Human Herpesvirus 6 DNA in Cerebrospinal Fluid Specimens from Allogeneic Bone Marrow Transplant Patients: Does It Have Clinical Significance?

Fu-Zhang Wang, Annika Linde, Hans Hägglund, Marina Testa, Anna Locasciulli, and Per Ljungman

From the BMT Program, Huddinge University Hospital, Karolinska Institute, Huddinge, and the Department of Virology, Swedish Institute for Infectious Disease Control, Stockholm, Sweden; and the Department of Pediatrics, Hospital S. Gerardo, Monza, Italy

Cerebrospinal fluid (CSF) specimens from 22 allogeneic bone marrow transplant patients with central nervous system (CNS) symptoms (cases) and 107 patients who were immunocompromised but did not have CNS symptoms (controls) were assayed for human herpesvirus 6 (HHV-6) DNA. HHV-6 DNA was detected in CSF specimens from five (23%) of 22 cases and in CSF specimens from one (0.9%) of 107 controls ($P < .001$, Fisher’s exact test). In addition, none of the five cases with HHV-6 DNA detected in CSF samples had any other identified cause of their CNS symptoms, and none of the other 11 cases with known causes for their CNS diseases had HHV-6 DNA detected in CSF samples ($P = .03$, Fisher’s exact test). In three cases, HHV-6 variant B was identified, and the HHV-6 variant could not be defined in the other two cases. Prophylaxis with acyclovir did not prevent the occurrence of HHV-6-associated CNS disease after allogeneic bone marrow transplantation. Four cases’ conditions were improved or they were cured after treatment with either ganciclovir or foscarnet, and one case died of CNS disease despite foscarnet treatment.

The incidence of CNS complications after allogeneic bone marrow transplantation (BMT) varies between 11% and 37% at different BMT centers, and CNS disease is frequently associated with a fatal outcome [1–4]. Several different etiologies of CNS symptoms in patients who have undergone BMT have been described, such as pulmonary compromise, renal failure, hepatic dysfunction, hemorrhage in the CNS, drug toxicity, and various kinds of infections. However, a large proportion of CNS symptoms after BMT remain unexplained.

Human herpesvirus 6 (HHV-6) is a recently discovered herpesvirus, and HHV-6 isolates can be classified into variants A and B according to DNA sequences, cell tropism in vitro, and antigenicity [5]. HHV-6 can infect glial cell lines, and both of the HHV-6 variants can productively infect primary astrocytes [6–8]. Previous studies have suggested that HHV-6 can invade the CNS during primary infection and that the CNS may be one site of latency for HHV-6 [9–11]. Cases of fatal CNS infections caused by HHV-6 have been described in immunocompetent individuals as well as in patients infected by HIV or liver transplant recipients [12–15]. One case of fatal encephalitis due to HHV-6 variant B has been reported after allogeneic BMT [16]. Both HHV-6 variants are susceptible to foscarnet in vitro [17–20]. HHV-6 variant B strains are also susceptible to ganciclovir, while variant A may be less susceptible [17–21]. There are no data available regarding the need for and efficacy of antiviral therapy for HHV-6 infections in patients who have undergone allogeneic BMT; thus, further studies on the role of HHV-6 in CNS disease after allogeneic BMT are warranted since HHV-6 is susceptible to the antiviral drugs mentioned above.

The aims of this study were to analyze the frequency of HHV-6 DNA detection in CSF specimens from immunocompromised patients with or without CNS symptoms and to elucidate the clinical significance of detectable HHV-6 DNA in CSF after allogeneic BMT.

Patients and Methods

Controls. Ninety-four CSF samples were collected from 74 pediatric patients (mean age, 6.5 years; range, 1–18 years) before they received intrathecal prophylaxis for CNS leukemia with methotrexate as part of chemotherapy for hematologic malignancies at Hospital S. Gerardo, Monza, Italy. In addition, 41 CSF samples were collected from 29 patients with hematologic malignancies 1 week before BMT and from 6 patients after allogeneic or autologous BMT at routine CSF examinations or before intrathecal prophylaxis for CNS leukemia at Huddinge University Hospital, Huddinge, Sweden, or at Hospital S. Gerardo. Two patients donated CSF specimens both before and after BMT; therefore, the total number of controls was 107. The characteristics of the controls are given in table 1.

