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Hemorrhagic Necrotizing Encephalitis Secondary to Human Herpesvirus 3 Infection: A Case Report

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Abstract: Human herpesvirus type 3 is also known as varicella-zoster virus (varicella zoster virus, VZV). VZV causes chickenpox after primary infection in children and herpes zoster after infection in adults. The skin and mucous membranes are rarely involved in the central nervous system. Hemorrhagic necrotizing encephalitis is one of the most serious types of encephalitis. It is characterized by cerebral parenchymal hemorrhage and necrotic lesions and is usually triggered by severe infection, which is a virus or autoimmune reaction. HSV-1 is the main cause, but VZV-induced hemorrhagic necrotizing encephalitis is very rare and rarely reported at home and abroad. A case of hemorrhagic necrotizing encephalitis secondary to VZV infection was reported in this paper.

Keywords: Human Herpesvirus Type 3; Hemorrhagic Necrotizing Encephalitis; Antiviral Therapy; Immunotherapy.

1. Case Report

The patient was a 73-year-old male who was admitted to the Department of Neurology of our hospital on January 6, 2025 due to unconsciousness for 2 days. Two days before admission, the patient had no obvious cause of confusion, increased sleep, difficult to wake up in the daytime, unable to answer with family members after awakening, with fever, unknown maximum temperature, no nausea, vomiting, no convulsions, incontinence, etc. Visit the emergency department of our hospital to check the cranial CT: The density of the cerebral sickle and tentorium of the cerebellum is increased. It is recommended to check the SWI if necessary. Chest CT: Two-lung retrograde changes. Income from "consciousness disorder (to be checked)." The patient was fit. Physical examination after admission: T38.8℃, P76 times/min, R22 times/min, BP 139/79mmHg. The breath sounds of both lungs were thick, wet rales of both lungs could be heard, and no obvious positive signs were found in the heart and abdomen. Physical examination of nervous system: Coma, double pupil isometropia, slow light reflex, pain stimulation can show contraction of limbs, positive bilateral Babinski sign, positive meningeal stimulation sign, other nervous system examination does not cooperate. Initial diagnosis: Consciousness disorder to be investigated. After admission, nimodipine was given for vasospasm, mannitol dehydration and levetiracetam for epilepsy. Perfection after admission: ECG: 1.Sinus rhythm 2.Roughly normal ECG. Head DWI: No obvious abnormality. GCS: 7pts, NIHSS: 14pts, Caprini: 6pts Very high risk, APACHEII: 20pts. Considering the critical condition of the patient, the patient was transferred to Neurocritical Department for further diagnosis and treatment after consultation with Neurocritical Department after admission. Day 1: Complete blood gas analysis: PH: 7.46↑, carbon dioxide partial pressure: 33.77mmHg↓, oxygen partial pressure: 66.97mmHg↓, lactic acid: 2.74mmol/L↑; Blood analysis: NEUT: 80.50%%, lymphocyte: 11.90%%, neutrophil (NEUT#): 7.39×10^9/L, lymphocyte (LYMP#): 1.09×10^9/L; Rapid BNP: 956pg/ml; Five coagulation items: Prothrombin time (PT): 12.8 s, D- dimer: 3.05 mg/mL↑; Five myocardial enzymes: Lactate dehydrogenase: 256 .4U/L↑, alpha hydroxybutyrate dehydrogenase: 217 .6U/L↑, myoglobin: 203ng/mL↑. The patient's current consciousness disorder is to be investigated, except for subarachnoid hemorrhage, central nervous system infection, intracranial venous thrombosis, etc. Xuebijing shall be given to remove inflammatory factors, doxofylline to relieve asthma, nimodipine to prevent cerebral vasospasm, eprapiprazole sodium to protect the stomach, glycerol fructose to reduce cranial pressure, Lacosamide anti-epilepsy, oxycodone hydrochloride analgesia, remazolam benzene sulfonate sedation, piperacillin sodium tazobactam sodium to prevent infection, etc. Day 2, perfect lumbar puncture: Light yellow cerebrospinal fluid, cranial pressure: 220mmH2O. CSF WBC: 451.00×10^6/L, CSF sugar: 4.39mmol/L, CSF total protein: 292 .56 mg/dL. PCTs: 0.184ng/mL, considering the presence of CNS infection, perfecting NGSs, to be reported. Craniocerebral CT showed bilateral temporal lobe hematoma and peripheral low-density shadow. Mr plain scan +DWI was recommended (Fig. 1). Consider hemorrhagic necrotizing viral encephalitis, plus acyclovir antiviral therapy for 8 days. The patient was positive for influenza A virus antigen and was given anti-viral treatment with Marbarosavir tablets. On the 3rd day, the cranial CTV showed that the left transverse sinus, sigmoid sinus and left internal jugular vein were smaller than the contralateral one. Descriptive results of CSF exfoliation cytology: Lymphocytes: 37%, monocytes: 40%, activated lymphocytes: 2%, activated monocytes: 17%, red blood cells: Scattered distribution. Human Herpesvirus 3 (VZV) (1414882) (Fig.2). Therefore, the revised diagnosis was: (Hemorrhagic necrotizing) herpesvirus encephalitis (human herpesvirus type 3). Immunotherapy with human immunoglobulin infusion for 5 days. On the 4th day, the

