The preceding hyponatremia is a useful hallmark for the diagnosis of HHV-6 encephalitis after allogeneic hematopoietic stem cell transplantation

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Abstract

Human herpes virus-6 (HHV-6) encephalitis is one of the life-threatening complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Early diagnosis and intervention are important for the prevention of poor prognosis and sequelae. Although hyponatremia is known to be associated with HHV-6 encephalitis, it is unclear whether the preceding hyponatremia is a useful hallmark for the diagnosis of HHV-6 encephalitis. We retrospectively reviewed 134 consecutive patients who underwent allo-HSCT at our institution and evaluated the relationship between HHV-6 encephalitis and hyponatremia. Interestingly, 7 (50%) of 14 patients who developed HHV-6 encephalitis presented hyponatremia within a week before the onset of HHV-6 encephalitis. On the other hand, only 14 (11.7%) out of 120 patients without HHV-6 encephalitis developed hyponatremia. Hyponatremia, treating as a time-dependent covariate, was significantly correlated with the incidence of HHV-6 encephalitis. Moreover, the diagnostic accuracy analysis showed that the coexistence of hyponatremia and central nerve system (CNS) dysfunction strongly suggests HHV-6 encephalitis. In conclusion, our study suggests the likelihood of HHV-6 encephalitis significantly increases in the patients with CNS dysfunction following hyponatremia after allo-HSCT and this combination may help in early diagnosis and intervention of HHV-6 encephalitis after allo-HSCT.

Introduction

Reactivation of human herpes virus-6 (HHV-6) is common after allogeneic hematopoietic stem cell transplantation (allo-HSCT), and is associated with the development of HHV-6 encephalitis.[1–5] HHV-6 encephalitis is not only associated with significant mortality but also many survivors suffer neurological sequelae.[6–9] Nevertheless, optimal prevention or preemptive intervention for HHV-6 encephalitis has not yet been established. HHV-6 encephalitis presents a variety of neurological symptoms including delirium, amnesia, confusion, ataxia, and seizures,[3, 7, 10] but none of these symptoms are specific for HHV-6 encephalitis. Although polymerase chain reaction (PCR) testing of the cerebrospinal fluid (CSF) is useful for the diagnosis of HHV-6 encephalitis,[11, 12] the procedure of lumbar puncture may be hesitated at early after allo-HSCT due to cytopenia or hemorrhagic tendency. Moreover, false-positive results for HHV-6 DNA in CSF may occur and hence the results must be interpreted carefully in conjunction with clinical symptoms and patient's backgrounds.[13] Therefore, the diagnosis of HHV-6 encephalitis remains problematic.

A recent systematic review article suggested the association of HHV-6 encephalitis and hyponatremia.[14] However, since most case reports did not specify the timing of onset of hyponatremia and HHV-6 encephalitis, it is unclear whether the preceding hyponatremia is a useful hallmark for the diagnosis of HHV-6 encephalitis.

In this study, we analyzed the dynamics of serum sodium levels after allo-HSCT, mainly focused on hyponatremia, and investigated whether hyponatremia could be a new auxiliary diagnostic marker for HHV-6 encephalitis after allo-HSCT.

Patients And Methods

Patients

We conducted a retrospective analysis of adult patients aged 18 or older who received allo-HSCT between April 2018 and December 2020 at Sapporo Hokuyu Hospital in Japan. We identified a total of 134 allo-HSCT recipients during this period and reviewed their medical records. This study was approved by the institutional review board of Sapporo Hokuyu Hospital and conducted in accordance with the Declaration of Helsinki.