Cases. Three hundred thirty-eight patients underwent allogeneic BMT at Huddinge University Hospital between 1 January 1990 and 30 April 1997. Of these 338 patients, 24 (7.1%) developed CNS symptoms. The median age of the 24 patients...
with CNS symptoms was 17 years (range, 1–53 years). Ten (5.5%) of 182 patients with matched sibling donors developed CNS symptoms, while 14 (10%) of 140 patients with unrelated donors developed CNS symptoms (P = .14, Fisher’s exact test). None of 16 patients with HLA mismatched sibling donors developed CNS symptoms.

No CSF samples from two of the 24 patients with CNS symptoms were available for analysis of HHV-6 DNA, and these two patients were excluded from the study. Of these two patients, one had verified CNS leukemia, and the other had bacterial meningitis. Two CSF samples were collected from two patients before BMT at routine CSF examination, and one CSF sample was collected from one patient 2 weeks before CNS symptoms were noticed. Twenty-four CSF samples were collected from 22 patients at the time of CNS symptoms, and four CSF samples were collected from four patients after recovery following antiviral therapy. Therefore, 31 CSF samples from 22 patients with CNS symptoms (cases) were available for analysis in this study. The characteristics of the 22 cases are shown in table 1. Fourteen of the 22 cases had unrelated donors, while eight had HLA identical sibling donors.

In addition to the CSF samples, 30 peripheral blood leukocyte (PBL) samples were collected from six of the 22 cases before and during the period when CNS symptoms were noticed.

The study was approved by the Ethical Committees at Huddinge University Hospital and Hospital S. Gerardo.

**Conditioning regimens.** Patients with malignancies were treated either with cyclophosphamide (60 mg/kg) for two consecutive days followed by total body irradiation (TBI; 10 Gy with the lungs shielded for a dose of 9 Gy) or with busulfan (4 mg/kg) for four consecutive days followed by cyclophosphamide (60 mg/kg) for two consecutive days. Patients with aplastic anemia were treated with cyclophosphamide (50 mg/kg) together with antithymocyte globulin for four consecutive days. Children with metabolic disorders were given therapy with busulfan and cyclophosphamide. Patients with nonmalignant diseases and unrelated donors were usually treated with cyclophosphamide in combination with TBI, although other regimens were also used in individual cases. Of the 22 cases included in this study, 15 received TBI, while seven did not.

**Antiviral prophylaxis.** During the study period, different strategies were used for antiviral prophylaxis. Low doses of acyclovir (200 mg orally four times daily) were used for preventing herpes simplex virus (HSV) infection in patients at high risk starting 1 week before BMT, and this therapy was discontinued 3 weeks after BMT. Patients with high titers of IgG to HSV (10,000) were given low doses of acyclovir. The main strategy used for prevention of cytomegalovirus (CMV) disease was preemptive therapy based on the results of PCR analysis, but some patients also received high doses of acyclovir (500 mg/m² intravenously three times daily) or valacyclovir (2,000 mg orally four times daily) as prophylaxis for CMV infection.

Four of the 22 cases were receiving antiviral prophylaxis at the time when CNS symptoms developed: one with high doses of acyclovir, one with low doses of acyclovir, and two with valacyclovir. Prophylaxis for three patients was discontinued at the time of CNS symptoms. Valacyclovir therapy was continued for the fourth patient because of an unclear etiology of the CNS symptoms. No patient in this study had received prophylactic ganciclovir or foscarnet.

**Identification of pathogens causing CNS symptoms.** All 22 cases were routinely screened for infection with bacterial, fungal, and virological agents by isolation, serology, or PCR analysis at Huddinge University Hospital. All the CSF samples were analyzed for DNA from HSV types 1 and 2 and CMV by PCR methods. PCR analyses for varicella-zoster virus (VZV), Epstein-Barr virus (EBV), enterovirus, and JC and BK viruses were also performed if clinically suggested. Routine PCR methods at the Department of Virology, Huddinge University Hospital, were used. Finally, CSF samples also underwent histopathological examination and fluorescence-activated cell sorting analysis for malignant cells.

