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CASE REPORT

Severe Herpes Simplex Virus Encephalitis in an Adult

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SUMMARY

Background: **Herpes simplex encephalitis is rare. The diagnosis and treatment of such infections are often delayed, and disability rate is high.**
Methods: **Appropriate laboratory tests, next generation sequencing, and magnetic resonance imaging were used in this study.**
Results: **A 33-year-old healthy male with fever and headache as the predominant clinical features. Neurological manifestations are insidious and delayed. Timely diagnosis of disseminated herpetic encephalitis using brain magnetic resonance imaging and high-throughput genetic testing of cerebrospinal fluid. After treatment with acyclovir, antiviral drugs, and glucocorticoids, the patient's condition improved significantly without significant complications.**
Conclusions: **Physicians treating patients with fever, headache, and refractory hyponatremia as the main clinical features should be alert to herpes simplex encephalitis.**
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KEYWORDS

Herpes simplex virus, magnetic resonance imaging, refractory hyponatremia

CASE PRESENTATION

Herpes simplex encephalitis (HSE) is a rare disease [1]. With the use of antiviral drugs such as acyclovir, the case fatality rate in patients with HSE has dropped from 79% to less than 20%, but the disability rate in survivors is still as high as 58% [2]. These patients have long-term behavioral and cognitive problems, which bring a heavy burden to the patients' families and society [3]. Therefore, the biggest problem faced by clinicians is how to efficiently and accurately diagnose and treat HSE.

The patient was a 33-year-old male with no underlying disease. He was admitted to the Department of Respiratory Medicine of the North China University of Science and Technology Affiliated Hospital on June 9, 2024, mainly due to "fever for 3 days". The patient complained of fever after fatigue 3 days prior, with a maximum temperature of 39.4°C, accompanied by chills, palpita-

tions, and headaches. He had diarrhea once during the period, accompanied by nausea, vomiting, and muscle aches. He was administered ibuprofen sustained-release capsules, oseltamivir capsules, and cephalosporin antibiotics, but the effect was poor, and he still had intermittent fever.

Physical examination: body temperature 38.6°C; pulse 104 times/minute; clear consciousness. Pharyngeal congestion. Soft neck. Clear breath sounds in both lungs. Limb strength and muscle tension were normal, with bilateral Babinski sign (-) and meningeal irritation sign (-). The novel coronavirus nucleic acid was negative; influenza A virus antigen was negative; influenza B virus antigen was negative; C-reactive protein was negative; procalcitonin was negative; erythrocyte sedimentation rate was negative; urine routine test was normal; peripheral blood routine test results showed that the white blood cell count was 8.2 x 10^9/L, the neutrophil count was 5.95 x 10^9/L, the hemoglobin level was 129 g/L, and the platelet count was 145 x 10^9/L; blood biochemistry: liver function and kidney function were normal, blood sodium was 130.4 mmol/L, blood potassium was 3.28 mmol/L, and blood chloride was 94.9 mmol/L. Chest computed tomography (CT) revealed multiple nodules in the right upper lobe, left lower lobe, and right horizontal fissure. The patient received antiviral, anti-infective, and antipyretic therapy, but the effect was poor. The patient still had a high fever, with body temperature fluctuating between 38°C - 40.3°C, and gradually developed changes in consciousness. Initially, he was mentally excited, his hands moved involuntarily, and gradually developed into a state of confusion, with no command movements. On June 11, 2024, the patient was transferred to ICU. The blood routine examination showed a white blood cell count of 11.4 x 10^9/L and a neutrophil count of 9.30 x 10^9/L; inflammatory indicators procalcitonin, G test, GM test, and blood culture were all (-), and blood sodium 128.1 mmol/L, blood potassium 3.44 mmol/L, and blood chloride 96 mmol/L. After active electrolyte supplementation, the blood sodium level remained below 130 mmol/L. Urine electrolyte test showed 430.6 mmol of sodium at 24 hours. The calculated blood osmolality was 262.33 mOsm/L, and there was no polyuria, considering that the patient had refractory hyponatremia and hypoosmolality. Combined with the patient's fever, headache, and altered consciousness, central nervous system infection was not ruled out. The intracranial pressure was 240 mmH_2O, cerebrospinal fluid biochemistry: total protein 0.57 g/L, chloride 121.8 mmol/L. The smears for Cryptococcus and tuberculosis were normal, and the virus series was negative. Complete brain MRI (Figure 1) showed abnormal signals in the bilateral frontal lobes and temporal insula and local abnormal signals in the left thalamus, suggesting inflammatory lesions. The results of second-generation high-throughput genetic testing of cerebrospinal fluid indicated herpes simplex virus type 1, sequence number: 41,284, and the diagnosis was severe herpes simplex virus encephalitis (HSV-1). We administered intravenously injected acyclovir (0.5 g 3/day), methylprednisolone sodium succinate (80 mg 1/day), mannitol (250 mL 3/day), human immunoglobulin (20 g 1/day), and provided antipyretic treatment. After 7 days of treatment, the patient's fever symptoms were significantly relieved, his consciousness improved significantly and became clear, and his expression was indifferent. However, he was not cooperative on physical examination, his memory remained poor, his reaction was slow, and his calculation ability had decreased. The intracranial pressure was 240 mmH_2O, cerebrospinal fluid biochemistry, total protein 1.06 g/L, chloride 122.7 mmol/L. Re-examination of cranial MRI (Figure 2) showed local abnormal signals in the bilateral frontal lobes and temporal insula, and the left thalamus; the range was larger than before, considering inflammatory lesions and abnormal signals in the left cingulate gyrus, considering a small amount of bleeding. Blood sodium 126.7 mmol/L, blood chloride 92.9 mmol/L, continue to use acyclovir 0.5 g 3/day intravenous injection, dexamethasone injection 10 mg 1/day intravenous injection, mannitol 150 mL 3/day intravenous injection and correct hyponatremia treatment. On the 19th day after admission, the patient was conscious but indifferent during physical examination, and had better reaction ability than before. Although his cognitive ability was acceptable, his memory was still poor, and his calculation ability was the same as before. The intracranial pressure was 175 mmH_2O, cerebrospinal fluid biochemistry: total protein 0.74 g/L, chloride 118.8 mmol/L. Re-examination of cranial MRI (Figure 3) showed local abnormal signals in the frontal lobe and temporal insula on both sides and in the left thalamus, and the range was smaller than before, considering inflammatory lesions, abnormal signals in the left cingulate gyrus, and a small amount of bleeding. Laboratory test results indicated that the transaminase level was higher than before, which was considered to be related to acyclovir; therefore, the medication and mannitol were discontinued. The dose of dexamethasone was reduced to 5 mg 1/day intravenously to reduce inflammation and edema. The patient was transferred to the general ward the following day for further treatment. Finally, nearly one month after discharge, the patient was followed up and had good cognitive function and basic self-care.

