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ORIGINAL ARTICLE

Hyponatremia associated with human herpesvirus-6 (HHV-6) encephalitis after allogeneic hematopoietic stem cell transplantation: A presentation different from HHV-6 myelitis

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Abstract Human herpesvirus-6 (HHV-6) encephalitis and myelitis following allogeneic hematopoietic stem cell transplantation (HSCT) is frequently life-threatening. We retrospectively evaluated the clinical significance of hyponatremia in cases of HHV-6 encephalitis/myelitis. Using an institutional database and medical records, we identified and retrospectively analyzed 16 cases of HHV-6 encephalitis and/or myelitis after allogeneic HSCT. HHV-6 encephalitis and myelitis were defined as the symptoms/signs with HHV-6-DNA in the cerebrospinal fluid. Seizure and memory disorder were defined as symptoms/signs of encephalitis, and dysesthesia and vesicorectal disorder as those of myelitis. Five patients developed encephalitis with or without myelitis, and 11 patients developed myelitis alone. Hyponatremia (median 129.1 mEq/L; range 125.9–130.1) was observed in all five patients with HHV-6 encephalitis at diagnosis, and values were significantly lower than those in patients with HHV-6 myelitis alone (median 137.6; range 134.0–142.2; $P < 0.01$). In three of the five patients with encephalitis, the decrease in sodium level preceded the clinical onset of encephalitis by one or two days. These results suggest that hyponatremia may be an important manifestation of HHV-6 encephalitis, but not of myelitis, and could be a useful tool for the early prediction or diagnosis of HHV-6 encephalitis.

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Introduction

Reactivation of human herpesvirus-6 (HHV-6) has been reported after allogeneic hematopoietic stem cell transplantation (HSCT), and has led to the development of central nervous system disorders such as encephalitis and myelitis [1, 2]. These disorders are not only life-threatening, but also have the potential to cause neuropsychological sequelae [3]. At present, optimal prophylactic or preemptive intervention for HHV-6-associated CNS disorders has yet to be established [4]. HHV-6 encephalitis and myelitis present a variety of symptoms that include seizure, memory disorder, confusion, abnormal sensation, involuntary movement, unsteadiness, and ileus. However, none of these symptoms are unique to these disorders, making the diagnosis of HHV-6 encephalitis difficult. Recently, we experienced a case of HHV-6 encephalitis developing hyponatremia, and sporadic similar cases have been reported in the literature [5–7]. This experience prompted us to evaluate the clinical significance of hyponatremia in cases of HHV-6 encephalitis and myelitis.

Patients and methods

Patients

Using an institutional database and the medical records of patients who underwent allogeneic HSCT between January 2000 and March 2016 at the Division of Hematology

at Keio University Hospital (Tokyo, Japan), we identified 16 patients who developed HHV-6 encephalitis or myelitis. We used the following definitions to make these diagnoses. All 16 patients were evaluable and enrolled into this retrospective analysis. This study was approved by the ethics committee of Keio University School of Medicine.

Definitions of hyponatremia and HHV-6 encephalitis/myelitis

Hyponatremia was defined as a serum sodium concentration less than 135 mEq/L. The diagnosis of encephalitis/myelitis was made based on neurological symptoms or signs in combination with the detection of HHV-6-DNA in the cerebrospinal fluid (CSF) by real-time polymerase chain reaction (PCR). Real-time PCR was performed as we previously described [8]. Seizure and memory disorder were defined as symptoms/signs of encephalitis, and dysesthesia and vesicorectal disorder as those of myelitis. In this study, onset was defined as the first day when symptoms of encephalitis were observed in patients with encephalitis (±myelitis) and when those of myelitis were observed in patients with myelitis alone.

Statistical analysis

Comparisons between patients with HHV-6 encephalitis and those with myelitis were made using the Mann–Whitney *U* test or Fisher's exact test as appropriate. Values of $P < 0.05$ were considered statistically significant. Statistical analyses were performed with EZR software [9].