Of the 22 cases, 11 had the etiology of the CNS symptoms identified by the methods described above. The infectious etiologies were as follows: HSV type 1, 1 patient; VZV, 2; CMV, 1; EBV, 1; parainfluenza virus, 1; and enterovirus, 1. The other causes were drug toxicity (2 patients), bleeding in the CNS (1), and leukemia relapse in the CNS (1). It is interesting that one (0.5%) of 182 patients with matched sibling donors vs. six (4.3%) of 140 patients with unrelated donors had a viral etiology of the CNS symptoms (P = .046, Fisher’s exact test).

**Definitions.** Engraftment of neutrophils was defined as an absolute neutrophil count of >0.5 × 10^9/L for two consecutive days;
engraftment day of platelets or RBCs was defined as the first day after transfusion for platelets or RBCs, respectively, was stopped. Acute GVHD was defined according to Thomas et al. [22].

Preparation of CSF samples for PCR analysis for HHV-6 and human herpesvirus 7 (HHV-7). CSF samples were stored at \(-20^\circ C\) before analysis. CSF samples were heated for 15 minutes at 94\(^\circ\)C, and 10 \(\mu\)L was used for each PCR analysis.

Detection of HHV-6 and HHV-7. Two previously reported nested PCR methods were used for detection of HHV-6 DNA and HHV-7 DNA, respectively [23, 24]. The PCR method for HHV-6, which yields a final product of 130 bp, has a sensitivity of 20–30 genomes for HHV-6 variants A and B. HHV-6 variants A and B were also differentiated by a previously described nested PCR method, which yields products of different sizes for each variant [24]. The sensitivity of the PCR method for HHV-6 is around 50 genomes for both HHV-6 variants. The sensitivity of the PCR method for HHV-7 has not been defined.

Sterilized water was used as a negative control for every three to five CSF samples in the PCR methods for both HHV-6 and HHV-7. Culture supernatant from the GS strain and/or Z 29 strain was used as a positive control for the PCR assays for HHV-6. An HHV-7 DNA–positive saliva sample from a patient with AIDS was used as a positive control for the PCR assays for HHV-7.

All the CSF samples from the cases were analyzed at least twice in the PCR assays for both HHV-6 and HHV-7.

Detection of HHV-6 DNA in peripheral blood leukocyte (PBL) samples. PBL samples were analyzed for HHV-6 DNA and HHV-6 variants according to a previously reported method with the same PCR methods as described above [23]. DNA representing \(5 \times 10^6\) PBLs was used for each PCR assay. PCR assay of PBL samples for HHV-6 was performed in the same way as that for the CSF samples, and the HHV-6 variants in the PBL samples were differentiated by the same method as described above.

Results

Detection of HHV-6 DNA in CSF samples from controls. HHV-6 DNA was detected in two (1.5%) of 135 CSF samples from the controls. The two CSF samples with detectable HHV-6 DNA were collected from the same patient 4 months apart, but no CNS symptoms were noticed during this period or later during 2 years of follow-up. Thus, HHV-6 DNA was detected in CSF samples from one (0.9%) of 107 controls.

Detection of HHV-6 DNA in CSF samples from cases. HHV-6 DNA was detected in five (16%) of 31 CSF samples from five (23%) of 22 cases. Furthermore, none of the five cases with detectable HHV-6 DNA in CSF samples had any previously defined cause of their CNS symptoms. Thus, five (45%) of 11 cases without previously defined causes of their CNS symptoms compared with zero of 11 cases with previously defined causes of their CNS symptoms had detectable HHV-6 DNA in CSF samples \((P = .03, \text{ Fisher’s exact test})\). HHV-7 DNA was not detected in any of the 31 CSF samples.

HHV-6 DNA was detected in the CSF sample from one patient 2 weeks before the CNS symptoms appeared and in CSF samples from four patients at the time when CNS symptoms were noticed. Three of the HHV-6 DNA–positive CSF samples contained HHV-6 variant B, and the HHV-6 variants in the other two samples could not be defined. Of the five patients with detectable HHV-6 DNA in CSF samples, two patients had CSF samples available before allogeneic BMT, and three patients had CSF samples collected after antiviral therapy when the CNS symptoms abated; HHV-6 DNA was not detected in any of these CSF samples. In addition, no other microbiological causes were detected in any of the CSF samples, and none of the CSF samples contained malignant cells.

