necrotizing Encephalopathy-Like Syndrome in Early Pregnancy

Brandon B. Holmes, MD, PhD[1], Amber Nolan, MD, PhD[2], Charmian Wong, BS, MHS[1], and Chung-Huan Sun, MD[1,3]

Abstract

Acute necrotizing encephalopathy (ANE) is a rare and life-threatening disease. It is caused by a cytokine-mediated injury to the brain with characteristic hemorrhagic and edematous lesions involving the bilateral thalami, brainstem, and other subcortical structures. The disease is commonly associated with antecedent viral triggers such as influenza, parainfluenza, and more recently, SARS-CoV-2, with subsequent neurologic deterioration occurring within days to weeks. Here, we present a case of a pregnant adult woman who developed a hyperacute form of ANE, progressing to brain death within 36 hours of symptom onset. Her diagnosis was confirmed via brain imaging, CSF studies, and neurohistopathological analysis. This case highlights the importance of establishing an early diagnosis for this under-recognized disease, and also suggests an association between ANE and early pregnancy.

Keywords

neuroinflammation, infection, cytokine storm, neuropathology

Introduction

Acute necrotizing encephalopathy (ANE) is a rare and devastating disease characterized by fever, vomiting, seizures, and impaired consciousness. The disease was first described in 1995 among a cohort of Japanese children,[1] but it is now recognized to occur worldwide and to even affect adults, albeit rarely.[2] Radiographically, the disease is highly conserved and features symmetric hemorrhagic lesions of the bilateral thalami, putamen, cerebellum, and brainstem.[3] Additionally, ANE has both sporadic and genetic subtypes. The genetic form of ANE is mediated by missense mutations in *RANBP2* which render individuals susceptible to multiphasic disease attacks.[4,5] The sporadic form is often triggered by antecedent respiratory tract infections associated with influenza A, influenza B, H1N1, human herpes virus 6, parainfluenzae, and more recently, SARS-CoV-2.[6-8] Given the current COVID-19 pandemic and the impending 2020-2021 influenza season, both of which can serve as pathogenic triggers, it is increasingly important to understand the clinical and pathological manifestations of this under-recognized disease.

Here, we describe a case of a previously healthy adult female, who was diagnosed with an ANE-like syndrome that progressed to fulminant cerebral edema and herniation within 36 hours of symptom onset. The patient was 5 weeks pregnant, but had no known concomitant viral triggers or underlying immunological conditions. We performed an extensive workup including serologic, radiographic, and histopathologic studies. To our knowledge, this is the first reported case of a hyperacute form of ANE that evolved within such a dramatic timeframe.

Case Description

A healthy 37-year old woman at 5-weeks gestation presented to the emergency department with altered mental status. The night prior to presentation, the patient was in her usual state of health. Upon wakening, the patient was found to be confused and unable to speak. She had emesis en route to the ED, and upon arrival, had a Glasgow Coma Scale of 7, diffuse rigidity, hyper-reflexia, and abnormal eye movements. Her past medical history was significant for a prior 1 week confusional episode with amnesia attributed to a UTI 1 year prior, and a recent spontaneous abortion earlier in the year. Per

[1] Department of Neurology, University of California, San Francisco, CA, USA
[2] Department of Pathology, University of California, San Francisco, CA, USA
[3] Neuroscience Institute, The Queen's Medical Center, Honolulu, HI, USA

Corresponding Author:
Chung-Huan Sun, Department of Neurology, University of California, San Francisco, CA 94143, USA.
Email: chsun@queens.org