level of consciousness of the patient was better than before, and the patient was able to open his eyes on his own initiative, obey some orders simply, and feel aphasia. Special ambulatory EEG: Roughly normal EEG, no abnormal discharge. Change Lacosamide to oral to prevent epilepsy. Sputum is not easy to cough out, oxygenation is poor, give broncho fiberscope suction sputum and meropenem anti-infection treatment. On the fifth day, the patient's consciousness improved, and he was able to express his headache autonomously. Pain stimulation showed pain expression, and reading instructions could be executed. Retest for influenza A virus antigen: Negative. Electromyography and electromyography: 1. Nerve conduction velocity measurement: The sensory conduction amplitude of bilateral median nerve and left ulnar nerve decreased; The distal extensor digitorum brevis of motor conduction of left common peroneal nerve was recorded with incubation period lengthening and amplitude decreasing, and the anterior tibial muscle was recorded with normal range. Sensory conduction velocity of left superficial peroneal nerve was slightly slower; The amplitude and velocity of sensory conduction of bilateral sural nerve decreased; No abnormal changes were found in the other examined nerves; 2.Reflex measurement: The bilateral tibial nerve H reflex did not elicit positive waveform; Measurement of incubation period prolongation by bilateral tibial nerve F wave 3.Electromyography: Spontaneous potentials are occasionally seen in the resting phase of the right tibial anterior muscle, and light and heavy contractions cannot be matched; There was no spontaneous potential in the resting period of the left tibial anterior muscle. Conclusion: Peripheral nerve damage in limbs (sensory fiber involvement). Gabapentin was given pain relief and nutritional nerve therapy. On the 8th day, the patient was clear- minded, aphasia sensation, good spirit, the inflammatory index was lower than before, meropenem was stopped, and ceftriaxone was adjusted for anti-infection treatment. Poor enteral nutrition, metoclopramide to promote gastrointestinal motility. Recheck lumbar puncture cranial pressure: 93mmH2O, reduce mannitol consumption. CSF white blood cell: 622.00×10^6/L, CSF total protein: 271 .18 mg/dL. Descriptive results of CSF exfoliation cytology: Lymphocytes: 67%, monocytes: 19%, activated lymphocytes: 14%, red blood cells: Scattered distribution. Considering that there is still central infection, considering the current symptoms of the patient, considering that the infection is controlled, the condition is relatively stable, and transferred to the general ward for further treatment. On the 10th day, after the patient was transferred to the general ward, the CT scan of the craniocerebral reexamination showed that the bilateral temporal hematomas had a lower density and a slightly lower range than before. Chest CT showed that both lungs were scattered inflammation, which was lower than the former range and density. Bilateral lung droposis. Chronic bronchitis is highly probable. CT findings of abdomen and pelvis: The right kidney is slightly lower and slightly higher in density. Enhanced CT is recommended. The prostate was obviously enlarged. After catheterization, there was an air accumulation in the bladder. Colorectal gas dilatation. Color Doppler ultrasound showed a small amount of aortic regurgitation and a small amount of bicuspid regurgitation. Venous ultrasound of lower extremity: No obvious abnormality was found. Blood gas analysis: Carbon dioxide partial pressure: 51.49mmHg↑, sodium concentration: 132 .70mmol/L↓, strengthen sputum suction, monitor blood gas; Give sodium supplementation and monitor electrolytes. At present, patients with viral encephalitis and pneumonia should be consulted by the pharmacy department for advice: Check more than pathogen kinds of nucleic acid in respiratory tract, stop acyclovir, give ganciclovir 0.25 g intravenous drip q12h, combine with phosphonic acid 3g intravenous drip q8h, and monitor renal function and blood cell count. Follow consultation advice and change to ganciclovir antiviral therapy for 11 days. On Day 12, blood analysis: White blood cell count: 5.06×10^9/L, NEUT: 76.70%%, lymphocyte: 17.80%%, PCT: 0.049ng/mL. Sputum culture results: Klebsiella pneumoniae infection, CRP, IL-6, respiratory tract pathogen multiple nucleic acid testin: No obvious abnormalities. According to the results, the patients were given compound neostigmine and ceftazidime avibactana 2.5 g intravenous drip anti-infection treatment. On day 15, oral feeding was attempted and the gastric tube was removed. Recheck lumbar puncture cranial pressure: 95mmH2O, CSF white blood cell: 292.00×10^6/L, CSF total protein: 253 .64 mg/dL. On day 18, the patient was relatively stable and ordered to get out of bed. On day 20, lumbar puncture pressure: 130mmH2O, cerebrospinal fluid white blood cell: 216.00×10^6/L, cerebrospinal fluid total protein: 202 .12 mg/dL. On the 23rd day, the cranial DWI+MRA was perfected: Bilateral temporal hematomas. The cranial MRA accorded with arteriosclerotic changes. Head MRI+SWI: Bilateral temporal hematoma (subacute late stage).

