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Review

Herpesvirus Infections of the Central Nervous System

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CONTENTS:

SUMMARY: In recent years, advances in the diagnosis and treatment of herpes simplex encephalitis (HSE) have been achieved due to the prevalence of antiviral drugs and the introduction of the polymerase chain reaction (PCR) to test the cerebrospinal fluid. The several clinical forms of herpes simplex virus type 1 (HSV-1) infections of the central nervous system (CNS), including acute disseminated encephalomyelitis and brainstem encephalitis, have been clarified. However, fatal, prolonged, or relapsed cases are still observed, and early detection and appropriate treatment is necessary to lead to a good prognosis for these intractable HSE cases. In adult HSV-2 infections, meningitis and myelitis associated with genital herpes are common. In the past, HSV-2 myelitis has been reported as a form of fatal necrotizing myelopathy; however, using PCR and magnetic resonance imaging studies, mild surviving cases are increasingly likely to be identified. Meanwhile, various CNS syndromes resulting from the herpes group viruses, including varicella-zoster virus and Epstein-Barr virus have also been reported. These herpesviruses have several characteristics in common, e.g., they exist in the latent state and they occur in both mucocutaneous and CNS infections. Adult HSV-1 and -2 infections of the CNS are discussed together with other herpes group virus infections of the CNS.

1. Introduction

Herpes simplex encephalitis (HSE) is the most important cause of sporadic encephalitis in Japan. Two antigenic types of herpes simplex virus (HSV) are distinguished by neutralizing testing. HSV-l (oral type) usually causes adult acute encephalitis and brainstem encephalitis, whereas HSV-2 (genital type) produces meningitis or myelitis (Table 1) (1, 2). For more than 10 years, anti-herpesvirus drugs have been used to treat these diseases, and diagnostic tools such as the enzyme-linked immunosorbent assay (ELISA, or EIA) and the polymerase chain reaction (PCR) have been widely applied for clinical use. HSE has come to be widely recognized as diagnosable and treatable at an early stage of the disease (3-9). In contrast, central nervous system (CNS) infections resulting from other herpes group viruses such as varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesviruses 6, 7 (HHV-6, -7), have tended to increase in both healthy population and in immunocompromised patients such as those with acquired immunodeficiency syndrome (AIDS) (10-17). In this paper, we discuss adult HSV-1 encephalitis and HSV-2 infections of the CNS along with other CNS infections resulting from herpes group viruses.

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2. HSV-1 encephalitis

2-1. Incidence and pathogenesis

HSE, which is primarily caused by HSV-1, is estimated to occur in 1 in 5×10^5 people per year in North Americans (18). A nationwide survey in Japan (19) showed an incidence

Table 1. Herpesvirus group and CNS infections

Herpesviridae		CNS infections	Other important diseases
herpes simplex virus type 1	HSV-1	acute encephalitis brainstem encepalitis	mucocutaneous infections keratoconjunctivitis
type 2	HSV-2	myelitis meningitis	genital herpes disseminated infection of baby
varicella-zoster virus	VZV	encephalopathy, cerebellar ataxia meningitis	varicella herpes zoster, Hunt syndrome
Epstein-Barr virus	EBV	encephalitis, cerebellar ataxia chronic CNS infections	infectious mononucleosis chronic active EBV infection
cytomegalovirus	CMV	congenital CID ventriculoencephalitis	opportunistic infections
human herpesvirus 6, 7	HHV-6, -7	encephalopathy	exanthema subitum

CNS, central nervous system; CID, cytomegalic inclusion body disease.

of 3.5 cases diagnosed per year among 10^6 people, while our data on the Kyushu and Okinawa regions of Japan showed an incidence of 0.31 in 5×10^5 (20). In our study, the number of cases diagnosed within 3 years, 27, was low; this low rate is probably due to the fact that we limited this survey to patients in the neurology and pediatric units of the participating hospital, and because we did not include the internal medicine and psychiatry departments. Our 27 patients ranged in age from one year old to 70 years old, with peaks seen in the 20s and 50s. The incidence of infection among patients in their 50s in our population group was slightly higher than in those in their 20s. As compared with the results of a survey of HSV encephalitis conducted in Japan in 1982, the peak incidence of HSV infections of the CNS appears to have shifted from people in their 20s to those in their 50s.