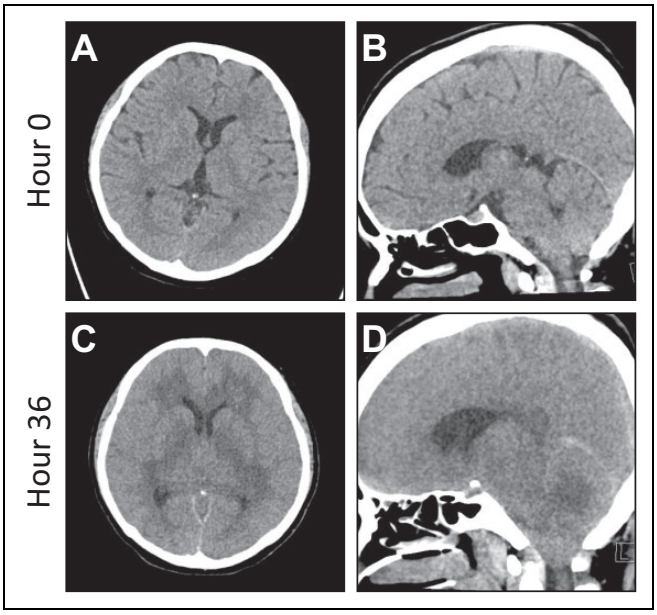

Figure 1. Non-contrast head CT on arrival to the emergency department (A, B) and 36 hours later (C, D). Initial CT scan, axial (A) and sagittal (B) cuts, demonstrated a small hypodensity in the left frontal lobe; there was no observed cerebral edema. Thirty-six hours later, a repeat non-contrast head CT, axial (C) and sagittal (D) cuts, revealed extensive and diffuse cerebral edema with associated mass effect, effacement of the sulci, cisterns, and the third and fourth ventricle, and bilateral uncal and tonsillar herniation.

family discussion, there were no recent URI symptoms, sick contacts, ingestions, or prescription or recreational drug use.

On mental status testing, she was unresponsive with eyes closed, briefly opening to tactile stimulation, not attending or following commands, and not verbalizing. She had horizontal roving eye movements without nystagmus. Her pupils were reactive and she had an intact corneal, cough, and gag reflex. She had diffuse appendicular rigidity and noxious stimulation elicited flexor and extensor posturing of the upper and lower extremities, respectively. She had hyper-reflexia in the biceps, triceps, patellas, and Achilles tendons, as well as upgoing toes bilaterally. She was intubated for airway protection.

A non-contrast head CT demonstrated hypodensities in the bilateral cerebellar vermis and temporal lobes and in the left frontal lobe; there was no significant cerebral edema (Figure 1A and B). A brain MRI with and without contrast revealed symmetric abnormal restricted diffusion, FLAIR signal abnormality, and hemorrhage involving the thalami, basal ganglia, midbrain, corpus callosum, periventricular white matter, hippocampii, and cerebellar hemispheres (Figure 2) without evidence of thrombus. The patient underwent an extensive infectious disease workup including blood and fungal cultures, influenza A/B PCR, respiratory viral panel, SARS-CoV-2 PCR and serologies, and HIV testing, all of which were negative. CSF analysis demonstrated colorless fluid with an opening pressure of 24 cmH_20, glucose concentration of 66 mg/dL (serum glucose, 129 mg/dL), elevated protein concentration of 240 mg/dL (normal range, 15-45 mg/dL), 4 white blood cells, 7 red blood cells, CSF IgG index of 0.64 (normal range, 0.28 - 0.66), and 0 unique oligoclonal bands. CSF was negative for a broad infectious disease workup (Table 1). Mass spectrometry-based toxicology tests were unrevealing. Tests for autoimmune disease were largely negative, except for mildly elevated erythrocyte sedimentation rate and C-reactive protein, positive anti-nuclear antibodies (titer 1:40), low complement levels, and a possible positive lupus anticoagulant. Autoimmune encephalitis panels from both serum and CSF were negative (Table 1). An EEG demonstrated diffuse slowing with mild superimposed high frequency elements but no seizures.