Detection of HHV-6 DNA in PBL samples from the five cases with detectable HHV-6 DNA in CSF samples. Nineteen PBL samples were collected weekly from four of the five cases with detectable HHV-6 DNA in CSF samples before and during the time when CNS symptoms were noticed. HHV-6 DNA was detected in 15 of 18 PBL samples from three cases (nos. 2, 4, and 5 in table 2). In all three cases, HHV-6 variant B was detected in PBL samples. There was only one PBL sample available from case 3. This sample was collected at the time when CNS symptoms were noticed. HHV-6 DNA was not detected in this PBL sample.

CNS symptoms of the five cases with detectable HHV-6 DNA in CSF specimens. The types of CNS symptoms of the five cases with detectable HHV-6 DNA in CSF samples are shown in table 2. All five cases had symptoms characterized as encephalitis including confusion (four of five) and somnolence (three of five). Three cases developed CNS symptoms before engraftment, while two developed CNS symptoms after engraftment. The three cases with early CNS symptoms were more severely affected.

Biochemistry analysis of CSF samples showed elevated albumin levels in all four cases analyzed. One patient had an elevated WBC count with a predominance of mononuclear cells. The electroencephalogram showed mild or severe diffuse abnormalities in all four cases analyzed. CT indicated pathological changes in only two cases, and in case 3, a subarachnoid hemorrhage that was indicated by CT could not be confirmed at autopsy performed 2 days later. MRI showed signs of an old hemorrhage in one of three cases analyzed, while the other two scans were normal.

The clinical characteristics, treatment regimens, and outcomes of the five cases with detectable HHV-6 DNA in CSF specimens are shown in table 3. Four patients were receiving antiviral prophylaxis or antiviral treatment when the CNS symptoms appeared. One case was receiving high doses of acyclovir, one was receiving valacyclovir, and two were receiving ganciclovir (5 mg/kg intravenously twice daily) as preemptive therapy for CMV infection. All the five cases received antiviral therapy after the appearance of CNS symptoms. Four cases were treated with foscarnet (60 mg/kg intravenously three times daily), and one was treated with ganciclovir (5 mg/kg...
intravenously twice daily). HHV-6 DNA was not detected in any of the three CSF samples from cases 2, 4, and 5, respectively, after foscarnet treatment and recovery.

Three cases were considered cured: case 1 survived for 3 weeks without CNS symptoms and died of bleeding, and cases 4 and 5 were still alive >2 years after BMT and were well without CNS symptoms. Case 2 responded to foscarnet therapy with improved mental status but died later of multiple organ failure. The patients recovered within 1–2 weeks after the start of treatment, and the treatment was continued for another 2 weeks at full doses after the symptoms disappeared. No patient received chronic suppressive antiviral therapy.

The CNS disease in case 3 progressed rapidly, and the patient died despite treatment with foscarnet. An autopsy was performed. Tissue specimens from the white matter of the frontal lobe of the cerebral cortex, basal ganglia, medulla oblongata, and pons were abnormal, and the pathology consisted of diffuse edema, perivascular aggregates of monocytes and macro-

### Table 2. Symptoms of allogeneic bone marrow transplant recipients with CNS symptoms (cases) who had HHV-6 detected in their CSF samples.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>CNS symptoms</th>
<th>Neurological signs</th>
<th>WBC/RBC counts (/mL)</th>
<th>Albumin level* (mg/L)</th>
<th>Electroencephalogram</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confusion, excitement</td>
<td>Neck stiffness, uncontrollable muscle movements</td>
<td>2/154(^1)</td>
<td>ND</td>
<td>Mild diffuse abnormality</td>
<td>Normal</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>Somnolence, speech abnormalities</td>
<td>Weakness in one arm, increased reflexes</td>
<td>0/0</td>
<td>538</td>
<td>Mild diffuse abnormality</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>Headache, seizures, coma</td>
<td>Increased reflexes, wide pupils</td>
<td>6/1,250(^1)</td>
<td>12,880</td>
<td>Severe diffuse abnormality</td>
<td>Subarachnoid bleeding(^2)</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>Confusion, speech abnormalities</td>
<td>Loss of muscle coordination</td>
<td>49/3</td>
<td>941</td>
<td>ND</td>
<td>Low attenuated changes</td>
<td>Old hemorrhage</td>
</tr>
<tr>
<td>5</td>
<td>Confusion, somnolence, vomiting</td>
<td>None</td>
<td>4/6</td>
<td>965</td>
<td>Pronounced pathological episodes</td>
<td>Normal</td>
<td>ND</td>
</tr>
</tbody>
</table>