Definitions

CNS dysfunction was defined as the presence of disorientation as to time and place, loss of consciousness, memory loss and convulsions. Lumbar puncture and cerebrospinal PCR test for HHV-6 DNA were performed as soon as possible when these CNS dysfunction appeared in allo-HSCT recipients. As the previous reports,[5, 7, 10, 15, 16] HHV-6 encephalitis was diagnosed if the patient satisfied all of following criteria: (1) presence of CNS dysfunction, (2) a positive PCR result for HHV-6 DNA in CSF, and (3) absence of other identified causes of CNS dysfunction, including other infectious agents.[5, 7, 15–17] The diagnosis date of HHV-6 encephalitis was defined as the testing day on which PCR result for HHV-6 DNA became positive firstly. On the other hand, we did not include HHV-6 myelitis in this analysis because previous study reported that hyponatremia was not observed in the patients with HHV-6 myelitis.[18] The serum sodium levels were checked about three times a week at the discretion of the treating physicians. Based on the median sodium levels at the onset of HHV-6 encephalitis from previous reports,[14, 18–23] we had set a cutoff of 130mEq/L or less as robust hyponatremia, while hypernatremia was defined as a serum sodium concentration 150 mEq/L or more. We classified the conditioning regimen either myeloablative conditioning (MAC) or reduced intensity conditioning (RIC) as described.[24] The degree of human leukocyte antigen (HLA) matching for related donors was assessed using allele data at the HLA-A, -B, -DRB1, whereas that for unrelated donors was assessed using allele data at the HLA-A,- B, -C, DRB1. Disease risk of the patients was determined according to the refined disease risk index (DRI).[25] Since previous study suggested that the method of graft-versus-host disease (GVHD) prophylaxis was also associated with the incidence of HHV-6 encephalitis,[10] we also collected the methods of GVHD prophylaxis. Engraftment syndrome (ES) and pre-engraftment immune reaction (PIR) were defined according to the criteria descried elsewhere.[26–28]

Statistical considerations

In patient and transplant characteristics analysis, Fisher's exact test was used to compare categorical values and Mann-Whitney U test was used to compare continuous values. The cumulative incidence of HHV-6 encephalitis and sodium abnormalities were estimated by Gray's method while treating death as a competing risk. In the risk factor analysis, the Fine-Gray proportional hazard regression analysis was used, treating hyponatremia as a time-dependent covariate. The following all variables reported as risk factors for HHV-6 encephalitis were considered in univariate analysis: recipient's gender, disease status,

HLA matching, donor source, the intensity of conditioning regimen, the methods of GVHD prophylaxis, and ES or PIR before the onset of HHV-6 encephalitis.[5, 8, 10, 29] Factors associated with at least borderline significance ($P < 0.10$) in the univariate analysis were subjected to a multivariate analysis. To assess the diagnostic values of each finding, we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio of a positive test result (LR+), likelihood ratio of a negative test result (LR-), and diagnostic odds ratio (DOR).[30] Statistical significance was defined as a two-tailed P value < 0.05. All statistical analyses were performed with EZR ver 1.52 (Jichi Medical University Saitama Medical Center), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[31]

Results

Patient and transplant characteristics

Patient and transplant characteristics are summarized in Table 1. The median age at allo-HSCT was 53 years (range, 19 to 72). Two thirds of allo-HSCT recipients were male. The underlying disease included acute myeloid leukemia (n = 59), acute lymphoblastic leukemia (n = 31), myelodysplastic syndrome / myeloproliferative neoplasms (n = 22), chronic myeloid leukemia (n = 1), malignant lymphoma (n = 14), adult T-cell leukemia/lymphoma (n = 3), and others (n = 4). According to the refined DRI, 58 patients were classified as intermediate risk, and 76 patients were classified as high or very high risk. Of these patients, 29, 45, and 60 patients underwent bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSCT), and cord blood transplantation (CBT), respectively. Most patients (80.6%) received myeloablative conditioning regimens. GVHD prophylaxis was performed with tacrolimus (TAC) with short-term methotrexate (sMTX) in 44 patients, TAC with MTX and anti-thymocyte globulin (ATG) in 10 patients, TAC with mycophenolate mofetil (MMF) in 33 patients, TAC alone in 17 patients, and post-transplantation cyclophosphamide (PTCY) with TAC and MMF in 30 patients, respectively (Supplementary Table). TAC alone and TAC with MMF were mainly performed in CBT. All PTCY with TAC and MMF were performed in HLA-haploidentical PBSCT.

