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CASE REPORT

A Case of Acute Necrotic Encephalopathy Associated with Influenza A Virus in Adults

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SUMMARY

Background: **Acute necrotizing encephalopathy is a rare acute, explosive, and severe form of encephalopathy that predominantly occurs in children; however, it is infrequent in adults. The patient is typically caused by viral infection, with rapid onset of fever, convulsion, disturbance of consciousness, and other symptoms. It presents symmetrical, multifocal, involving bilateral thalamic damage and other typical imaging features. This disease has a poor prognosis and can lead to severe neurological symptom sequelae such as epilepsy, coma and even necrotic encephalopathy [1], and its fatality rate can be as high as 52% [2]. Early identification and timely treatment are the key to reducing the fatality rate.**

Methods: **Laboratory routine examinations, encompassing blood routine, biochemistry, influenza PCR, cytokines, and blood gas, were carried out for the patient. Moreover, imaging examinations such as skull CT were also conducted. Based on the combination of clinical symptoms, the patient was diagnosed and treated.**

Results: **Auxiliary examination: The white blood cell count was 2.33 x 10^9/L, the lymphocyte percentage was 62.3%, the platelet count was 83.0 x 10^9/L, the CRP was 7.4 mg/L, the PCR was positive, the partial pressure of oxygen was 59.3 mmHg, the partial pressure of carbon dioxide was 26.6 mmHg, the lactic acid was 6.98 mmol/L, the ALT was 1,892 U/L, the AST was 6,804 U/L, the IL6 was > 1,1836 pg/mL, the plasma D-dimer determination was > 35.20 mg/L, the 3P test was positive, the PT was > 180 sec, and the fibrinogen was 0.1 g/L. Skull CT revealed a small number of low-density changes in the bilateral thalamus. Treatment: Oral tube intubation, ventilator-assisted ventilation, cranial pressure reduction, pressure enhancement, methylprednisolone injection for anti-inflammation, plasma and platelet transfusion, and oseltamivir capsule for antiviral purposes. After MDT consultation, acute necrotic encephalopathy was considered, and intravenous shock therapy with immunoglobulin and methylprednisolone needle was added. Forty-eight hours after admission, the patient's condition deteriorated, multiple organ failure occurred, and the family gave up treatment.**

Conclusions: **Acute necrotizing encephalopathy is infrequent in adults, prone to being overlooked and misdiagnosed, and the disease progresses rapidly with a high fatality rate. Clinicians should enhance the early recognition ability of the disease and actively administer glucocorticoid treatment combined with immunoglobulin, which is conducive to a better prognosis for patients.**

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KEYWORDS

acute necrotic encephalopathy, adult, influenza A virus, disturbance of consciousness

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CASE PRESENTATION

The patient, a 33-year-old male, had been in good health previously. Two days prior, he manifested fever, chills, recurrent dry cough, self-administered antipyretic drugs, and presented with symptoms such as unconsciousness, shortness of breath, generalized sweating, and urinary and fecal incontinence. He was transported by ambulance to the emergency rescue room of our hospital. Upon admission for physical examination, the patient's body temperature was 40.4℃, heart rate 166 beats per minute, blood pressure 105/49 mmHg, finger pulse oxygen 89%, shallow coma, bilateral pupil diameter of 3 mm, sluggish light reflex, and bilateral Pap sign negative. After 40 minutes, the patient had shallow, short breaths, further decreased oxygen saturation and bilateral pupil diameter of 5 mm, sluggish light reflex. He was sent to the EICU after endotracheal intubation. The patient rapidly entered a deep coma, pupil of 7 mm, no light reflex and sustained bleeding after blood collection. He had low urine output, decreased blood pressure, and scattered specks could be observed on the limbs. Auxiliary examinations: White blood cell count: 2.33 x 10^9/L, lymphocyte percentage: 62.3%, platelet count: 83.0 x 10^9/L, CRP: 7.4 mg/L, partial pressure of oxygen: 59.3 mmHg, partial pressure of carbon dioxide: 26.6 mmHg, lactic acid: 6.98 mmol/L, ALT: 1,892 U/L, AST: 6,804 U/L, IL6: > 1,183,6 pg/mL, plasma D-dimer determination: > 35.20 mg/L, INR: 1.58, TPI: 1.87 ng/mL. Blood ammonia and anti-nuclear antibody spectra were normal. Skull CT revealed a small number of low-density changes in the bilateral thalamus. Due to the rapid progression of the patient's illness, lumbar puncture and MRI examinations were not performed. Therapeutic course: After treatment with norepinephrine for pressure enhancement, fluid expansion, glycerol fructose for reducing cranial pressure, acid correction, methylprednisolone injection for anti-inflammation, platelet and plasma transfusion, and liver protection, platelets decreased to 23.0 x 10^9/L, PT > 180 seconds, INR increased to 4.35, plasma D-dimer determination remained > 35.20 mg/L, and the 3P test was positive. Fibrinogen was 0.1 g/L. Combined with shock and multiple systemic ecchymosis, the patient developed DIC. Then, the PCR was positive for influenza, a virus, and oseltamivir capsules were added for antiviral treatment. After MDT multidisciplinary consultation, the patient was diagnosed with acute necrotic encephalopathy. He was treated with immunoglobulin injection (3 g/day, 1 day) and methylprednisolone (1 g/day, 1 day). During the diagnosis and treatment process, the patient experienced oliguria, increased serum creatinine to 514 μmol/L, potassium ion to 5.87 mmol/L, multiple organ failures, and the survival rate was extremely low. The family gave up treatment 48 hours after admission.