Out of concern for acute necrotizing encephalopathy versus acute hemorrhagic leukoencephalitis, the patient was started on methylprednisolone 1 gm daily. She was treated empirically with broad-coverage anti-bacterial and anti-viral agents. At approximately 36 hours after presentation, the patient's examination revealed mid-sized and fixed pupils bilaterally, loss of corneal, vestibulo-ocular, cough, and gag reflexes, and spontaneous flexor posturing of the arms. She was given mannitol 100 gm and 60 mL of 23% normal saline without return of brainstem reflexes. A repeat non-contrast head CT showed extensive cerebral edema with tonsillar and uncal herniation (Figure 1C and D). Regarding her pregnancy, β-HCG downtrended and she passed clots consistent with a spontaneous abortion. Upon allowing family members sufficient time to arrive at bedside, the patient was formally declared brain dead per our institutional guidelines.

Post autopsy, neuropathologic examination identified diffuse and severe cerebral edema with extensive tissue necrosis and prominent involvement of the periventricular white matter (Figure 3A), basal ganglia, and thalamus. Microscopy showed widespread hypoxic-ischemic changes throughout the brain characterized by acute neuronal necrosis in the gray matter (Figure 3B) and oligodendrocyte apoptosis in the white matter (Figure 3C). Perivascular demyelination could not be evaluated due to a generalized loss of myelin in the white matter secondary to severe ischemia. However, the periventricular white matter and basal ganglia displayed prominent petechial perivascular hemorrhages with varying degrees of endothelial cell necrosis and macrophage accumulation, but without an accompanying lymphocytic inflammatory infiltrate (Figure 3D-F). Vessel thrombosis was absent.

Discussion

The clinical course of ANE is diverse with a pattern of progression beginning with a prodromal stage, followed by acute encephalopathy, and eventually, recovery – all of which spans a period of days to weeks.[3] Here, we report a case of a 37 year-old female who developed a hyper-rapid and fulminant form of acute necrotizing encephalopathy without a documented prodrome that progressed to brain death within 36 hours of symptom onset.