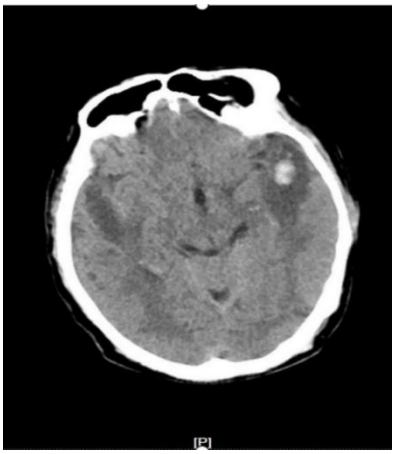

Figure 1. The cranial computed tomography (CT) suggests: bilateral temporal lobe hematomas with surrounding hypodense areas.

Small malacia of left basal ganglia. On day 26, lumbar puncture pressure: 105mmH2O, cerebrospinal fluid white blood cell: 202.00×10^6/L, cerebrospinal fluid total protein: 150 .76 mg/dL. The white blood cells and protein count of cerebrospinal fluid showed a decreasing trend, indicating that intracranial anti-infection treatment was effective. On the 31st day, the patient was aware of the problem, was able to communicate with people, was able to eat orally, had strong hands, was able to walk out of bed, the symptoms were improved, the condition was stable,

and agreed to be discharged. Patients were given methylprednisolone tablets for 28 mg 1/days after discharge. Follow-up after half a year: The patient did not complain of worsening symptoms, and could take care of himself.

