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Herpes Simplex Virus Encephalitis–Associated Hyponatremia and Anti-NMDA Receptor Encephalitis

Herpes Simplex Virüs Ensefaliti İlişkili Hiponatremi ve Anti-NMDA Reseptör Ensefaliti

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Abstract

A 78-year-old male presented to the emergency department with a two-day history of high-grade fever and confusion. Cerebrospinal fluid analysis was positive for *Herpes simplex* virus type 1 (HSV-1) via polymerase chain reaction, and intravenous acyclovir therapy was initiated. During hospitalization, the patient developed hyponatremia, which was attributed to cerebral salt wasting syndrome based on elevated urinary sodium levels and clinical hypovolemia. Hyponatremia and consciousness improved following acyclovir therapy and aggressive isotonic fluid replacement. After being discharged, the patient experienced recurrent cognitive decline, leading to a second hospitalization. Further evaluation resulted in a diagnosis of anti–N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Treatment with intravenous immunoglobulin resulted in gradual improvement in consciousness. This case highlights the coexistence of HSV encephalitis–associated cerebral salt wasting syndrome and subsequent anti-NMDAR encephalitis.

Keywords: Encephalitis, *Herpes simplex* virus, hyponatremia, cerebral salt wasting syndrome, anti-NMDAR encephalitis

Öz

Yetmiş sekiz yaşında erkek hasta, iki gündür devam eden yüksek ateş ve bilinç değişikliği şikayetiyle acil servise başvurdu. Beyin omurilik sıvısı incelemesinde polimeraz zincir reaksiyon yolu ile *Herpes simplex* virüsü tip 1 (HSV-1) için pozitif saptandı ve asiklovir 30 mg/kg/günden IV tedavi başlandı. Takiplerinde hiponateremi gelişen hastanın idrar sodyum atılımının yüksek olması ve hipovolemisi serebral tuz kaybı sendromunu düşündürdü. Asiklovir tedavisinin yanı sıra agresif izotonik tedavi ile hiponatremisi ve bilinci düzeldi. Taburculuğu sonrası yeniden bilinç değişikliği gelişmesi üzerine ikinci kez hastaneye yatırıldı. Yapılan incelemeler sonucunda anti- N-metil- D-aspartat reseptör (Anti-NMDAR) ensefaliti tanısı konuldu. İntravenöz immunoglobulin tedavisi sonrası hastanın bilinci kademeli olarak düzeldi. Bu olgu HSV ensefalit ilişkili serebral tuz kaybı sendromuna ve sonrasında gelişebilecek anti-NMDAR ensefalitine karşı farkındalığı artırmak amacı ile sunuldu.

Anahtar Kelimeler: Ensefalit, *Herpes simplex*, hiponatremi, serebral tuz kaybı sendromu, anti-NMDAR ensefalit

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Introduction

Herpes simplex virus (HSV) is the most common cause of acute sporadic viral encephalitis in adults. Hyponatremia frequently occurs in central nervous system disorders, including HSV encephalitis[1]. Although the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a well-recognized cause of renal sodium loss, a similar electrolyte disturbance may also arise from cerebral salt wasting syndrome (CSWS). CSWS is characterized by excessive renal sodium excretion in the setting of intracranial pathology, resulting in hyponatremia accompanied by a reduction in extracellular fluid volume[2,3]. Differentiating CSWS from SIADH is essential because management strategies differ substantially: SIADH typically requires fluid restriction, whereas CSWS necessitates aggressive isotonic fluid replacement.

In addition, patients recovering from HSV encephalitis may develop post-infectious autoimmune encephalitis, most commonly anti–N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. This risk underscores the importance of continued clinical vigilance after hospital discharge. In a prospective cohort of 51 patients with HSV encephalitis, autoimmune encephalitis developed in 14 (27%), and neuronal antibodies were identified in all affected individuals; among these cases, anti-NMDAR antibodies were detected in 9 (64%) patients[4].

Here, we report a case of HSV encephalitis–associated hyponatremia followed by anti-NMDAR encephalitis and review the relevant literature.

Case Presentation

A 78-year-old man presented to the emergency department with a two-day history of high fever and altered consciousness. His medical history was notable only for benign prostatic hyperplasia managed with tamsulosin; no other comorbidities or medications were reported. On admission, his temperature was 37.8 °C, blood pressure 110/70 mmHg, and respiratory rate 16 breaths/min. He was unresponsive, non-cooperative, disoriented, and exhibited no meningeal signs.