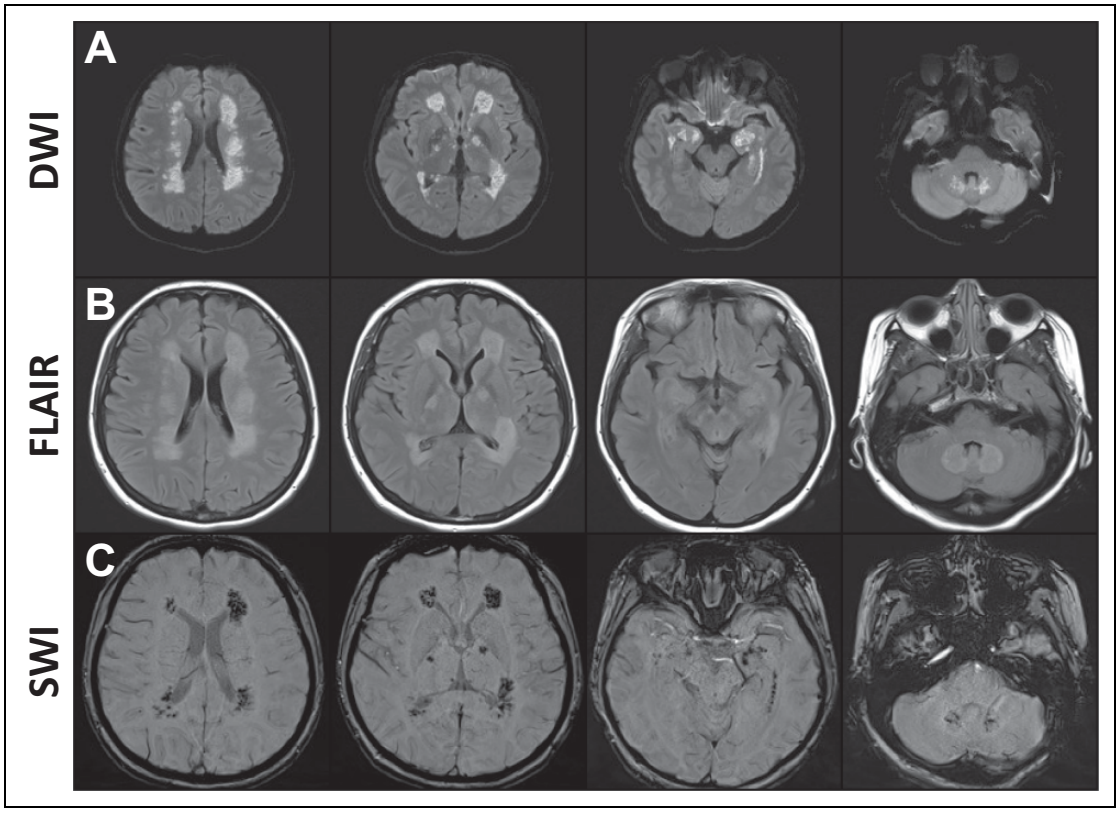

Figure 2. A brain MRI at 12 hours of presentation revealed symmetric abnormal restricted diffusion (A), FLAIR signal abnormality (B), and hemorrhage (C) involving the periventricular white matter, thalamus, basal ganglia, midbrain, corpus collosum, and hippocampii.

The cardinal radiographic features of ANE are the symmetric, multi-focal, and hemorrhagic brain lesions involving the bilateral thalami and deep nuclei.[3] Pathologically, these changes correlate with edema, necrosis of the gray and white matter, and blood-brain barrier compromise.[1] Therefore, ANE must be differentiated from other acute disorders that produce bilateral deep nuclei lesions such as neurometabolic disorders, Wernicke's encephalopathy, carbon monoxide poisoning, thrombosis, and acute hemorrhagic leukoencephalitis. Given the patient's normal metabolic profile and lack of environmental exposures, metabolic and toxic etiologies were safely ruled out. Thrombotic mechanisms are also unlikely given lack of evidence on MRI, the intact vessels on histopathology, and more extensive lesion distribution than those supplied by a single artery or vein. Finally, her disease process is not compatible with an inflammatory disorder such as acute hemorrhagic leukoencephalitis given the presence of CSF albuminocytologic dissociation, the striking symmetry of the brain lesions, and the absence of perivascular and meningeal lymphocytic inflammatory infiltrate.[1,5,9,10] Mechanistically, ANE is distinct from neuroimmunological conditions such as acute hemorrhagic leukoencephalitis or viral encephalitis as there is no direct invasion of immune cells or pathogens into the ANE brain parenchyma. Rather, neuroinflammation is thought to be mediated at a distance through a systemic cytokine surge in response to environmental or viral triggers resulting in damage to the blood brain barrier and neurotoxicity.[3] Elucidating the specific cytokine profile that mediates this disease process remains a key area of investigation.[11]

In addition to the hyper-acuity of the patient's presentation, our case illustrates other illuminating features of ANE including (1) the absence of an antecedent infection, (2) co-occurrence during the first trimester of pregnancy, and (3) the possibility of recurrent prior disease episodes. While ANE is typically considered a parainfectious disease triggered by upper respiratory viruses, our patient did not have infectious disease symptoms and a comprehensive infectious disease evaluation was unrevealing (Table 1). This raises the possibility that other immune system perturbations may have incited this syndrome. For example, the maternal immune system during pregnancy is highly complex with phases of immune activation and suppression during various gestational ages.[12] Indeed, with the exception of rheumatoid arthritis, many autoimmune diseases are worsened during pregnancy including autoimmune thyroiditis, immune thrombocytopenia, and APLS; and at least 4 cases of limbic encephalitis during pregnancy have been reported of which all occurred during the first half of gestation.[13,14] Notably, the first trimester of pregnancy is marked by heightened immune activation mediated by a dramatic increase in the number of $CD56^{+}$

Table 1. Comprehensive Laboratory Results From the Patient's Diagnostic Evaluation. For Tests That Were Repeated During Hospitalization, Only the First Test Result is Presented in the Table.