HSE can occur at any age, but is commonly found in those over age 20. In 53 of 76 patients with HSE, Nahmias et al. (21) identified seropositivity by a neutralizing test or immunofluorescent indirect IgG assay at onset. Mizutani et al. (22) reported a predominant IgG response at 70% in the adult HSE patients. These findings suggest that HSE most often occurs as a result of the endogenous reactivation of a virus, rather than from primary infection. During the primary infection, the virus becomes latent in the trigeminal ganglia. Years later, nonspecific stimuli can cause a reaction, which is usually manifested as herpes labialis. Whitely et al. (23) analyzed both HSV strains using endonucleous restriction enzyme from herpes labialis and brain materials in eight patients with HSV encephalitis; they reported finding the same strain in five patients and different strains in three, suggesting an etiology of endogenous reactivation, with a few cases of reinfection.

2-2. Pathology

The frontal and temporal lesions tend to be necrotic, inflammatory, or hemorrhagic. Eosinophilic intranuclear inclusion bodies are present in the neurons and glial cells. Such inclusions containing viral antigen and herpesvirus particles have been recognized on immunohistochemistry and electron microscopic examination, respectively. Nicoll et al. (24) have reported pathological changes largely confined to the temporal and frontal lobes in long-term survivors of HSV-l encephalitis, and HSV-DNA persisting over several years in both the cerebrum and brainstem. Further, Baringer and Pisani (25) have found latent states of HSV by PCR analysis in parts of the limbic system such as in the cerebellar amygdala and hippocampus in normal brain.

Twomey et al. (26) described the presence of intranuclear inclusion bodies in the olfactory mucosa in cases of HSE, and Dinn (27) has reported HSV particles in the necrotic olfactory bulb in an autopsy case of HSE. Presumably, the virus can reach the brain through branches of the trigeminal nerve to the basal meninges, resulting in localization of the encephalitis to the temporal and orbital frontal lobes.

2-3. Clinical features

The most common symptoms and signs of HSE are fever and signs of meningeal irritation such as headache, altered consciousness, and seizures. Nuchal rigidity or other signs of meningeal irritation are often found. Mental deficits include confusion and personality changes, varying from withdrawal to agitation with hallucinations. Herpetic skin lesions are seen in only a few cases.

Cerebrospinal fluid (CSF) pressure may be moderately or greatly increased. The pleocytosis in the CSF varies from less than 10 to 1,000 cells/mm^3; lymphocytes may be predominant. Red blood cells are frequently seen. The electroencephalogram (EEG) is usually abnormal with diffuse slowing or focal changes over temporal areas; periodic lateralized epileptiform discharges against a slow-wave background may be seen. Brain computed tomography (CT) and magnetic resonance imaging (MRI) demonstrate approximately 70 - 80% abnormal lesions in the frontal and temporal lobes; FLAIR or diffusion MRI is more sensitive.

HSV brainstem encephalitis (28), caused by HSV-1, is characterized by brainstem bulbar symptoms and abnormal lesions in the brainstem visualized by MRI. HSV- related acute disseminated encephalomyelitis (ADEM) can be diagnosed by CSF PCR, by the presence of multifocal neurological symptoms, and by multiple brain lesions by means of MRI (20).

2-4. Diagnosis

HSE is diagnosed by clinical symptoms, and also by CSF, EEG, CT, MRI, and virologic tests such as PCR and ELISA (3-8) (Table 2, Fig.1). Rapid diagnosis is essential for early treatment. The optimal time to begin administration of anti-herpesvirus drugs remains a controversial issue. Generally, anti-herpesvirus drugs are started when HSE is suspected based on CSF findings (increased cell count, elevated protein, and normal sugar concentration), or when the blood or CSF samples are sent for PCR or ELISA testing within a few hours after admission. In Japan, medical lawsuits for delaying the initiation of antiviral drug (acyclovir) therapy or misdiagnosis have increased in number.