Results

Patient characteristics and clinical course

Patient characteristics are shown in Table 1. The stem cell sources were bone marrow from an unrelated donor in 9 patients, and cord blood in 7. Eleven patients were diagnosed as having HHV-6 myelitis only. Five patients were diagnosed as having HHV-6 encephalitis, and 4 of the 5 patients with encephalitis were complicated with myelitis. In 2 of the 4 patients with encephalitis complicated with myelitis, symptoms of myelitis preceded those of encephalitis. Day 20 post-transplant was the median day of the onset of HHV-6 encephalitis or myelitis (range 16–31). Of the 5 patients with HHV-6 encephalitis, symptoms/signs considered due to encephalitis were impaired

Table 1 Patient and transplant characteristics

	All patients ($N = 16$)	Encephalitis ± myelitis ($N = 5$)	Myelitis ($N = 11$)	*P* value
Median age, years (range)	52 (17–68)	47 (29–68)	53 (17–59)	0.955
Sex, male/female	9/7	4/1	5/6	0.308
Underlying disease				0.104
Acute leukemia	9	1	8	
Malignant lymphoma	4	2	2	
Myelodysplastic syndrome	2	1	1	
Multiple myeloma	1	1	0	
Disease status at transplant				0.093
Complete remission/response	6	0	6	
Other	10	5	5	
Stem cell source				1.000
Cord blood	7	2	5	
Bone marrow from unrelated donor	9	3	6	
Conditioning regimen				0.596
Myeloablative	9	2	7	
Reduced-intensity	7	3	4	
GVHD prophylaxis				1.000
Cyclosporine-based	5	2	3	
Tacrolimus-based	11	3	8	
HHV-6 DNA in cerebrospinal fluid at onset				0.069
Median copies/mL (range)	8000 (600–100,000)	40,000 (1000–100,000)	3000 (600–30,000)	

GVHD graft-versus-host disease, *HHV-6* human herpes virus-6, *DNA* deoxyribonucleic acid

consciousness in 5 patients, seizure in 4, and memory disorder in 3. Of the 11 patients with myelitis alone and 4 patients with myelitis complicated with encephalitis, symptoms/signs considered due to encephalitis were dysesthesia in 12 patients and vesicorectal disorder such as paralytic ileus in 4. Brain T2 or diffusion-weighted magnetic resonance images (MRI) revealed increased signals somewhere in the medial temporal lobes, frontal lobes, and/or thalamus in 4 of the 5 evaluated patients with encephalitis. MRI did not show any abnormal findings in the spinal cord in 10 evaluated patients with myelitis alone. Although copy number of HHV-6 DNA in the CSF at the onset tended to be higher in patients with encephalitis, there were no significant differences in patient and transplant characteristics between the patients with encephalitis (±myelitis) ($N = 5$) and those with myelitis alone ($N = 11$; Table 1). All patients responded to antiviral treatment, and no patient died directly due to HHV-6 encephalitis/myelitis.

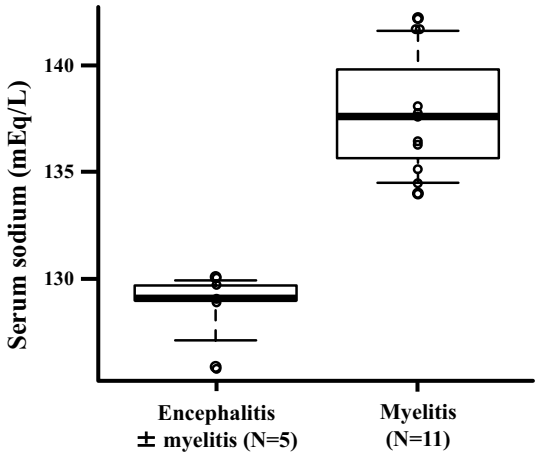

Fig. 1 Comparison of serum sodium levels between patients with human herpesvirus-6 (HHV-6) encephalitis and those with myelitis alone. At the onset of HHV-6 encephalitis/myelitis, the sodium level was significantly lower in patients with encephalitis

Levels of serum sodium

At the onset of HHV-6 encephalitis, serum sodium levels decreased in all 5 patients with encephalitis, and the median of 129.1 mEq/L (range 125.9–130.1) was significantly lower than that of patients with myelitis alone [137.6 mEq/L (range 134.0–142.2], $P < 0.01$, Fig. 1). The difference was also significant as compared with that around day 20 post-transplant in 80 control patients without HHV-6 encephalitis/myelitis who underwent allogeneic HSCT at our institute [137.7 (range 130.8–145.0), $P < 0.001$]. Serial changes in serum sodium levels at, before and after the onset in patients with encephalitis are shown in Fig. 2. In 3 of the 5 patients (Cases 3, 4, and 5), hyponatremia, less than 135 mEq/L, preceded the onset of encephalitis by 1 or 2 days. In association with the onset of hyponatremia, possible etiologies such as administration of diuretics and nephrotoxic agents and inappropriate dosing of calcineurin inhibitors were not identified. Serum sodium levels increased in 1–4 days after the onset of encephalitis in all patients (Fig. 2).