Incidences of HHV-6 encephalitis and sodium abnormalities

Among 134 allo-HSCT recipients, 14 (10.4%) patients developed HHV-6 encephalitis at a median of 24 days (range, 9–48 days) after allo-HSCT (Fig. 1A). The incidence of HHV-6 encephalitis was significantly higher in the recipients of unrelated donors than in those of related donors (15.1% vs 2.1%, P = 0.018), in CB recipients than in BM or PBSC recipients (16.7% vs 5.4%, P = 0.046), and in the recipients treated with TAC alone as GVHD prophylaxis than in those treated with multiple drugs combinations (29.4% vs 7.7%, P = 0.018).

Since all HHV-6 encephalitis developed within 50 days after allo-HSCT, we analyzed serum sodium dynamics in this period. During this period, a total of 31 (23.1%) patients presented with sodium

abnormalities (Fig. 1B). Of these, 10 (7.5%) patients developed hypernatremia at a median of 16 days (range, 6–26 days) after allo-HSCT, while 21 (15.7%) patients developed hyponatremia at a median of 19 days (range, 8–48 days) after allo-HSCT.

Risk factors for HHV-6 encephalitis

Next, we analyzed risk factors for the development of HHV-6 encephalitis after allo-HSCT (Table 2). In univariate analysis, CBT (HR 4.748, 95%CI: 1.087–10.490, $P = 0.029$), GVHD prophylaxis with TAC alone (vs. multiple drugs combination) (HR 8.064, 95%CI: 1.537–13.830, $P = 0.005$), and hyponatremia (HR 9.615, 95%CI 2.946–31.380, $P = 0.0001766$), treating as a time-dependent covariate, were significantly correlated with the development of HHV-6 encephalitis. In multivariate analysis, hyponatremia (HR 9.501, 95%CI 2.534–35.620, $P = 0.0008399$) was identified as a significant risk factor for the development of HHV-6 encephalitis.

Timing of hyponatremia and HHV-6 encephalitis

Finally, we investigated whether hyponatremia could precede the onset of HHV-6 encephalitis. The serial change of serum sodium levels before and at the onset of HHV-6 encephalitis in each patient are shown in Fig. 2. In the 14 patients who developed HHV-6 encephalitis, seven (50.0%) patients had preceded hyponatremia within a week before the diagnosis of HHV-6 encephalitis. On the other hand, 14 of 21 patients who had hyponatremia did not develop HHV-6 encephalitis (data not shown). From these results, the sensitivity, specificity, PPV, NPV, LR+, and LR- of hyponatremia for the diagnosis of HHV-6 encephalitis were 50%, 88.3%, 33.3%, 93.8%, 4.286, and 0.566, respectively (Table 3). Although the presence of CNS dysfunction is essential for the diagnosis of HHV-6 encephalitis, allo-HSCT recipients may develop CNS dysfunction due to many other factors than HHV-6 encephalitis.[32, 33] In our study, only 14 out of 41 patients with CNS dysfunction after allo-HSCT were caused by HHV-6 encephalitis. The sensitivity, specificity, PPV, NPV, LR+, and LR- of CNS dysfunction for the diagnosis of HHV-6 encephalitis were 100%, 77.5%, 34.1%, 100.0%, 4.444, and 0.000, respectively (Table 3). CNS dysfunction alone was insufficient for the diagnosis in terms of the specificity. Therefore, we investigated whether the coexistence of CNS dysfunction and hyponatremia could improve the diagnostic accuracy of HHV-6 encephalitis. The sensitivity, specificity, PPV, NPV, LR+, and LR- of the coexistence of CNS dysfunction and hyponatremia for the diagnosis of HHV-6 encephalitis were 50%, 98.3%, 77.8%, 94.4%, 30.000, and 0.508, respectively (Table 3). The coexistence of hyponatremia and CNS dysfunction remarkably increased DOR from 7.571 to 59.000 compared to the hyponatremia alone (Table 3).