To measure HSV antibody levels, complement fixation antibody (CF), neutralizing antibody (NT), and ELISA are available; in addition, CSF ELISA is sensitive and useful for

Table 2. Laboratory diagnosis of HSV-1 encephalitis

1. 4-fold elevation of HSV antibody
• enzyme-linked immunosorbent assay for IgG & IgM
• neutralizing test
• complement fixation test
2. Serum/CSF antibody ratio <20
antibody index ≧ 1.91
3. HSV DNA detection by PCR in CSF
HSV isolation from CSF
chemiluminescence assay

CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

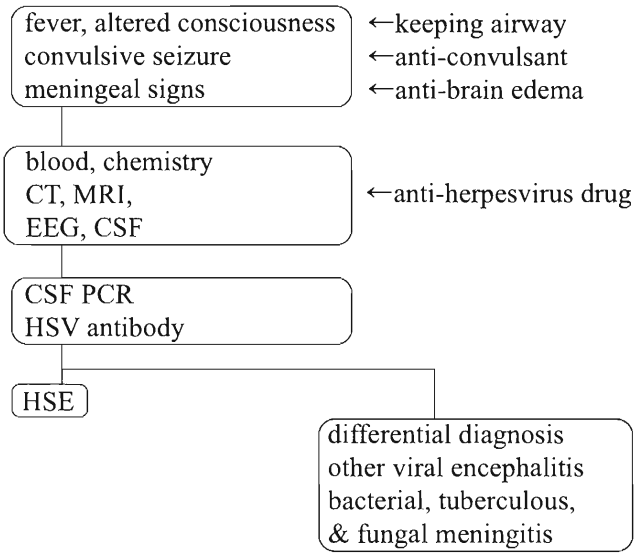

Fig. 1. Diagnostic and therapeutic algorithm for suspected herpes simplex encephalitis (HSE). CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram; CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

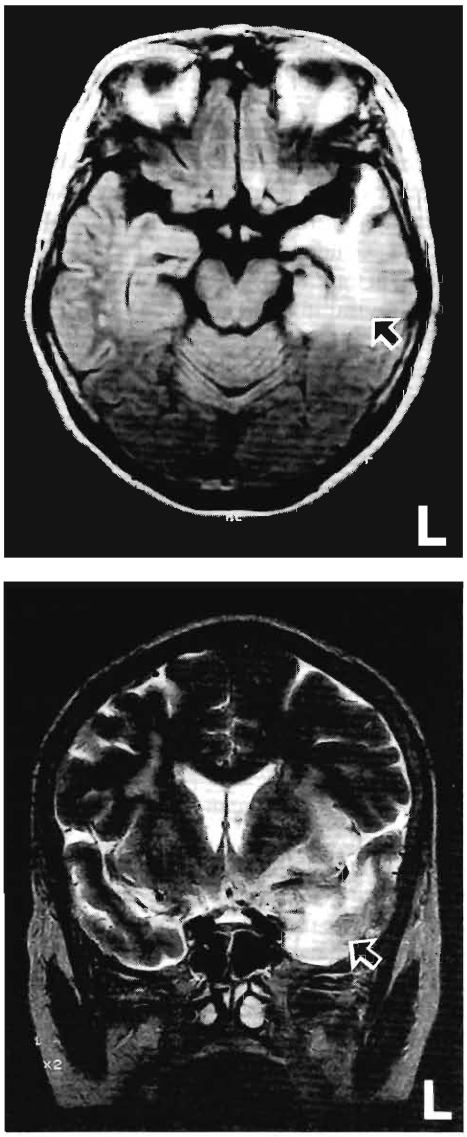

Fig. 2. MRI of HSV-1 encephalitis
A: T2-weighted axial MRI showing abnormal signal lesions in the left temporal lobe, including in the left hippocampi and amygdala (arrow). B: T2-weighted coronal MRI demonstrating the same distribution as that described in A.

early diagnosis. However, normal adults and the elderly have serum HSV antibodies, and simple antibody leaks from the serum to the CSF are often seen. Accordingly, intrathecal antibody production should be determined as follows: i) a serum/CSF antibody level below 20, and ii) an antibody index of over 1.91 (29).