Pathogen Type	Detected Pathogen
Bacteria	/
Mycobacterium	/
Fungus	/
DNA Virus	Human Herpesvirus Type 3 (VZV) (1414882), Human Parvovirus B19 (179)
RNA Virus	/
Parasite	/
Chlamydia/Rickettsia, etc.	/

Figure 2. NGS Result Report: Human Herpesvirus Type 3 (VZV)

2. Discussion

VZV belongs to the family Herpesviridae, which is a double-stranded DNA virus. The first infection is usually manifested as varicella. The virus can lurk in the sensory ganglion for a long time after being infected with human body. When stimulated by factors such as decreased immune function, the virus can be activated, causing herpes zoster or other serious complications, such as central nervous system infection[1]. VZV infection involving the central nervous system can lead to a variety of diseases, among which hemorrhagic necrotizing encephalitis is a rare but extremely serious type[2]. After VZV infection, the central nervous system can be invaded by various pathways. It is believed that viral activation retrograde along the nerve fibers to the central nervous system, causing a local inflammatory response[3]. In this case, it is speculated that the virus first replicates in the peripheral ganglion, then breaks through the blood-brain barrier and invades the brain parenchyma, resulting in hemorrhagic necrotic changes in the brain parenchyma. Virus infection may trigger the immune response of the organism, and the immune cells release a variety of cytokines. On the one hand, it tries to clear the virus, on the other hand, it also causes the immune damage to the brain tissue, aggravates the inflammatory response, and promotes the occurrence of hemorrhagic necrosis. The results show that VZV infection can lead to cerebral vasculitis, vascular endothelial cell damage, vascular wall integrity destruction, and then lead to vascular rupture and hemorrhage and local cerebral ischemia and necrosis, which may be one of the important mechanisms of hemorrhagic necrosis encephalitis[4]. Patients usually have the prodromal manifestations of VZV infection, such as skin herpes, but some patients may not have typical rash, which makes early diagnosis difficult[1]. Once hemorrhagic necrotizing encephalitis occurs, the onset of the disease is rapid, the disease progresses rapidly, often accompanied by hyperpyrexia, headache, vomiting and other intracranial pressure symptoms, as well as disorders of consciousness, mental abnormalities, convulsions, limb paralysis and other brain parenchymal damage[5]. In this case, the patient did not present with herpes in order to be unconscious with fever onset, and then rapidly progressed to coma with neurological localization signs, in line with the clinical features of the disease. Compared with other types of encephalitis, hemorrhagic necrosis encephalitis is more dangerous, the prognosis is worse and the mortality is higher.

The diagnosis of this disease mainly depends on the comprehensive judgment of clinical signs, laboratory examination and imaging examination. Cerebrospinal fluid examination is of great significance in diagnosis. The typical manifestation is increased pressure, increased number of white blood cells, mainly lymphocytes, polynuclear cells, increased protein content, sugar and chloride are generally normal. However, in hemorrhagic necrotizing encephalitis, cerebrospinal fluid may be hemorrhagic or yellowish. Virus nucleic acid testin (such as polymerase chain reaction technique) can find VZV DNA, which has key value for diagnosis. On imaging aspect, MRI can show intracerebral hemorrhage and necrosis focus, mostly patchy or confluent change, high signal on T1WI, mixed signal on T2WI, enhanced scan can show focus enhancement. It is important to note that early imaging may not be significantly abnormal in some patients and typically occurs as the disease progresses, so dynamic reexamination of MRI should be performed in highly suspected patients[6]. In addition, it should be distinguished from other virus infection caused by encephalitis (such as herpes simplex virus encephalitis), stroke middle disease.

Anti-virus therapy is the main treatment, acyclovir is the first choice for the treatment of VZV infection. The recommended dose is 10 - 15 mg/kg, administered intravenously every eight hours for a period of 10 - 14 days. At the same time, dehydration should be given to reduce cranial pressure, prevention of complications and other symptomatic support treatment. Corticosteroids may be used, as appropriate, to reduce inflammatory reactions in patients with severe disease at risk of significant cerebral edema or herniation, but adverse reactions should be noted[7][8]. However, even after active treatment, the prognosis of hemorrhagic necrotizing encephalitis is still not ideal. Patients often leave serious neurological sequelae, such as cognitive impairment, epilepsy, limb disability, etc. Some patients even died from the severity of their condition[9][10].In this case, although the vital

signs were maintained after treatment, there were still severe neurological deficits, indicating that clinicians should attach great importance to this disease and strengthen early diagnosis and treatment to improve the prognosis of patients.

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