Discussion

In this study, we demonstrated that the preceding hyponatremia is a specific hallmark for HHV-6 encephalitis after allo-HSCT and the coexistence of hyponatremia and CNS dysfunction improved the diagnostic accuracy of HHV-6 encephalitis after allo-HSCT.

HHV-6 encephalitis develops between 2 and 6 weeks after allo-HSCT, most frequently in week 3 after transplantation.[3, 6, 10] Neurological symptoms worsen by the hour and often require the artificial ventilation in patients with aggressive disease course, and also survivors suffer from neurological sequelae.[3, 6–9] Therefore, initiation of antiviral therapy as early as possible is desirable in patients with suspected HHV-6 encephalitis. Monitoring of plasma HHV-6 DNA may be useful to predict HHV-6 encephalitis.[5, 8] However, several approaches such as plasma HHV-6 DNA-guided preemptive approaches and prophylactic foscarnet had failed to completely prevent the development of HHV-6 encephalitis.[34–37] Based on these studies, routine screening of HHV-6 DNA in blood and anti-HHV-6 prophylactic or preemptive therapy after allo-HSCT is not recommended.[11, 12] Cerebrospinal PCR testing is useful for the diagnosis of HHV-6 encephalitis,[11, 12] but positive results do not always mean HHV-6 encephalitis.[13] Furthermore, magnetic resonance imaging (MRI) demonstrated characteristic features in HHV-6 encephalitis,[3, 7, 8, 19, 34, 36] but it is not useful for early diagnosis because these changes appear a week after the onset.[15] For the above reasons, a useful and early auxiliary marker that enables to diagnose and to initiate the antiviral therapy against HHV-6 encephalitis is unmet medical needs.

Hyponatremia is one of the most common electrolyte disorders and the incidence after allo-HSCT at single center was reported to be 40%.[38] The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most definitely documented pathogenesis of hyponatremia after allo-HSCT [22, 38, 39] and was reported the association with HHV-6 encephalitis.[20, 40, 41] Although not all cases had been tested to formally diagnose SIADH in this study, 2 out of 14 patients with HHV-6 encephalitis and 1 out of 120 patients without HHV-6 encephalitis were diagnosed with SIADH. Regarding the timing of hyponatremia and HHV-6 encephalitis, Murakami et al. reported that all 5 patients with HHV-6 encephalitis showed hyponatremia on or a few days before the onset.[18] Our study indicated that the preceding hyponatremia specifically observed within a week before the onset of HHV-6 encephalitis. In addition, the coexistence of hyponatremia and CNS dysfunction strongly suggests HHV-6 encephalitis. Thus, this coexistence in allo-HSCT recipients prompt to assess the CNS disease by lumbar puncture and may lead to the early initiation of anti-HHV-6 therapies with more efficiently.

The current study had several limitations. First, this was the small number study and retrospective in nature. Therefore, it is still unclear whether the cutoff value of 130mEq/L or less is appropriate for the differential diagnosis of HHV-6 encephalitis. It is necessary to set an appropriate cutoff value by collecting a large number of cases from multiple centers. Second, we did not evaluate other factors that may affect serum sodium level such as fluid replacement, diuretic drugs, vomiting, and diarrhea.[42, 43]

In conclusion, our study suggests the possibility of HHV-6 encephalitis significantly increases when appearing CNS dysfunction following hyponatremia after allo-HSCT. When hyponatremia emerge after allo-HSCT, we should monitor carefully about the symptoms of HHV-6 encephalitis. In future, a large-scale prospective studies are warranted to confirm our findings.