Since 1990, CSF PCR is used for early diagnosis, and the detection rate has been reported to be 60 - 80% within the seventh day of illness (4-8). Although PCR is a noninvasive method, there remains the need for standardization, including that of the primer or in expression of the detection rate. In North American and European studies, PCR has been the primary method for early diagnosis and monitoring of the therapy (7,8).

We present herein a case of HSE followed by a recently developed method of quantitative real-time PCR.

A 65-year-old woman presented with a history of repeated oral herpes and was disoriented with regard to date and place beginning in October 2000. Three days later, generalized tonic seizures appeared togethr with a fever of 37.8°C. A brain MRI revealed a lesion of abnormal intensity in the left temporal lobe and limbic system (Fig. 2). The patient's CSF contained 22 cells/mm^3; protein, 30 mg/dl; glucose, 73 mg/dl. The patient was transferred to our University Hospital. Upon admission, a neurological examination revealed a score of 30 on the Japan Coma Scale (JCS). The serum HSV CF titer was 8x, and the ELISA was 72.5 (positive 4≦). HSV ELISA IgG in the CSF was 0.45. Both the serum and CSF were tested by real-time PCR using the HSV UL 19 region and the Taq Man Probe (Kazuyama Y, personal communication, 2000); these tests revealed HSV genomes at a rate of 300,000 copies/ml in the CSF. HSV-1 was detected in the CSF by nested PCR; i.e., the PCR product was not digested by the restriction enzyme Bam *HI* and was identified as HSV-1. Prompt treatment with acyclovir 1.5 g/day was initiated. At both 2 and 4 weeks, HSV genomes were under 50 copies/ml, and the nested PCR analysis was negative. HSV CSF ELISA IgG had increased significantly by 4 weeks. One month later, the patient began to recover gradually, and she was discharged.

It is of note that the patient's HSV genomes rapidly disappeared after treatment with acyclovir. Several other cases have showed similar results. On the other hand, in one case that was resistant to therapy, the HSV genome persisted at high level for over 2 weeks. Real-time PCR is quantitative; in

contrast to single and nested PCR; real-time PCR is moreover advantageous due to its relative rapidity. Therefore, real-time PCR is a useful method of measuring the effectiveness of acyclovir therapy.

2-5. Differential diagnosis

The differential diagnosis of HSV-l encephalitis includes the following: other viral and postinfectious types of encephalitis and bacterial meningitis, including fungal and tuberculous meningitis, are excluded on the basis of a decrease of glucose concentrations in the CSF. In cases of postinfectious encephalitis, preceding viral infections such as measles and rubella should be excluded.

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) are sometimes manifested and are prone to relapse in later life in cases involving the clinical picture of HSV-l encephalitis (30). When encephalitic symptoms are repeated, mitochondrial cytopathy should also be considered.

During an intensive survey and study of HSE, acute nonherpetic limbic encephalitis was identified as a new subgroup (31). This subgroup is differentiated from those with HSE, as it lacks evidence of the HSV genome or ELISA antibody. In addition, the MRI findings tend to be localized in the bilateral hippocampi and the cerebellar amygdala, although MRIs of HSE primarily show unilateral involvement of the temporal lobe. To date, approximately 30 cases have been reported in Japan. This new subtype is thought to occur along the spectrum with HSE and paraneoplastic limbic encephalitis.

2-6. Prognosis

The recommended antiviral treatment for HSE is a 14-day course of acyclovir given intravenously at a dosage of 10 mg/kg every 8 hours. The disease has been fatal in approximately 30% of the reported cases in Japan. Since induction of the acyclovir treatment, the mortality rate has decreased to 8.2% in Japan; 30% of the cases have remaining sequelae such as amnestic syndrome, while others are able to return home or to work within 6 months. To date, HSE has been regarded as a treatable disease. However, HSE cases that develop to an apallic state and even to death continue to occur, despite early treatment. It is conceivable that in the future, early detection and appropriate treatment will lead to a better prognosis for patients with intractable HSE.