**NOTE.** HHV-6 = human herpesvirus 6; ND = not done.

* Normal level, <320 mg/L.

\(^1\) Contaminated by peripheral blood.

\(^2\) Was not confirmed at autopsy performed 2 days later.

### Table 3. Clinical characteristics of allogeneic bone marrow transplant recipients with CNS symptoms (cases) who had HHV-6 detected in their CSF samples.

<table>
<thead>
<tr>
<th>Patient no., age (y)/sex</th>
<th>Type of graft</th>
<th>Time to diagnosis after BMT (d)</th>
<th>Engraftment day absolute neutrophil/platelet/RBC (/mL)</th>
<th>Antiviral treatment</th>
<th>Time from diagnosis to death(^7) (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 45/M</td>
<td>HLA identical donor</td>
<td>I</td>
<td>22</td>
<td>35/51/38</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>2, 45/F</td>
<td>Unrelated donor</td>
<td>I</td>
<td>10</td>
<td>18/33/31</td>
<td>Valacyclovir</td>
</tr>
<tr>
<td>3, 44/M</td>
<td>Unrelated donor</td>
<td>I</td>
<td>18</td>
<td>17/21/19</td>
<td>None</td>
</tr>
<tr>
<td>4, 28/M</td>
<td>Unrelated donor</td>
<td>0</td>
<td>64</td>
<td>16/22/13</td>
<td>Ganciclovir</td>
</tr>
<tr>
<td>5, 41/F</td>
<td>Unrelated donor</td>
<td>II</td>
<td>75</td>
<td>11/30/93</td>
<td>Ganciclovir</td>
</tr>
</tbody>
</table>

**NOTE.** BMT = bone marrow transplantation; GVHD = graft-vs.-host disease; HHV-6 = human herpesvirus 6.

* Drugs were used at the time when the CNS symptoms developed.

\(^3\) Date of diagnosis was defined as the first day when the CNS symptoms were noticed.

\(^4\) Died of bleeding.

\(^5\) Died of multiple organ failure.

\(^6\) Died of CNS disease.
phages, microglial proliferation, and accumulation of granulocytes and macrophages and atypical inflammatory cells in the tissues. The leptomeninges were fibrotic. No abnormality was observed in the cerebral cortex, hippocampal gyrus, mesencephalon, or cerebellum. The involved brain tissues were screened for DNA from HSV types 1 and 2, VZV, CMV, EBV, JC virus, adenovirus, and HHV-6 by the same PCR methods that were mentioned under Patients and Methods, and only HHV-6 DNA was detected in the involved brain tissues.

Four of 14 cases with unrelated donors had HHV-6-associated CNS disease vs. one of eight cases with HLA identical sibling donors. In addition, four of 15 cases who underwent TBI had HHV-6 DNA detected in CSF samples vs. one of seven cases who did not undergo TBI.

**Discussion**

CNS symptoms are common in patients who have undergone allogeneic BMT, and the cause of the symptoms frequently remains undetermined. In our study, the incidence of CNS disease among patients who underwent allogeneic BMT was 7%, which is similar to rates in previous reports [1–4].

HHV-6 can actively infect glial cell lines and primary astrocytes, and cases of CNS infection with HHV-6 have been described in both immunocompromised patients and immunocompetent individuals [9–16]. There is no established clinical or radiological method to differentiate HHV-6 infections from other CNS complications after allogeneic BMT. A significant correlation between detection of CMV and other viral DNA in CSF and viral meningitis or encephalitis has been indicated in recent reports [25–27]. However, HHV-6 DNA can be detected in normal brain tissues as well as in cellular components of CSF collected from patients with noninflammatory neurological symptoms [10, 28, 29]. Data regarding detection of HHV-6 in CSF samples from immunocompromised patients without CNS symptoms are lacking; therefore, it has been difficult to assess the importance of detection of HHV-6 DNA in CSF specimens from immunocompromised patients presenting with CNS symptoms.