Declarations

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AUTHORSHIP CONTRIBUTIONS

SY and TA designed the study, reviewed and analyzed data, and wrote the paper; KO collected data and revised the manuscript; YM, ST, KK and EK collected data. MI, TT, and SO revised the manuscript. All authors contributed to the final version of the manuscript and approved it for the publication.

CONFLICT OF INTEREST

The authors have no conflicts of interest associated with this article.

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

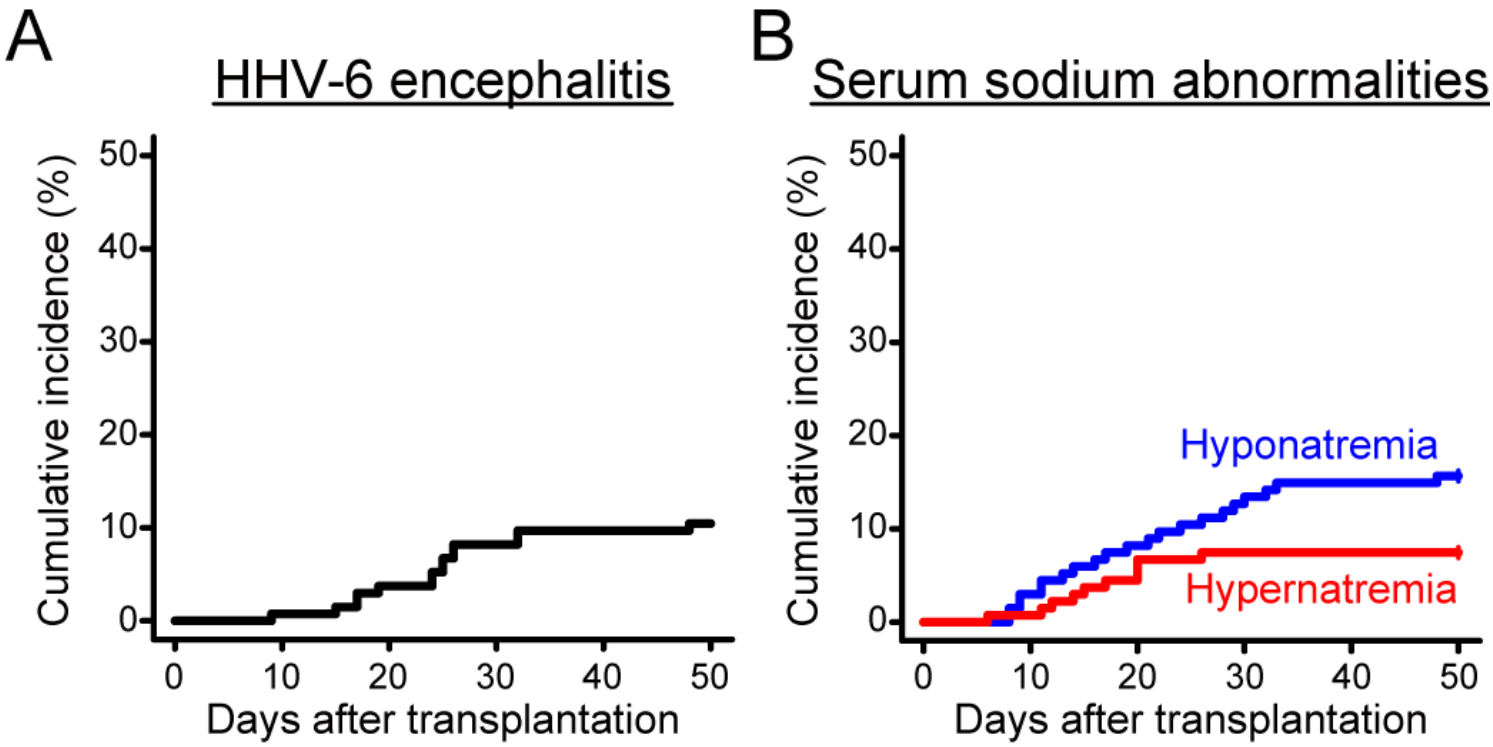

Figure 1

Cumulative incidences of HHV-6 encephalitis and sodium abnormalities.