A tentative definition of the subtypes of intractable cases of HSE are as follows:

(i) Cases of HSE that develop to an apallic state and then to fatality.

(ii) Prolonged cases that require more than 6 months' hospitalization.

(iii) Recurrent cases.

It seems likely that the main reasons for the development of intractable HSE are a profound consciousness disturbance and a delay in the initiation of antiviral drug therapy. Conventionally, in the US, a profound disturbance of consciousness in patients with HSE who are over 40 years of age has been regarded as a factor in a fatal prognosis (32). Dennett et al. (33) have reported PCR results were negative, and increased myelin basic protein was detected in the CSF at the time of relapse in cases of recurrent HSE, although PCR positive is found in infantile recurrent HSE. Intractable cases are often attributed to prolonged viral infection or to secondary encephalitis (postinfectious/autoimmune encephalitis). The former indicates that the use of higher doses of acyclovir therapy may be necessary, or suggests the possibility of an acyclovir-resistant HSV; the latter indicates the usefulness of the application of corticosteroids. Further virologic and immunologic studies will be necessary to investigate real-time PCR, specific PCR for acyclovir-resistant HSV, myelin basic protein, and the various cytokines involved in HSV infection.

3. HSV-2 and other herpes group viruses infections of the CNS

3-1. HSV-2 acute encephalitis

HSV-2 (genital type) infections occur primarily via the birth canal in newborn baby and by sexual contact in adults. Although HSV-2 infection in the newborn baby is divided into the disseminated type and the localized type, encephalitis of either type is associated with high mortality. In the adult, meningitis and myelitis associated with genital herpes are common. The treatment is similar to that for HSV-1 encephalitis.

Only a few adult HSV-2 encephalitis have been reported (34); Baker et al. (35) have described adult HSV-2 encephalitis, and Perry et al. (36) have reported a 64-year-old woman with HSV-2 encephalitis and bilateral acute retinal necrosis syndrome after craniotomy.

On the other hand, it has been reported that HSV-2, as an opportunistic infection accompanying AIDS, causes acute encephalitis and acute necrotizing myelopathy. With regard to cases of HSV-2 encephalitis associated with AIDS, Levy et al. (37) have reported a case of acute encephalitis with periodic synchronous discharges on EEG, after which HSV-2 was isolated and identified. They have also reported a case complicated by CMV, an atypical encephalitis predominantly involving white matter.

HSV-2 causes meningitis with or without genital herpes than does HSV-1. In addition, Mollaret's meningitis, a benign type of recurrent aseptic meningitis, has been associated with HSV infections (38); HSV-2 has been identified as responsible for the majority of these cases. Kojima et al. (39) have reported HSV-2 recurrent meningitis (Mollaret's meningitis), for which oral valaciclovir is administered with the aim of preventing HSV-recurrent meningitis.

Regarding HSV type differentiation, recent cases have been analyzed by CSF PCR using restriction endonuclease analysis. CSF PCR is applied primarily for acute-stage HSV infections of the CNS, whereas an ELISA kit using type-specific glycoprotein G can differentiate between HSV-1 and -2 in serum from patients in the convalescent stage. In our recent study (40), of 17 patients with HSV infections of the CNS, HSV-1 and HSV-2 antibodies were found to be present in 13 patients. Furthermore, 11 patients with HSV-1 and two patients with HSV-2 were identified; the data were quite compatible with the results of studies involving the PCR type of differentiation. These findings suggest that HSV-type specific ELISA is a useful test for identifying HSV types.