Initial laboratory evaluation showed serum creatinine 1.28 mg/dL, sodium 140 mmol/L, and C-reactive protein 1.3 mg/L. Brain magnetic resonance imaging (MRI) revealed T2-FLAIR hyperintense lesions in the left temporal lobe and hippocampus (Figure 1). Lumbar puncture demonstrated cerebrospinal fluid (CSF) with 210 leukocytes/mm³ (predominantly lymphocytes), 50 erythrocytes/mm³, glucose 49 mg/dL (serum glucose 98 mg/dL), and protein 69 mg/dL. Intravenous empirical therapy with ceftriaxone 4 g/day, ampicillin 12 g/day, and acyclovir 30 mg/kg/day was initiated. CSF polymerase chain reaction (PCR) subsequently returned positive for HSV-1; antibiotic therapy was discontinued, and acyclovir was continued.

On the 7th day of his hospitalization, serum sodium had decreased to 134 mmol/L, and spot urine sodium was elevated at 99 mmol/L. Physical examination revealed dry mucous membranes and reduced skin turgor, consistent with hypovolemia. A diagnosis of CSWS was made, and aggressive isotonic saline administration (4–5 L/day) was initiated. Urine sodium levels remained ≥110 mmol/L, while serum sodium stabilized between 133 and 135 mmol/L.

During the first 2 weeks, the patient remained markedly lethargic, responding only with facial expressions. Following a generalized tonic–clonic seizure, levetiracetam therapy was started. Blood and urine cultures were obtained after inflammatory markers increased (CRP 60 mg/L; procalcitonin 0.21 ng/mL). Meropenem 3 g/day was added for suspected nosocomial infection, and *Pseudomonas aeruginosa* was isolated from the urine culture. By the end of the second week, the patient's consciousness improved and oral intake resumed. Meropenem was administered for a total of 7 days, and acyclovir was discontinued after 21 days. The patient subsequently underwent physiotherapy, showed clinical and laboratory improvement, and was discharged in stable condition.

One week after discharge, he again developed altered consciousness and experienced a focal seizure involving the right upper extremity. Upon readmission to another hospital,

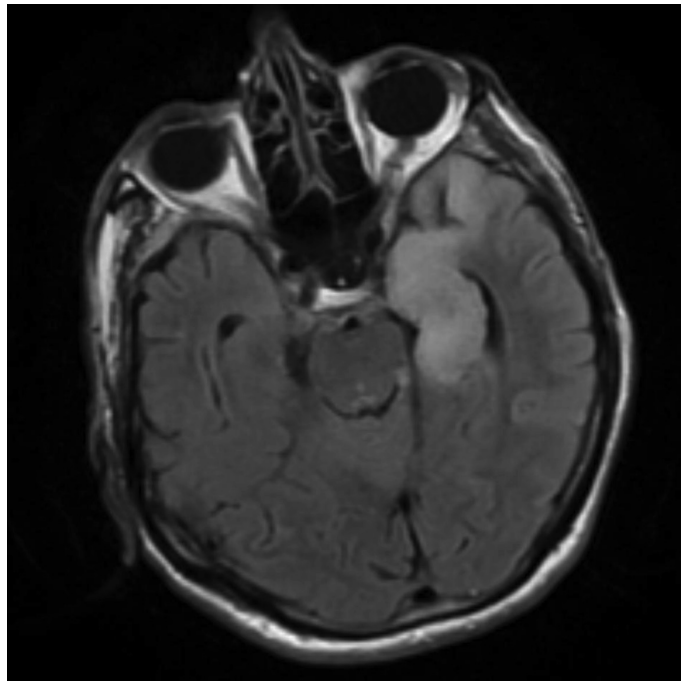

Figure 1. Brain MRI demonstrating T2-FLAIR hyperintense lesions in the left temporal lobe and hippocampus.

CSF testing was positive for anti-NMDAR antibodies, confirming anti-NMDAR encephalitis. After transfer to our facility, the patient received intravenous immunoglobulin therapy, resulting in gradual restoration of consciousness. He was eventually discharged with significant clinical improvement.

Discussion

HSV encephalitis is the most common cause of sporadic encephalitis in adults and carries significant mortality despite timely antiviral treatment[5]. MRI often reveals temporal lobe involvement. CSF may show lymphocytic pleocytosis, elevated protein levels, and erythrocytes. HSV PCR in CSF has >95% sensitivity and specificity for diagnosis. Hyponatremia has been reported in 33–83% of patients with HSV encephalitis cases. Başaran et al.[1], evaluated 67 patients with infectious encephalitis. Hyponatremia was detected in 56% of those with HSV encephalitis and in 19% of patients with other infectious encephalitis forms without HSV; this difference was shown to be statistically significant. Hyponatremia, disorientation, and the presence of lesions on initial brain computed tomography are poor prognostic indicators in HSV encephalitis, as demonstrated by Riancho et al.[5] in a Spanish study.