DISCUSSION

Acute necrotizing encephalopathy (ANE) represents a rare form of acute, explosive, and severe encephalopathy. In 1995, Mizuguchi et al. [3] initially reported ANE, which mainly encompassed two types: one was the familial or recurrent ANE resulting from RANBP2 gene mutation [4,5], and the other was the sporadic ANE mainly caused by viral infection, particularly by influenza, HHV-6, COVID-19, and other viruses [5-7]. Currently, the pathogenesis of ANE remains unclear. The majority of scholars contend that a sharp increase in the level of cytokines following viral infection gives rise to a "cytokine inflammatory storm" within the human body [4], which can lead to acute liver injury, kidney failure, DIC, and other symptoms. Studies have revealed that the levels of IL-6 and TNF-α in the serum and cerebrospinal fluid of ANE patients are significantly elevated, and these cytokines will enhance vascular permeability and undermine the blood-brain barrier [8]. This results in plasma exudation, brain edema, spot-like bleeding, and the destruction of neurons and glial cells [9]. Mizuguchi et al. [10] proposed the following diagnostic criteria for ANE: 1) Acute encephalopathy symptoms, such as consciousness disturbance or convulsion, occur rapidly within 1 - 3 days after a virus-induced febrile illness; 2) Head imaging examinations (CT or MRI) indicated symmetrical and multiple lesions, which must be located in the bilateral thalamus; the supporting parts included periventricular white matter, internal capsule, putamen, brainstem, and cerebellum. 3) The number of cells in the cerebrospinal fluid increased, and the level of common proteins rose; 4) Serum aminotransferase increased to varying degrees, and blood ammonia was normal; 5) Other diseases, such as brain infection, metabolic, toxic, mitochondrial diseases, and autoimmune diseases, were excluded. At present, there is no specific treatment for this disorder, and a combination of intensive care, symptomatic treatment, and empirical treatment is typically employed. If it is caused by swine flu, early antiviral therapy is necessary, and immunosuppressants are actively utilized, especially those that inhibit the production of cytokines, including intravenous glucocorticoids, immunoglobulins, and plasma exchange. Hosie et al. [11] discovered that the use of IL6 receptor antagonists to block inflammatory storms within the first 24 hours of the disease had a favorable effect in the treatment of acute necrotizing encephalopathy in children. Compared with ANE in children, the prognosis of ANE in adults is relatively poor [12]. Yu Fang et al. [2] found that among the patients who died of ANE, the proportion of males was higher, the score of Glasgow Coma Scale was lower, and the level of IL-6 was correlated with brain stem injury. Serum IL-6 level might be a more useful laboratory indicator for the diagnosis of encephalopathy associated with influenza virus infection and the assessment of disease severity [13]. In this case, the patient was male with serum IL-6 >

11,836 pg/mL, and the prognosis was extremely poor, which was in line with literature reports.

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Declaration of Interest:
All authors declare that they have no competing interests.

References:

1. Abdel-Mannan O, Eyre M, Lobel U, et al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. JAMA Neurol 2020;77(11):1440-5. (PMID: 32609336)

2. Fang Y, Gao Q, Jin W, et al. Clinical characteristics and prognostic analysis of acute necrotizing encephalopathy of childhood: a retrospective study at a single center in China over 3 years. Front Neurol 2023;14:1308044. (PMID: 38178890)

3. 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):555-61. (PMID: 7745402)

4. 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. (PMID: 32426208)

5. AlQasim E, Alawfi A, Hamad A, Alghamdi F, Albaradi BA. Human Herpesvirus-6 Encephalitis Associated With Acute Necrotizing Encephalopathy in an Immunocompetent Child: A Case Report and Literature Review. Cureus 2023;15(6):e39897. (PMID: 37404398)

6. Geng C, Zhao W, Wang Z, et al. Acute necrotizing encephalopathy associated with COVID-19: case series and systematic review. J Neurol 2023;270(11):5171-81. (PMID: 37695531)

7. Cleuziou P, Renaldo F, Renolleau S, et al. Mortality and Neurologic Sequelae in Influenza-Associated Encephalopathy: Retrospective Multicenter PICU Cohort in France. Pediatr Crit Care Med 2021;22(11):e582-e587. (PMID: 33950890)

8. Galea I. The blood-brain barrier in systemic infection and inflammation. Cell Mol Immunol 2021;18(11):2489-501. (PMID: 34594000)

9. Weisheng H, Hui Z, Shuang W, et al. A sudden death due to acute necrotizing encephalopathy associated with influenza A virus infection: An autopsy case report. Leg Med (Tokyo) 2022;58: 102098. (PMID: 35662069）

10. Mizuguchi M, Yamanouchi H, Ichiyama T, Shiomi M. Acute encephalopathy associated with influenza and other viral infections. Acta Neurol Scand Suppl 2007:186:45-56. (PMID: 17784537)

11. Hosie PH, Lim C, Scott T, et al. Treatment of severe acute necrotizing encephalopathy of childhood with interleukin-6 receptor blockade in the first 24 hours as add-on immunotherapy shows favorable long-term outcome at 2 years. Brain Dev 2023;45(7): 401-7. (PMID: 36967317)

12. 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. (PMID: 31466711)

13. Aiba H, Mochizuki M, Kimura M, Hojo H. Predictive value of serum interleukin-6 level in influenza virus-associated encephalopathy. Neurology 2001;57(2):295-9. (PMID: 11468315)