3-2. HSV myelitis

HSV myelitis occurs primarily in response to HSV-2. It reveals acute ascending myelopathic symptoms such as back pain or urinary disturbance. Fewer than half of all cases show mucocutaneous symptoms. In the past, autopsy cases have been reported as necrotizing myelopathy; however, with the introduction of diagnostic tools such as MRI and CSF PCR, mild surviving cases are likely to be identified (41). Although contamination of the HSV-1 infection is rarely seen in patients with HSV myelitis, we have encountered a case of HSV-1 myelitis with a favorable outcome (42). Lesions (Fig. 3) can be found relatively frequently on MRI of the posterior funiculus of the spinal cord. Such findings may reflect the

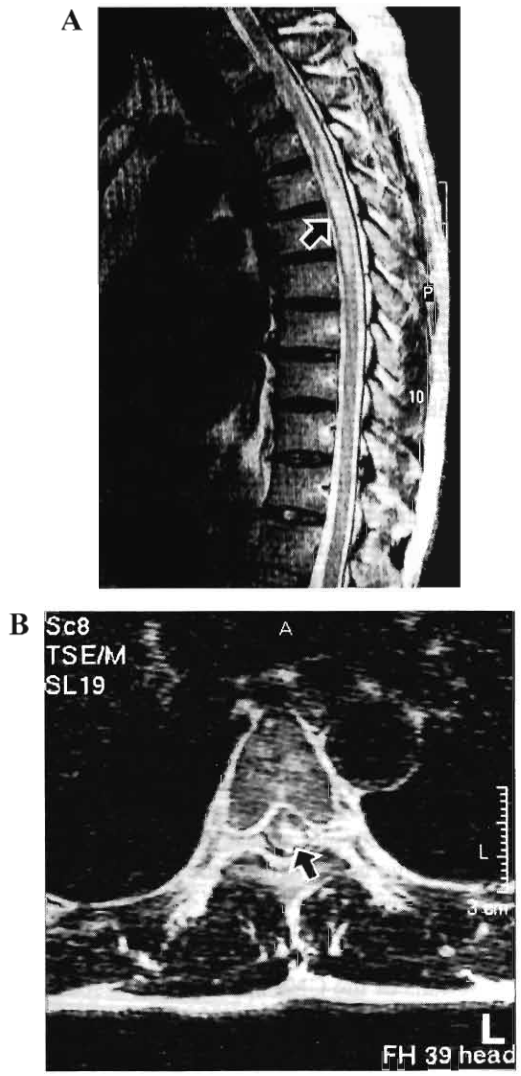

Fig. 3. MRI of HSV-1 myelitis
A: T2-weighted sagittal MRI presenting a lesion with high signal intensity extending from the 3rd to 7th thoracic level. B: T2-weighted axial MRI revealing an intra-axial longitudinal lesion in the thoracic spinal cord, predominantly on the left side (arrow).

neural spread of HSV from the infected dorsal root into the spinal cord. In an experiment using mice, Nakajima et al. (43) showed a worsening of myelitis in response to Th 2 cytokine-IL-4 and -IL-10, induced by monocyte chemotactic protein-1. This result may suggest the usefulness of immunosuppressant and cytokine therapy. Administration of acyclovir and corticosteroids is usually recommended for patients with HSV myelitis.

3-3. VZV infections of the CNS

The virus causing herpes zoster lesions is identical to VZV, the causative agent of chickenpox. It is thought that herpes zoster is the lesion by reactivation of latent VZV, originally acquired in a childhood attack of chickenpox. Common symptoms are impairment of cutaneous sensation and muscular weakness in the distribution of the affected root, headache, neck stiffness, and confusion. The presence of characteristic skin eruptions or scars are helpful for the diagnosis of VZV infections of the CNS, though HSV-l encephalitis accompanies skin lesions in only a small percentage of cases. The CNS syndromes appear to be more closely related to reactivation in the ganglia. Thus, nervous system infections associated with VZV meningitis have a relatively high incidence, followed by those associated with encephalitis, myelitis, and neuropathy (11). As in other forms, a delayed contralateral hemiplegia followed by trigeminal herpes zoster has been reported (44). The hemiplegia developed as a result of vasculitis along the internal artery from the trigeminal ganglionitis. In such cases, anti-viral drugs, similar to those used for HSE patients, are applied; in addition, corticosteroids are also used. Recently, opportunistic CNS infections concomitant with AIDS have been increasing in frequency (13, 45). These CNS syndromes are noteworthy for their lack of skin eruptions (Zoster sine herpete).