We detected HHV-6 DNA in CSF samples from five (45%) of 11 patients with CNS symptoms of undefined origin after allogeneic BMT (cases). In contrast, HHV-6 DNA was detected in the CSF sample from only one (0.9%) of 107 immunocompromised patients without CNS symptoms (controls) and in none of the 11 patients who underwent BMT for whom other causes for the CNS diseases were documented (cases). Furthermore, HHV-6 DNA was not detected either in the CSF samples collected before BMT or in the CSF samples collected after the CNS symptoms had abated following antiviral therapy. These data support a causative role for HHV-6 in these cases of encephalitis.

Another possible explanation for the detection of HHV-6 DNA in CSF could be that PBLs containing HHV-6 DNA had "contaminated" the CSF. However, we believe that this is an unlikely explanation since the numbers of WBCs in the HHV-6 DNA-positive CSF samples were very low and either HHV-6 DNA was undetectable or the levels of HHV-6 DNA were too low in the PBL samples from these patients to cause significant contamination of CSF considering the WBC content of these CSF samples (data not shown).

We have previously shown that patients who undergo allogeneic BMT frequently have several of the lymphotropic herpesviruses detectable in PBL samples during the first months after BMT [23]. HHV-7 is closely related to HHV-6 and has also been reported as a cause of exanthem subitum and CNS symptoms [30, 31]. HHV-7 DNA, however, was not detected in any of the CSF samples from the 22 cases.

The results of a retrospective comparison can be influenced by the choice of the control population. We chose a population of immunosuppressed patients to mimic the population for whom HHV-6 might be a clinical problem. It could be argued that the relevant controls might be either healthy individuals or a group including only patients who have undergone BMT. We believe that there would be no advantage to using healthy controls since we found only one control with HHV-6 DNA in the CSF sample, and it is unlikely that HHV-6 would have been more common in CSF specimens from immunocompetent individuals. Regarding the use of only patients who have undergone BMT, two control populations of patients who underwent BMT were in fact used in this study: asymptomatic patients and patients with other clearly defined causes of the CNS symptoms. HHV-6 DNA was not found in the CSF specimens from any of these patients who had undergone BMT.

Thus, our data suggest that the role of HHV-6 as a pathogen of CNS disease after allogeneic BMT might be underestimated. The results of a recent study involving patients with AIDS showed that only 2% of 500 AIDS patients with CNS symptoms due to other causes had HHV-6 DNA detected in CSF samples [32]. This finding suggests that the detection of HHV-6 DNA in CSF together with clinical symptoms of a CNS infection should be assumed to be a finding of clinical relevance.

An increasing number of patients undergoing allogeneic BMT receive transplants from unrelated donors. The intensified immunosuppression needed as prophylaxis for acute GVHD and acute GvHD itself probably predispose patients to viral reactivations. In our study, viral infections of the CNS were more frequent in patients whose transplants were from unrelated stem cell donors, including four of the five cases with CNS disease possibly due to HHV-6. Patients with unrelated donors are usually more immunosuppressed than those with HLA identical sibling donors, which may increase the risk for viral infection of the CNS. It might be possible that TBI may lead to HHV-6 reactivation in the CNS. However, this possibility was not supported by our data since our series included only five cases.

HHV-6 may affect both gray and white matter as well as the hippocampus and lead to progressive mental deterioration.
after allogeneic BMT [16]. Although all five cases in our study who had HHV-6 DNA detected in CSF samples had symptoms consistent with encephalitis and meningoencephalitis, the clinical presentation was in accordance with previous reports of HHV-6 infections of the CNS [13–16]. Like other patients with infectious CNS complications after allogeneic BMT, the differential diagnostic value of electroencephalography, CT, and MRI were not sufficient in establishing the diagnosis, the detection of HHV-6 DNA in CSF by means of PCR analysis provides an important tool for both diagnosis and monitoring of therapy.

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References