Discussion

Our findings indicated that serum sodium levels were decreased in patients developing HHV-6 encephalitis after allogeneic HSCT. In contrast, this phenomenon was not observed in patients with HHV-6 myelitis. To the best of our knowledge, this is the first report to show a significant difference in serum sodium levels between patients with HHV-6 encephalitis and those with myelitis developing after allo-HSCT.

Hyponatremia is occasionally observed after HSCT. Multiple factors or pathogeneses could contribute to the occurrence of hyponatremia in this setting, including antineoplastic agents, glucocorticoid, calcineurin inhibitors, diuretics, and malnutrition. However, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most definitively documented pathogenesis of hyponatremia in HSCT recipients [10–12]. In regard to HHV-6 encephalitis, several cases of hyponatremia probably due to SIADH have been reported [5–7]. SIADH is generally well recognized to occur in association with a variety of central nervous system disorders such as trauma and infections [13]. Among these causes, limbic encephalitis due to viral infection and potassium channel antibody-associated encephalopathy in particular has been reported to cause SIADH [14–16]. Limbic encephalitis is also one of the most common neurological features of HHV-6 encephalitis. Therefore, it is plausible that hyponatremia is due to SIADH caused by limbic encephalitis caused in turn by HHV-6. In this retrospective analysis, a diagnosis of SIADH could not been made because of a lack of necessary data. However, the fact that hyponatremia specifically developed in patients with encephalitis, but not in those with myelitis alone suggests that SIADH may be involved in the development of hyponatremia associated with HHV-6 encephalitis.

The precise mechanisms underlying SIADH associated with HHV-6 encephalitis causing hyponatremia remain to be clarified. One possible mechanism is the direct stimulation of the hypothalamus-pituitary system due to inflammation caused by HHV-6 encephalitis, which is suggested in other CNS disorders [14, 16]. Another possibility is the inappropriate production of

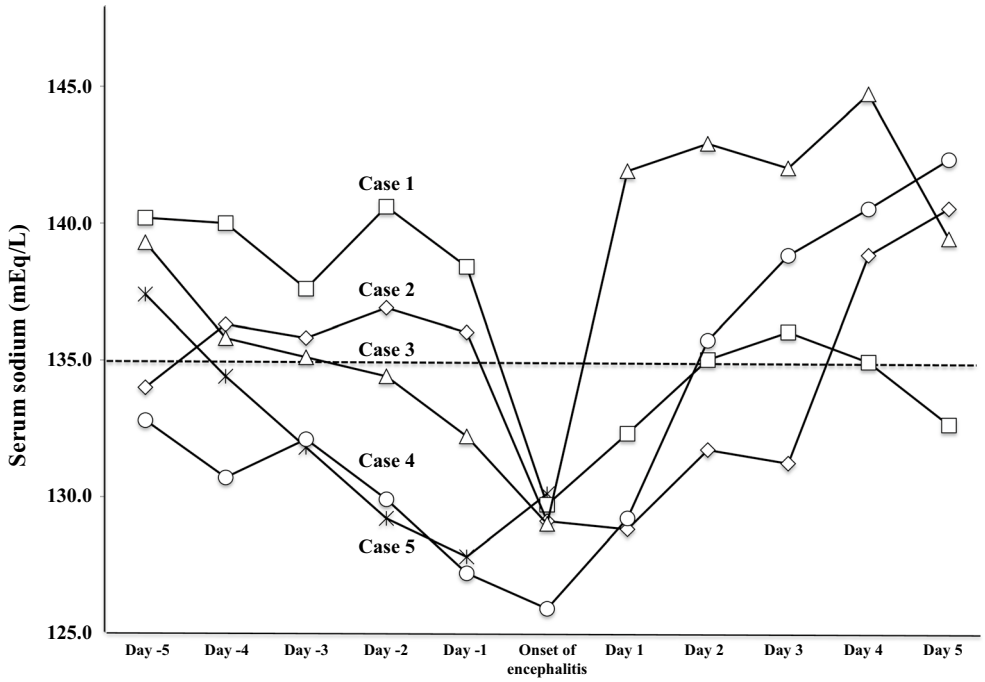

Fig. 2 Serial changes in serum sodium levels in 5 patients with HHV-6 encephalitis. In Cases 3, 4, and 5, a decrease in the sodium level preceded the onset of HHV-6 encephalitis by 1 or 2 days