Meanwhile, encephalitis, Reye's syndrome, and acute cerebellar ataxia are more familiar in CNS infections associated with varicella. Infantile acute encephalopathy, Reye's syndrome, is characterized by acute brain edema, convulsive seizure, impairment of consciousness, and hyperammoniazemia. Since 1985, when the Japanese Ministry of Health and Welfare recommended the prohibition of aspirin use for infantile influenza, the incidence of the syndrome has decreased.

3-4. EBV infections of the CNS

EBV targets B-lymphocytes, and is known to have both inflammatory and oncogenic characteristics. Infectious mononucleosis (IM) by EBV is characterized by fever, eruption, atypical lymphocytes in the peripheral blood, tonsilar and lymph node swelling, and liver dysfunction. EBV infections of the CNS appear to be associated with an IM or an IM-like syndrome. EBV infections of the CNS are very broad compared with HSV infections of the CNS. CNS syndromes such as encephalitis, ADEM, encephalopathy, acute cerebellar ataxia, myelitis, and Guillain-Barre syndrome have been reported. Among these, encephalitis or acute cerebellar ataxia has the highest incidence (10,12,46).

We have previously reported relapsing ADEM-associated chronic EBV infections. An ADEM case associated with chronic EBV infection was found to relapse after a year (47). At the time of relapse, the EBV genome was found by PCR to be negative in the CSF, and MRI abnormalities appeared in the opposite basal ganglia and in the right white matter, instead of at the locations noted in a first attack (Fig. 4). In the presence of white matter lesions and a favorable corticosteroid response, the pathogenesis was presumed to be an autoimmune mechanism triggered by chronic EBV infection. Several EBV CNS syndromes associated with chronic active EBV infection have been reported. Cases of chronic encephalitis or recurrent meningitis have also been described. CNS infections associated with chronic active EBV infection may characteristically produce frequently chronic or recurrent CNS syndromes.

Recently, Morita et al. (48) have reported three infantile cases of chronic active EBV infection with symmetrical calcification in the basal ganglia as well as hypersensitivity to mosquitoes and an increased number of natural killer (NK) cells. However, these cases did not reveal any inflammatory findings such as CSF pleocytosis. As such, further cases should be investigated regarding whether or not such cases belong to the same group associated with chronic EBV infection.

EBV-related CNS lymphoma in AIDS is increasing, and CSF PCR is useful for this diagnosis (49).

3-5. CMV infections of the CNS

CMV is an important member of the herpesvirus family that is among the common pathogens in humans. CMV infection in cells results in the appearance of large, swollen