Test name	Biologic fluid	Patient value	Normal range
Metabolic			
Sodium	Serum	139	136 - 145 mmol/L
Glucose	Serum	129	70 - 199 mg/dL
White Blood Cell Count	Serum	12.5	4.0 - 11.6 x 10^9/L
Hemoglobin	Serum	13.0	11.7 - 15.7 g/dL
Aspartate aminotransferase	Serum	18	10 - 41 U/L
Alanine aminotransferase	Serum	23	7 - 35 U/L
Alkaline phosphatase	Serum	88	42 - 98 U/L
TSH	Serum	1.06	0.37 - 4.42 μU/mL
Creatine Kinase	Serum	76 U/L	26 - 140 U/L
β-Human Chorionic Gonadotropin	Serum	12.24	< 5 U/L
Protein	CSF	242	20 - 60 mg/dL
Glucose	CSF	66	40 - 70 mg/dL
White Blood Cell Count	CSF	4	< 6 x 10^6/L
Toxic			
Tylenol	Serum	Not Detected	< 10 mg/dL
Salicylate	Serum	Not Detected	< 25 mg/dL
Ethanol	Serum	Not Detected	< 10 mg/dL
Heavy metal screen	Serum	Negative	Negative
Comprehensive Serum Toxicology (LC-MS)	Serum	Negative	Negative
Infectious			
HIV 1/2 Antigen and Antibodies	Serum	Negative	Negative
Cultures, bacterial and fungal	Serum and CSF	Negative	Negative
Influenza A/B	Nasopharynx	Negative	Negative
Respiratory Viral Panel	Nasopharynx	Negative	Negative
COVID-19 RNA	Nasopharynx	Not Detected	Not Detected
COVID-19 IgG and IgM	Serum	Not Detected	< 50 RFU
VZV PCR	CSF	Not Detected	Not Detected
HSV1 PCR	CSF	Not Detected	Not Detected
HSV2 PCR	CSF	Not Detected	Not Detected
EBV PCR	CSF	Not Detected	Not Detected
CMV PCR	CSF	Not Detected	Not Detected
Toxoplasma IgG	CSF	Negative	Negative
Cryptococcal Antigen	CSF	Negative	Negative
Metagenomics Next-Generation Sequencing	CSF	Negative	Negative
Inflammatory			
Erythrocyte Sedimentation Rate	Serum	21.0	< 15 mm/hr
C-Reactive Protein	Serum	55.2	< 3.1 mg/L
Protein C	Serum	155	83 - 168%
Protein S	Serum	57	57 - 131%
C3	Serum	33	86 - 184 mg/dL
C4	Serum	27	12 - 40 mg/dL
Anti-Nuclear Antibodies	Serum	1:40 (diffuse)	< 40
Anti-Proteinase 3 Antibody	Serum	< 20.0	< 20.0 CU
Anti-Myeloperoxidase Antibody	Serum	< 20.0	< 20.0 CU
Rheumatoid Factor	Serum	6.8	< 40.0 IU/mL
α-MOG	Serum	Negative	Negative
α-AQP4	Serum	Negative	Negative
Autoimmune Encephalitis Panel	Serum	Negative	Negative
Autoimmune Encephalitis Panel	CSF	Negative	Negative
IgG Index	CSF	0.64	0.28 - 0.66
Oligoclonal Bands	CSF	0	0 - 1

uterine natural killer (uNKs) cells within the decidua.[15] While considered less cytotoxic than peripheral blood NK cells, uNKs are a rich source for cytokines including TNF-α, IFN-γ, and IL-1β. Given uNK's role in vascular remodeling, they are heavily concentrated near the spiral arteries where they may serve as major reservoir for peripheral cytokine secretion.[16]