Hyponatremia may have several underlying mechanisms and may present with hypovolemia due to high fever, inadequate fluid intake, or vomiting, or euvolemia due to SIADH or CSWS. Characterizing the specific etiology underlying hyponatremia in these patients is often challenging. In hyponatremic presentations associated with central nervous system pathology and increased urinary sodium excretion, laboratory and clinical data must be interpreted together[6]. In another series of 79 encephalitis cases, hyponatremia occurred in 22 patients (27.8%): 12 were classified as SIADH, 2 as CSWS, and 8 remained unclassified[7]. SIADH and CSWS are the most frequent etiologies, and their treatments differ completely; SIADH requires fluid restriction, whereas CSWS mandates aggressive volume repletion. Unlike SIADH, CSWS is accompanied by extracellular volume depletion, although quantifying such losses is difficult. In our patient, diminished skin turgor, dry mucous membranes, and elevated urinary sodium excretion were observed. He received aggressive isotonic fluid resuscitation, after which serum sodium normalized. These findings were consistent with CSWS in the context of HSV encephalitis.

Anti-NMDAR encephalitis is an autoimmune encephalitis that predominantly affects the limbic system. It is mediated by immunoglobulin G antibodies targeting the NR1 subunit of the NMDA receptor in the central nervous system. The disease typically follows an acute or subacute course and presents with a combination of seizures, psychiatric disturbances, cognitive impairment, and movement disorders[8]. Titulaer et al.[9] reported that among patients aged ≥45 years, anti-NMDAR encephalitis occurs with similar frequency in males and females, and its heterogeneous clinical manifestations often result in a broad initial differential diagnosis. Although older age is generally associated with a milder disease course, delayed diagnosis and treatment can lead to poorer outcomes.

Anti-NMDAR encephalitis may develop during or after HSV encephalitis. The underlying mechanism involves HSV-induced neuronal injury, which exposes neuronal antigens and subsequently triggers autoantibody formation against NMDA receptors. Clinically, the two disease phases are distinct. The acute HSV encephalitis phase is characterized by fever, headache, seizures, and altered mental status, reflecting viral infection and inflammation localized to the temporal lobes. In contrast, the secondary autoimmune phase is dominated by psychiatric symptoms, memory impairment, speech dysfunction, dyskinesias, and behavioral abnormalities, often mimicking primary psychiatric disorders[10–12].

In a cohort of 58 patients with autoimmune encephalitis following HSV encephalitis, antibody positivity confirmed the diagnosis, and 74% had anti-NMDAR antibodies. The most common clinical features included behavioral changes (93%), decreased level of consciousness (57%), choreoathetosis (47%; observed in all children aged ≤4 years), seizures (38%), and dysautonomia (27%)[9].

First-line immunotherapy for anti-NMDAR encephalitis includes intravenous methylprednisolone and/or intravenous immunoglobulin (IVIG). In the present case, administration of IVIG resulted in marked clinical improvement and eventual full recovery.

Conclusion

Clinicians should be aware of the importance of recognizing hyponatremia due to CSWS during HSV encephalitis. Early differentiation of hyponatremia subtypes and timely initiation of appropriate antiviral therapy and fluid management are critical for optimizing patient outcomes. HSV encephalitis may also trigger an autoimmune encephalitis. After the diagnosis of HSV encephalitis, it is necessary to remain vigilant for persistent or newly developing symptoms, especially those related to the central nervous system or those that may present with similar psychiatric complaints. Early diagnosis and appropriate treatment significantly reduce mortality and morbidity, as patients who received early diagnosis and treatment had better outcomes at the end of therapy.

Ethics

Informed Consent: Written informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.U., S.ZU., S.D.Ç., Z.K., B.D., H.E., Concept: D.U., S.ZU., S.D.Ç., A.E., B.D., H.E., Design: D.U., S.ZU., S.D.Ç., Z.K., A.E., B.D., H.E., Data Collection or Processing: D.U., S.ZU., S.D.Ç., Z.K., A.E., B.D., H.E., Analysis or Interpretation: D.U., S.ZU., Z.K., A.E., B.D., H.E., Literature Search: D.U., S.ZU., H.E., Writing: D.U., S.ZU., A.E., H.E.

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