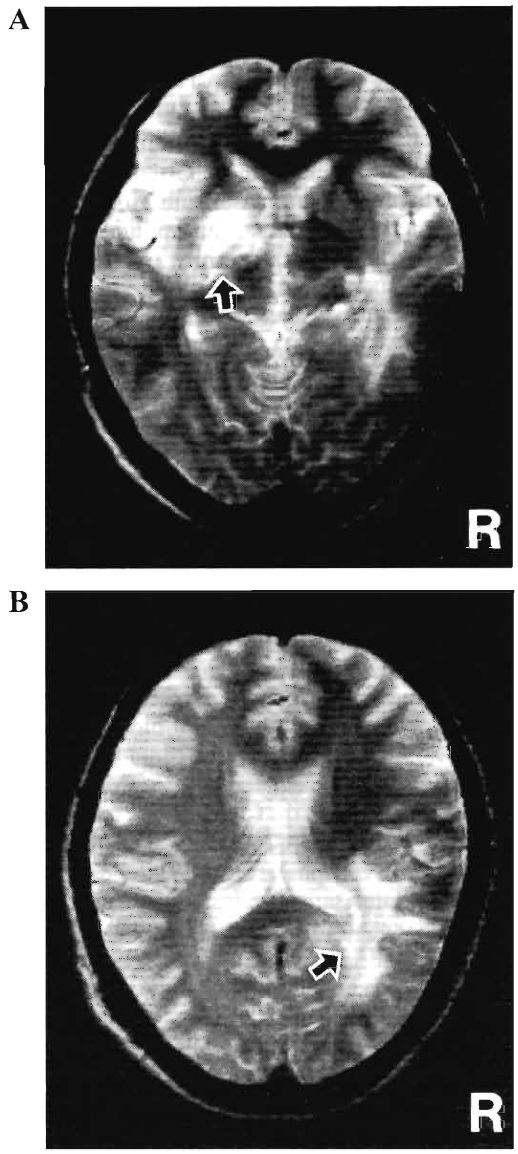

Fig. 4. MRI of ADEM associated with chronic active EBV infection A, B: At the time of recurrence, T2-weighted axial MRIs revealed new lesions in the opposite basal ganglia (arrow) and right temporal and parietal white matter (arrow).

cells that often contain large eosinophilic intranuclear and basophilic cytoplasmic inclusions. CMV infections may occur in adults, producing a mononucleosis-like syndrome; however, involvement of a CNS syndrome is unusual in adults. Ventriculoencephalitis or encephalopathy has increased in immunocompromised hosts such as AIDS patients (14), and recently, CMV lumbo-sacral radiculoneuritis has also been reported (15); its symptoms include progressive flaccid paralysis of limbs, areflexia, recto-urinary impairment, CSF pleocytosis, and PCR-positive CMV. In such cases, treatment with ganciclovir is effective. Usually, 15 mg/kg ganciclovir per day is administered intravenously.

3-6. HHV-6, -7 infections of the CNS

HHV-6 is divided into variants A and B; variant B causes infantile erythema (50). The diseases caused by variant A are thus far unknown. As HHV-6-related infantile CNS infections, convulsive seizure, encephalopathy, and meningitis are reported to be associated with infantile exanthema subitum. The pathogenesis ranges from direct viral invasion to vasculitis. Meanwhile, in adult and elderly patients, HHV-6 may be related to myelopathy and to multiple sclerosis without skin lesions. Mackenzie et al. (16) have reported detecting the HHV-6 genome in the spinal cord in a 75-year-old patient with myelopathy, and Carrigan et al. (17) have described the HHV-6 genome in a 72-year-old patient with subacute white matter encephalopathy; Akhyani et al. (51) have reported the increased prevalence of HHV-6A in patients with multiple sclerosis.

HHV-7 also causes infantile hemiplegia together with skin rash. Kaposi's sarcoma-associated herpesvirus/human herpesvirus type 8 might be related to encephalitis in immunosuppressed individuals, and should be considered in the differential diagnosis of unexplained viral encephalitis (52).

4. Conclusion

With the recent progress of PCR and other diagnostic tools, several clinical forms of HSV-1 infections of the CNS, including ADEM and brainstem encephalitis, have been reported. Although fatal, prolonged, or relapsed patient cases are still found, further virologic and immunologic studies are expected to help identify these intractable HSE cases. In adult HSV-2 infections, meningitis and myelitis associated with genital herpes are common. Previously, HSV-2 myelitis has been reported as fatal necrotizing myelopathy; however, with the introduction of PCR or MRI studies, mild surviving cases are likely to be identified.

The VZV CNS syndromes appear to be more closely related to reactivation of the latent virus in the ganglia. The nervous system infections associated with VZV meningitis have a relatively high incidence, followed by those associated with encephalitis, myelitis, and neuropathy.

EBV infections of the CNS appear to be associated with an IM or an IM-like syndrome. EBV infections of the CNS are very broad compared with HSV infections of the CNS. Several cases of chronic encephalitis or recurrent meningitis-associated chronic active EBV infection have been described. CNS infections associated with chronic active EBV infections may frequently produce chronic or recurrent CNS syndromes.

CMV ventriculoencephalitis or encephalopathy has increased in immunocompromised hosts such as AIDS patients. Recently, CMV lumbo-sacral radiculoneuritis has also been reported.

Finally, in adult and elderly patients, HHV-6 may be related to myelopathy and to multiple sclerosis without skin lesions.

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