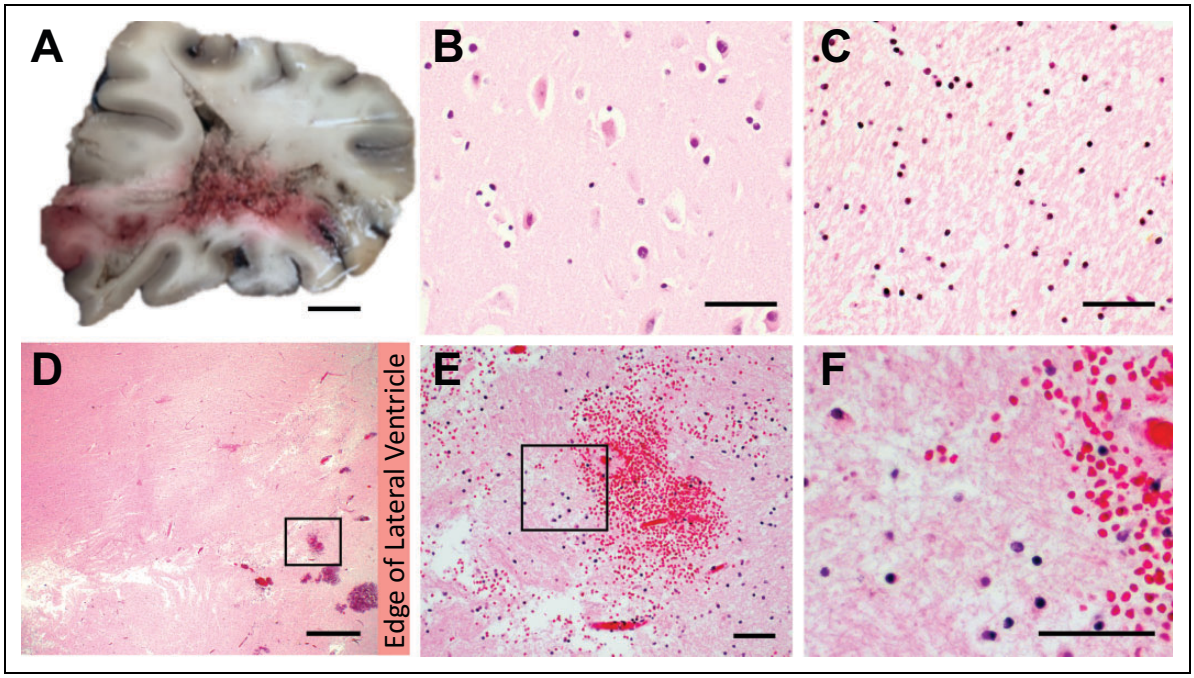

Figure 3. (A) Coronal section of the right frontal brain demonstrating prominent perivascular tissue destruction. (B) Representative H&E image of cortical gray matter highlighting acute neuronal necrosis. (C) Representative H&E image of the white matter showing the diffuse pallor associated with myelin loss and patchy apoptosis of oligodendrocytes. (D) Low power H&E image of the periventricular white matter demonstrating increasing degree of tissue destruction and the presence of petechial hemorrhages near the lateral ventricle. (E) Higher power view of black box in panel D showing the perivascular hemorrhage surrounding a necrotic vessel. (F) Higher power view of black box in panel E showing the presence of scattered macrophages, but the absence of an inflammatory infiltrate. Scale bars: 50 μm (B, C, E, F), 500 μm (D), 1 cm (A).

Strikingly, flow cytometry from peripheral leukocytes of patients with ANE reveals a high abundance of $CD56^{+}$ NK cells implying a possible role for NK biology in this disease.[17]

It is intriguing to speculate that, in a susceptible host, the local immune environment of pregnancy could predispose to ANE. Along these lines, our patient had at least one prior episode of a severe confusional state with prolonged amnesia, reportedly from a UTI, which may suggest that she harbored an innate predisposition to ANE. Indeed, susceptibility loci for ANE are well established and include mutations in *RANBP2*, *DRB/HLA DQB*, *CPT2* and likely others.[4,18,19] For future cases, we recommend both genetic evaluation of these gene candidates as well as peripheral and CSF cytokine profiling to further investigate the molecular associations of this disease, both of which are limitations to our current report. Early recognition and diagnosis may also provide opportunities to pursue targeted treatments with immunomodulatory agents such as tocilizumab or infliximab when patients are refractory to high-dose steroids. Mechanistic understanding of ANE, including the potential impact of pregnancy, will be required for the prompt diagnosis and early intervention of this devastating disease.