ADH by impairing the function of the limbic area [14]. The limbic area has the potential to suppress the hypothalamic–pituitary system (hypothalamic nuclei) involved in the production of ADH, and thus, it is possible that HHV-6 encephalitis affecting the limbic area could cause SIADH. Our findings that the hyponatremia specifically observed in patients HHV-6 encephalitis, but not in those with myelitis, could support these explanations.

It is well known that hyponatremia itself could cause various symptoms/signs such as fatigue, nausea, somnolence, and seizures, depending on the level of serum sodium. Such symptoms and signs are similar to those of HHV-6 encephalitis documented in the literature. Therefore, hyponatremia associated with HHV-6 encephalitis may affect or modify the neurological presentations of HHV-6 encephalitis. The net effect of hyponatremia in the clinical features of HHV-6 encephalitis is considered difficult to evaluate. However, physicians should recognize this issue and attempt to correct the serum sodium level simultaneously with specific treatment against HHV-6 infection if hyponatremia is present.

The results of our study clearly showed the presence of hyponatremia at the onset of HHV-6 encephalitis, but not at that of myelitis, and indicated that some patients presented hyponatremia 1 or 2 days prior to the clinical onset of HHV-6 encephalitis. In addition, 4 of the 5 patients with HHV-6 encephalitis were complicated with myelitis, which clinically preceded the onset of encephalitis in 2 patients. It is noteworthy that, in those 2 patients, serum sodium did not decrease at the presentation of the myelitis symptoms and decreased thereafter at the onset of encephalitis. These findings suggest that a decrease in the serum sodium level, which can be detected by an ordinary laboratory test, could have diagnostic and partially predictive value in HHV-6 encephalitis.

The serum sodium level promptly increased after the onset of HHV-6 encephalitis in all patients. The most possible explanation for this recovery is the massive administration of saline required for the prevention of the nephrotoxicity of foscarnet, which was given as the treatment of HHV-6 encephalitis. This finding suggests that hyponatremia associated with HHV-6 encephalitis could be corrected by sodium supplementation. In addition, improvement of HHV-6 encephalitis due to anti-viral treatment could have also contributed to the improvement of hyponatremia associated with HHV-6 encephalitis.

It is well documented that HHV-6 encephalitis occurs more frequently after cord blood transplantation (CBT) than after bone marrow or peripheral blood stem cell transplantation (BMT/PBSCT) [1, 17]. With regard to the relationship between hyponatremia and stem cell sources, Suzuki et al. reported a significant difference between the clinical features of SIADH developing after CBT and those developing after BMT/PBSCT [8]. SIADH developed significantly earlier and more seriously after CBT than after BMT/PBSCT. Although a definite diagnosis of HHV-6

encephalitis was made in only 1 patient and neurological symptoms were assessed due to hyponatremia in other patients, the difference between stem cell sources might be attributed to HHV-6 encephalitis. These findings suggest that hyponatremia and SIADH developing early after CBT should be carefully evaluated for the possibility of HHV-6 encephalitis. In addition, the association of hyponatremia with the diseases due to other viruses such as herpes simplex virus should also be investigated in a future study [18].

Our study has several limitations. The major limitations were the small number of patients evaluated and the retrospective nature of the study. Thus, future prospective studies with larger numbers of cases should be conducted to evaluate the causes or mechanisms of hyponatremia observed in HHV-6 encephalitis.

In conclusion, our findings suggest that hyponatremia could be a sign of HHV-6 encephalitis, but not of myelitis, after allogeneic HSCT, and may serve as a marker for the prediction or early diagnosis of HHV-6 encephalitis. In future, a large-scale prospective study is required to confirm our findings.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest associated with this study.

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