DISCUSSION

The most common clinical manifestations of HSE are fever and headache, which are often misdiagnosed as upper respiratory tract infections and respond poorly to treatment, with neurological symptoms such as behavioral changes, altered consciousness, and even seizures as the disease progresses [4]. However, these symptoms are not specific to HSE. HSE presents with fewer prodromal symptoms or focal neurologic deficits than immunocompromised patients, making diagnosis more challenging in this population [5].

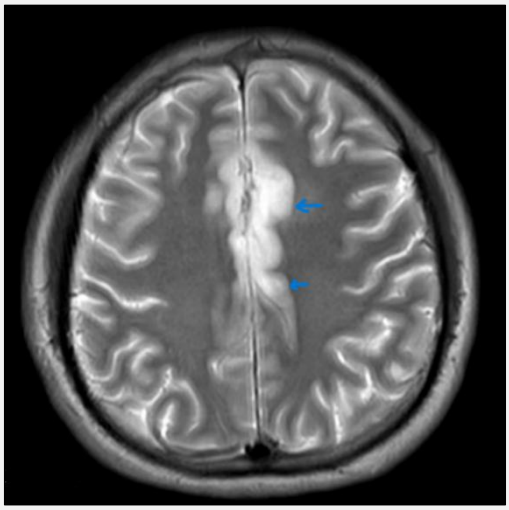

Figure 1. T2-weighted images of the brain MRI of the patient on the 5th day after admission showed local abnormal signals in the frontal lobe and temporal insula on both sides and the left thalamus (→).

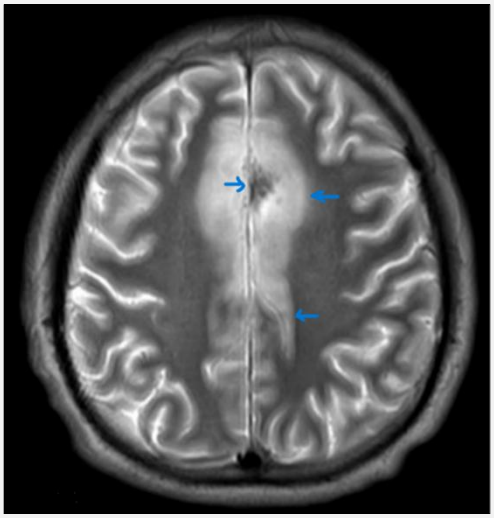

Figure 2. T2-weighted images of the brain MRI of the patient on the 12th day after admission showed local abnormal signals in the frontal lobes and temporal insula on both sides and the left thalamus, with a larger range than before (→).