Ancillary Statements

Per our institutional review board protocol, we obtained written consent from the patient's surrogate decision maker to draft, submit, and publish this case report.

Author Note

Chung-Huan Sun is also affiliated with the Neuroscience Institute, The Queen's Medical Center, Honolulu, HI, USA.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Brandon Holmes receives grant support: NIH 2R25NS070680.

ORCID iD

Brandon B. Holmes https://orcid.org/0000-0002-1153-840X

References

1. Mizuguchi M, Abe J, Mikkaichi K, et al. Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. *J Neurol Neurosurg Psychiatry*. 1995;58(5):555-561.
2. Abdelrahman HS, Safwat AM, Alsagheir MM. Acute necrotizing encephalopathy in an adult as a complication of H1N1 infection. *BJR Case Rep*. 2019;5(4):20190028.

3. Wu X, Wu W, Pan W, Wu L, Liu K, Zhang HL. Acute necrotizing encephalopathy: an underrecognized clinicoradiologic disorder. *Mediators Inflamm*. 2015;2015:792578.
4. Neilson DE, Adams MD, Orr CM, et al. Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2. *Am J Hum Genet*. 2009;84(1):44-51.
5. Levine JM, Ahsan N, Ho E, Santoro JD. Genetic acute necrotizing encephalopathy associated with ranbp2: clinical and therapeutic implications in pediatrics. *Mult Scler Relat Disord*. 2020; 43:102194. Epub 2020 May 15.
6. Dixon L, Varley J, Gontsarova A, et al. COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e789.
7. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. *Radiology*. 2020;296(2): E119-E120.
8. Virhammar J, Kumlien E, Fallmar D, et al. Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. *Neurology*. 2020;95(10):10.1212/WNL. 0000000000010250. Epub 2020 Jun 25.
9. Mastroyianni SD, Gionnis D, Voudris K, Skardoutsou A, Mizuguchi M. Acute necrotizing encephalopathy of childhood in non-Asian patients: report of three cases and literature review. *J Child Neurol*. 2006;21(10):872-879.
10. Waak M, Malone S, Sinclair K, et al. Acute hemorrhagic leukoencephalopathy: pathological features and cerebrospinal fluid cytokine profiles. *Pediatr Neurol*. 2019;100:92-96.
11. Lin YY, Lee KY, Ro LS, Lo YS, Huang CC, Chang KH. Clinical and cytokine profile of adult acute necrotizing encephalopathy. *Biomed J*. 2019;42(3):178-186.
12. Aghaeepour N, Ganio EA, McIlwain D, et al. An immune clock of human pregnancy. *Sci Immunol*. 2017;2(15):eaan2946.
13. Adams Waldorf KM, Nelson JL. Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. *Immunol Invest*. 2008;37(5):631-644.
14. Gildersleeve K, Kass J, Tomko S. Multiple autoimmune antibody limbic encephalitis: a case in a pregnant woman. *Neuroimmunol Neuroinflammation*. 2015;2(1):46-48.
15. Bulmer JN, Morrison L, Longfellow M, Ritson A, Pace D. Granulated lymphocytes in human endometrium: histochemical and immunohistochemical studies. *Hum Reprod*. 1991;6(6):791-798.
16. Bulmer JN, Williams PJ, Lash GE. Immune cells in the placental bed. *Int J Dev Biol*. 2010;54(2-3):281-294.
17. Kubo T, Sato K, Kobayashi D, et al. A case of HHV-6 associated acute necrotizing encephalopathy with increase of CD56bright NKcells. *Scand J Infect Dis*. 2006;38(11-12):1122-1125.
18. Seo HE, Hwang SK, Choe BH, Cho MH, Park SP, Kwon S. Clinical spectrum and prognostic factors of acute necrotizing encephalopathy in children. *J Korean Med Sci*. 2010;25(3):449-453.
19. Kumakura A, Iida C, Saito M, Mizuguchi M, Hata D. Pandemic influenza a-associated acute necrotizing encephalopathy without neurologic sequelae. *Pediatr Neurol*. 2011;45(5):344-346.