(A) Cumulative incidence of HHV-6 encephalitis until 50 days after allo-HSCT are shown. (B) Cumulative incidence of hypernatremia (red line) and hyponatremia (blue line) until 50 days after allo-HSCT are shown.

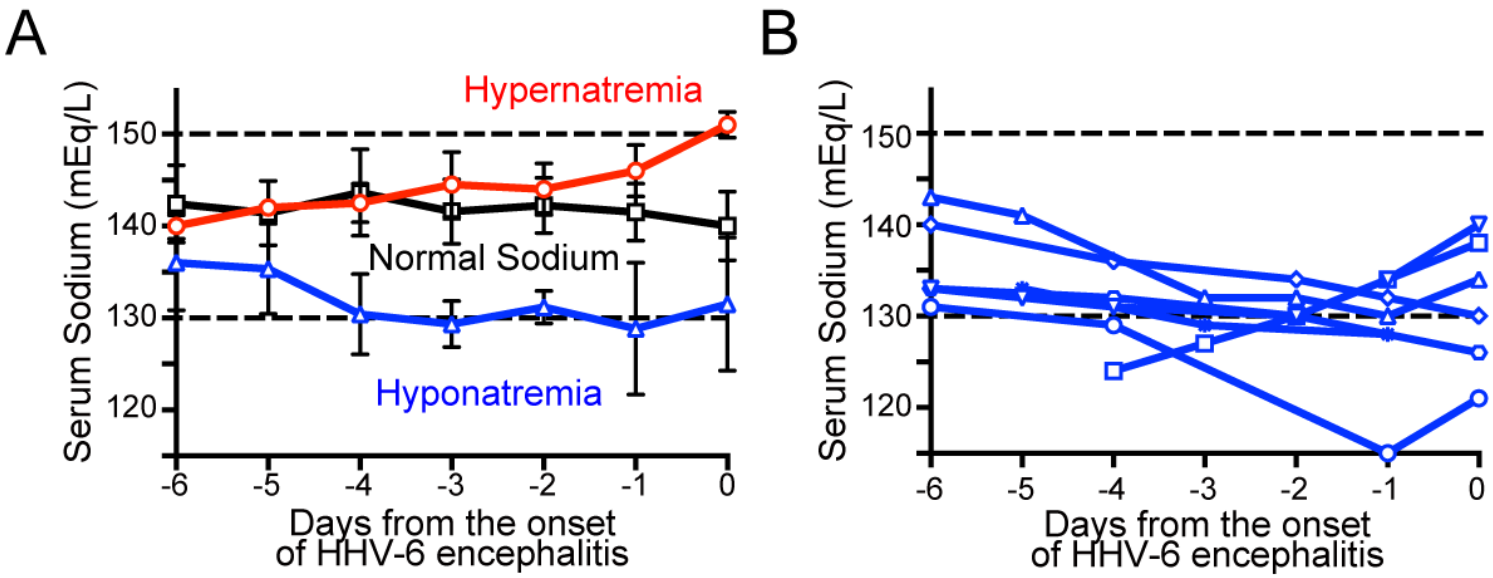

Figure 2

The serial changes of serum sodium levels a week before the onset of HHV-6 encephalitis.

(**A**) The serial changes of serum sodium levels a week before the onset of HHV-6 encephalitis in 2 patients with hypernatremia (red line), 5 patients with normal sodium level (black line), and 7 patients with hyponatremia (blue line) are shown. Data are shown as means ± SEM. (**B**) The serial changes of serum sodium levels a week before the onset of HHV-6 in each patient with hyponatremia are shown.

Supplementary Files

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- SupplementaryTable.pdf
- Table1.xlsx
- Table2.xlsx
- Table3.xlsx