The pathogenesis of HSE is not well understood. It is thought that there are three pathways to enter the brain from the initial site of peripheral infection. The first route is to reach the brain from the site of primary oropharyngeal infection through the trigeminal or olfactory nerves. The second mechanism involves the same neuronal pathways as the initial peripheral infection reactivation. The last mechanism is due to the reactivation of latent in situ HSV-1 in the brain [6]. The patient has pharyngeal congestion, which is thought to be associat-

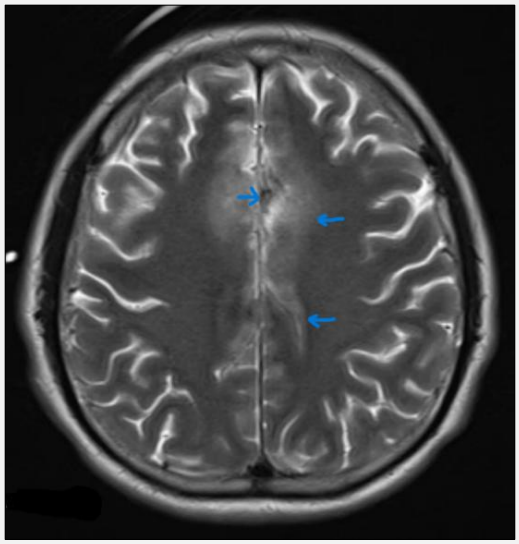

Figure 3. The T2-weighted images of the brain MRI examination of the patient on the 19th day after admission showed local abnormal signals in the frontal lobes and temporal insula on both sides and the left thalamus, with a smaller range than before (→).

ed with a primary oropharyngeal infection. HSE typically involves the temporal lobe and adjacent limbic system [7]. In this case, the lesions were concentrated in the frontal lobes, temporal insular lobes and left thalamus, combined with left cingulate hemorrhage, and brain MRI is the most sensitive and specific neuroimaging method for early diagnosis of HSE [8]. This patient has refractory hyponatremia, hypoosmolality, normal blood pressure, and no edema, which is considered to be isovolemic hyponatremia, and is accompanied by increased urinary sodium, suggesting the existence of syndrome of inappropriate antidiuretic hormone secretion (SIADH). The mean serum sodium level of HSV-1 encephalitis patients with limbic system and insular involvement was significantly lower than that of patients with limbic system and insular involvement [9]. The mechanism of its occurrence was caused by a variety of factors: 1) When the virus invades the limbic system (such as the temporal lobe, thalamus, amygdala, etc.), it can directly destroy neuroendocrine cells and stimulate abnormal secretion of antidiuretic hormone, resulting in increased renal water reabsorption and the formation of dilutive hyponatremia. In this case, MRI of the brain showed bilateral frontal, temporal islet, and left thalamus involvement, which is the regulatory center of ADH secretion and is directly related to the development of SIADH. It was consistent with the clinical manifestations of "ineffective sodium supplementation and persistent low sodium" in this patient; 2) The synergistic effect of the inflammatory cascade and the destruction of the blood-brain barrier: The level of inflammatory factors in the cerebrospinal fluid of HSE patients is increased, which enhances the sensitivity of renal tubular epithelial cells to antidiuretic hormone and further promotes water retention. In this case, the total protein of cerebrospinal fluid increased from 0.57 g/L to 1.06 g/L, indicating a significant increase in the permeability of the blood-brain barrier. After inflammatory factors enter the bloodstream, they can affect renal electrolyte regulation through systemic pathways; 3) Hypovolemic hyponatremia caused by fever and sweating or poor fluid intake due to altered mental status and vomiting. Hyponatremia has some reference value for the early diagnosis of HSV-1 encephalitis.

CONCLUSION

The core mechanism of HSV encephalitis complicated with persistent hyponatremia is SIADH-dominant, superimposed by inflammatory cytokine-mediated renal water and sodium regulation disorder. Hyponatremia in patients with severe HSV encephalitis is often "refractory" and closely related to disease severity. Patients with fever, headache, and refractory hyponatremia as the main clinical features need to complete cranial imaging (such as MRI) and second-generation gene sequencing of cerebrospinal fluid as soon as possible for comprehensive judgment, be alert to herpes simplex encephalitis, and avoid simple sodium supplementation

and ignore etiological intervention.

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Ethical Approval:
This study was approved by the ethics committee of North China University of Science and Technology Affiliated Hospital. All procedures performed in the studies were in accordance with the ethical standards. Informed consent was obtained.

Declaration of Interest:
No conflicts of interest.

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